

**NOVEL SUBSTITUED 1,2,4-TRIOXANES AS ANTIMALARIAL AGENTS AND A
PROCESS FOR PRODUCING THE SUBSTITUED 1,2,4-TRIOXANES**

Field Of The Invention

[0001] The present invention relates to novel substituted 1,2,4-trioxanes useful as anti-malarial agents. The invention also relates to a process for the preparation of novel substituted 1,2,4-trioxanes. More particularly, the invention relates to a process for the preparation of 6-[α -(hydroxyalkoxy substituted aryl) vinyl]-1,2,4-trioxanes and their esters useful as novel anti-malarial agents.

Background Of The Invention

[0002] Malaria is a killer disease in tropical countries. It is caused by *Plasmodium*. The four species of *Plasmodium* that infect human beings are *P. vivax*, *P. malariae*, *P. ovale* and *P. falciparum*. Some of the species that infect animals are *P. yoelii* in mice and *P. cynomolgi* in monkeys. These species cause severe complications in the patient that cause the patient to lapse into a coma and ultimately leads to death. In many parts of the world, there are several strains of *Plasmodium* that are resistant to drugs such as chloroquinone, mefloquine, halofantrine, quinine, etc. More than 270 million people suffer from the disease and more than 1.2 to 1.7 million die every year. Mortality among children under the age of 5 is common because such children are sensitive on account of their lack of immunity to the disease.

[0003] The need of the hour therefore is to develop novel anti-malarial drugs that can counter drug-resistant malarial infections.

Objects Of The Invention

[0004] The main objective of the invention is to provide novel substituted 1,2,4-trioxanes useful as anti-malarial agents.

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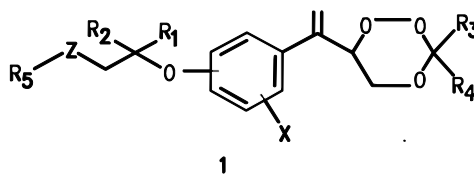
[0005] Another objective of the present invention is to provide novel intermediate compounds also capable of being used as anti-malarial agents.

[0006] Yet another objective of the present invention is to provide a process for the preparation of hydroxy-functionalized trioxanes and their esters of general formula 1, a new series of anti-malarial agents.

[0007] Still another object is to provide a process for the preparation of intermediate compounds that exhibit anti-malarial properties.

Detailed Description Of The Invention

[0008] Accordingly, the invention provides novel substituted 1,2,4-trioxanes useful as anti-malarial agents. The invention also provides a process for the preparation of hydroxy-functionalized trioxanes and their esters having general formula 1, wherein R_1 and R_2 represent a hydrogen, an alkyl group such as methyl, ethyl, propyl; R_3 and R_4 represent a hydrogen, an alkyl group such as methyl, ethyl, an aryl such as phenyl, naphthyl or part of a cyclic system; R_5 represents hydrogen, alkyl group such as methyl, ethyl, propyl, aryl such as phenyl or a carboxy alkyl group such as $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; X represents hydrogen or lower alkoxy such as OMe,



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[0009] Z represents O or OCO. These compounds have been tested against multi-drug resistant *P. yoelii* in mice and several of them show promising anti-malarial activity. Some of these compounds with promising anti-malarial activity have been tested against *P. cynomolgi* in monkeys and have been found effective. The invention thus relates to the

pharmaceutical industry. The trioxanes of general formula **1** are new chemical entities and they have not been prepared earlier. Trioxanes of general formula **1** are oil-soluble and can be administered as solution in oil such as groundnut oil. Some of the compounds of formula **1** are hemisuccinate derivatives and are soluble both in oil and aqueous NaHCO_3 solution and can be administered as a solution in groundnut oil or aqueous NaHCO_3 . The mode of administration can be oral, intra-muscular, subcutaneous or intravenous. The said compounds, the preferred compounds and the intermediate compounds are described herein below with reference to the accompanying drawings and examples which have been provided merely to illustrate the invention and should not be construed as limitations on the inventive concept.

Brief Description Of The Accompanying Drawings

[0010] In the drawings that accompany,

[0011] Fig. 1 represents the sequence of the process of the invention wherein compound of formula **2** is converted to compound having formula **1**.

[0012] Fig. 2 represents in series the structures of compounds **9** to **42**, wherein Fig.2 (a) represents the structural formulae of compounds **9** to **16**. Fig. 2(b) represents the structural formulae of compounds **17**, **18**, **19**, **20**, **21**, **22a** and **22b**. Fig. 2(c) represents the structural formulae of compounds **23**, **24**, **25**, **26**, **27** and **28**. Fig. 2(d) represents the structural formulae of the compounds having formula **29** to **36**. Fig. 2(e) represents the structural formulae of the compounds having formula **37** to **42**.

[0013] Formula **2** shown in figure 1 includes compounds of structural formulae **9** and **10** of the drawings. Formula **4** shown in figure 1 includes compounds of structural formulae **11** and **12** of the drawings. Formula **5** shown in figure 1 includes compounds of structural formulae **13** and **14** of the drawings. Formula **6** shown in figure 1 includes compounds of structural formulae **15** and **16** of the drawings. Formula **7** shown in figure 1 includes compounds of structural formulae **17** and **18** of the drawings. Formula **8** shown in figure 1 includes compounds of structural formulae **19** and **20** of the drawings.

Formula **1** shown in figure 1 includes compounds of structural formulae **23** to **42** of the drawings.

[0014] Similarly, in figure 2(a), the compounds **11** to **16** are intermediate compounds.

[0015] Accordingly, the present invention provides a process for the preparation of novel substituted 1,2,4-trioxanes and their esters of general formula **1** which comprises reacting hydroxyacetophenones of formula **2** wherein X represents hydrogen or lower alkoxy such as OMe, with α -haloesters of formula **3** wherein R₁ and R₂ represent hydrogen, alkyl group such as methyl, ethyl, propyl and Y represents halogen such as Cl or Br, in the presence of a base optionally in an organic solvent at a temperature in the range of room temperature to refluxing temperature to give ketoesters of general formula **4**, wherein R₁, R₂ and X have the same meaning as above; reacting ketoesters of general formula **4** under Reformatsky condition in an aprotic organic solvent in the temperature range of room temperature to refluxing temperature to give β -hydroxyesters of general formula **5**, wherein R₁, R₂ and X have the same meaning as above; dehydrating β -hydroxyesters of formula **5** using a catalyst in an organic solvent at a temperature in the range of room temperature to refluxing temperature to give α,β -unsaturated esters of general formula **6**, wherein R₁, R₂ and X have the same meaning as above; reducing α,β -unsaturated esters of general formula **6** with a complex metal hydride such as LiAlH₄ in an ether solvent at a temperature in the range of 0°C to room temperature to give allylic alcohols of formula **7** wherein R₁, R₂ and X have the same meaning as above; oxygenation of allylic alcohols of formula **7** in the presence of a sensitizer in an organic solvent at a temperature in the range of -10°C to room temperature to give β -hydroxyhydroperoxides of general formula **8** wherein R₁, R₂ and X have the same meaning as above; isolating and then reacting or reacting *in situ* β -hydroxyhydroperoxides of formula **8** with compounds containing aldehyde or ketone group in the presence of an acid catalyst in an organic solvent at a temperature in the range of 0°C to room temperature to give hydroxy-functionalized 1,2,4-trioxanes of general formula **1**, wherein R₁, R₂ and X have the same

meaning as above, R_3 and R_4 are hydrogen, alkyl group such as methyl, propyl, aryl group such as phenyl, naphthyl or part of a cyclic system, R_5 is H and Z is O; reacting hydroxy-functionalized trioxanes of general formula **1**, wherein R_5 is H and Z is O with an acid chloride or anhydrides in the presence of a base in an organic solvent at a temperature in the range of 0°C to room temperature to give trioxane esters of general formula **1**, wherein R_1 , R_2 , R_3 , R_4 and X have the same meaning as above, R_5 is alkyl group such as methyl, ethyl, propyl, aryl group such as phenyl, carboxyalkyl such as $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; and Z is OCO.

[0016] In the process hydroxyacetophenones of formula **2** are reacted with α -haloesters of formula **3** in the presence of a base such as Na_2CO_3 , K_2CO_3 , KHCO_3 in an organic solvent such as acetone, dimethylformamide, dimethylsulfoxide or without solvent, to give ketoesters of general formula **4**. These ketoesters can be isolated and purified by standard laboratory methods such as crystallization or chromatography using an adsorbent such as silica gel. All ketoesters of general formula **4** except **11a** (formula **11**, $R_1 = R_2 = X = \text{H}$), **11c** (formula **11**, $R_1 = \text{H}$, $R_2 = \text{Me}$, $X = \text{H}$) and **12a** (formula **12**, $R_1 = R_2 = \text{H}$) are new compounds and they have not been prepared earlier. Ketoesters **11a**, **11c** and **12a** are known compounds. [(a) *Chim. Ther.*, **8**, 574 (1973), *Indian J. Chem.*, **24**, 119 (1985), *Chem. Abstracts*, **124**, 8616e (1996)].

[0017] In the process ketoesters of general formula **4** are reacted with ethyl bromoacetate and Zn in an aprotic solvent such as benzene, diethyl ether, to give β -hydroxyesters of general formula **5**. These β -hydroxyesters can be isolated and purified by standard laboratory methods such as column chromatography using an adsorbent such as silica gel and a hydrocarbon solvent in combination with ethyl acetate as eluant or can be used without purification in the next step. β -hydroxyesters of general formula **5** are new compounds and they have not been prepared earlier. These hydroxyesters of general formula **5** have an additional ester group as part of substitution in the aromatic ring.

[0018] In the process dehydration of β -hydroxyesters of general formula **5** is accomplished in an hydrocarbon solvent such as benzene, toluene, CH_2Cl_2 , in the presence of a catalyst such as I_2 , p-toluene-sulfonic acid, P_2O_5 , or acidic resin such as Amberlyst-15 to give α,β -unsaturated esters of general formula **6**. These unsaturated esters can be isolated and purified by standard laboratory methods such as chromatography using an adsorbent such as silica gel. α,β -Unsaturated esters of general formula **6** have an additional ester group as part of substitution in the aromatic ring. These esters of general formula **6** are new compounds and they have not been prepared earlier.

[0019] In the process reduction of α,β -unsaturated esters of general formula **6** is done by reacting the compound with a complex metal hydride such as LiAlH_4 in an ether solvent such as diethyl ether, THF, to give allylic alcohols of general formula **7**. These allylic alcohols of general formula **7** have an additional hydroxyl group as hydroxyalkoxy substitution in the aromatic ring. These allylic alcohols of general formula **7** can be isolated and purified by standard laboratory methods such as chromatography using an adsorbent such as silica gel and a hydrocarbon solvent in combination with ethyl acetate as eluant. Compounds of general formula **7** are new chemical entities and they have not been prepared earlier.

[0020] In the process allylic alcohols of general formula **7** are converted to β -hydroxyhydroperoxides of formula **8** by passing oxygen gas in the solution of the alcohol in an organic solvent and in the presence of a dye and a light source which provides visible light. The dye which acts as a sensitizer, i.e. converts triplet oxygen to highly reactive singlet oxygen, may be such as methylene blue, Rose Bengal, and tetraphenylporphine. Organic solvent used may be such as CH_2Cl_2 , CH_3CN , acetone, methanol, and benzene. These β -hydroxyhydroperoxides of general formula **8** can be isolated and purified by known laboratory methods or can be used *in situ*, without purification and isolation, in the next step. These β -hydroxyhydroperoxides of formula **8** are new chemical entities and they have not been prepared earlier. Furthermore, these β -hydroxyhydroperoxides have an extra hydroxyl group in the form of hydroxyalkoxy

substitution in the aromatic ring. The novel feature of these β -hydroxyhydroperoxides is that this extra hydroxyl group which is present as a hydroxyalkoxy substituent in the aromatic ring, does not take part in the next reaction, i.e. condensation of hydroperoxides with aldehyde and ketones and thus provide 1,2,4-trioxanes which carry a hydroxy group suitable for further derivatization.

[0021] In the process β -hydroxyhydroperoxides of general formula **8** are converted to hydroxy-functionalized 1,2,4-trioxanes of general formula **1** ($R_5 = H$, $Z = O$) by reacting these hydroperoxides with carbonyl compounds of formulae **21-22** in the presence of an acid catalyst in an aprotic organic solvent. The carbonyl compounds used may be such as benzaldehyde, naphthaldehyde, acetone, ethyl methyl ketone, methyl propyl ketone, methyl isobutyl ketone, 4-heptanone, 5-nonanone, 6-undecanone, dibenzyl ketone and cyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone, bicyclic ketone such as norcomphor (**22a**) and tricyclic ketone such as 2-adamantanone (**22b**). The acid catalyst used may be HCl, H₂SO₄, p-toluene-sulfonic acid, BF₃.OEt₂, acidic resin such as Amberlyst-15. The organic solvent used may be CH₂Cl₂, CHCl₃, benzene, or CH₃CN. These trioxanes of general formula **1** ($R_5 = H$, $Z = O$) are stable compounds and can be isolated and purified by standard chromatographic techniques using an adsorbent such as silica gel and a hydrocarbon solvent in combination with polar organic solvent as eluant. These trioxanes of general formula **1** ($R_5 = H$, $Z = O$) are new chemical entities and they have not been prepared earlier. The novel feature of these trioxanes is that they are equipped with a primary hydroxyl group suitable for making derivatives of these trioxanes. This hydroxyl group is part of an alkoxy substituent in the aromatic ring. These trioxanes of general formula **1** ($R_5 = H$, $Z = O$) have been tested against malarial parasites in animal models and several of them show very promising anti-malarial activity, both against chloroquine sensitive and chloroquine resistant malaria. These trioxanes are oil-soluble and can be administered as solution in oil such as groundnut oil. Some of these trioxanes have shown significant gamatocidal activity.

[0022] In the process, reaction of trioxanes of general formula **1** ($R_5 = H$, $Z = O$) with acid chlorides of formula **29** or acid anhydrides of formula **30** wherein R_5 is an alkyl group such as methyl, ethyl, propyl, or an aryl group such as phenyl, is done in an aprotic organic solvent in the presence of a base to give trioxane esters of general formula **1** wherein R_5 is an alkyl group such as methyl, ethyl, propyl, or an aryl group such as phenyl, and Z is OCO. In the reaction, the hydroxyl group of trioxanes of formula **1** ($R_5 = H$, $Z = O$) is esterified. The acid chlorides and acid anhydrides used may be acetyl chloride, benzoyl chloride, propionic anhydride, butyric anhydride, and/or heptanoic anhydride. The base can be such as Et_3N , pyridine, with or without a catalyst such as 4-dimethylaminopyridine (DMAP). The organic solvent used may be for example, CH_2Cl_2 , $CHCl_3$, THF, or CH_3CN . These trioxanes of general formula **1** ($R_5 = \text{alkyl, aryl}$, $Z = OCO$) can be isolated and purified by known laboratory methods such as crystallization or chromatography using an adsorbent such as silica gel and hydrocarbon solvent in combination with polar organic solvents as eluant. The trioxanes are new chemical entities that have not been prepared earlier. These trioxanes are oil-soluble and can be administered as solution in edible oil such as groundnut oil. Some of the trioxanes of general formula **1** ($R_5 = \text{alkyl, aryl}$; $Z = OCO$) have shown promising anti-malarial activity in animal models.

[0023] In the process, trioxanes of formula **1** ($R_5 = H$, $Z = O$) are reacted with succinic anhydride in an aprotic solvent in the presence of tertiary amine with or without the presence of 4-dimethylaminopyridine (DMAP) to give carboxy functionalized trioxanes of general formula **1** ($R_5 = CH_2CH_2CO_2H$; $Z = OCO$). The tertiary amine may be for example, Et_3N or pyridine. Aprotic organic solvents may be for example, CH_2Cl_2 , $CHCl_3$, CH_3CN , toluene or THF. In the reaction, the hydroxyl group of the trioxanes of formula **1** ($R_5 = H$, $Z = O$) is esterified.

The trioxanes of general formula **1** ($R_5 = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; $Z = \text{OCO}$) have a carboxyl group and are soluble in aqueous bicarbonate or carbonate solutions. Thus they can be administered both as solution in oil or aqueous bicarbonate/carbonate solutions. Trioxanes of general formula **1** ($R_5 = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; $Z = \text{OCO}$) can be isolated and purified by known laboratory methods such as given above. Trioxanes of general formula **1** ($R_5 = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; $Z = \text{OCO}$) are new chemical entities that have not been prepared earlier. Some of these trioxanes have shown promising anti-malarial activity against both chloroquine-sensitive and resistant malaria in animal models. Some of these trioxanes also show significant gamatocidal activity.

[0024] The invention is further illustrated by the following examples, which should not, however, be construed to limit the scope of the present invention.

EXAMPLE 1

Ethyl (4-acetylphenoxy) acetate (compound 11a, formula 11, $R_1 = R_2 = X = \text{H}$)

[0025] A mixture of p-hydroxyacetophenone (50 g), ethyl chloroacetate (60 ml), K_2CO_3 (120 g) in acetone (450 ml) was refluxed with stirring for 24 h. The reaction mixture was filtered and the residue was washed with acetone. The combined filtrate was concentrated and the residue was redissolved in ether. The ether extract was washed with aqueous NaOH, and then with water, dried, concentrated and purified by chromatography on silica gel using hexane – ethylacetate as eluant to give 63.3 g (77% yield) of **11a**, m.p.64-68°C.

[0026] Compound **11a** was also prepared using the conditions as given in Table 1.

TABLE 1

α-Haloesters	Solvent	Base	Temp.	Time	Yield(%)
Ethyl bromoacetate	DMF	K ₂ CO ₃	Room temp.	5 h	16
Ethyl chloroacetate	DMSO	K ₂ CO ₃	Room temp.	6 h	68
Ethyl bromoacetate	Neat	K ₂ CO ₃	Room temp.	13 h	61
Ethyl chloroacetate	Neat	KHCO ₃	120°C	7.5 h	42
Ethyl chloroacetate	Neat	Na ₂ CO ₃	120°C	14 h	9

 β - Hydroxyesters 13a (formula 13, R₁ = R₂ = X = H)

[0027] To a mixture of ketoester **11a** (20 g) zinc metal (12 g), I₂ (20 mg) in benzene was added ethyl bromoacetate (10 ml) dropwise. The reaction mixture was refluxed for another 7 hr, cooled, acidified with aqueous HCl. The benzene layer was separated and the aqueous layer was extracted with benzene. Combined organic extract was washed with water and then aqueous NaHCO₃, dried and concentrated. The crude product was purified by column chromatography on silica gel using a mixture of hexane and ethylacetate as eluant to furnish β - hydroxyester **13a** (63% yield) as an oil.

[0028] Compound **13a** was also prepared using the conditions given in Table 2.

TABLE 2

α-Haloester	Solvent	Temp.	Time
Ethyl chloroacetate	Benzene	Reflux	21 h used in the next step without purification
Ethyl bromoacetate	Ether	Room Temp.	35 h used in the next step without purification

 α,β -Unsaturated ester 15a (formula 15, R₁ = R₂ = X = H)

[0029] A mixture of β - hydroxyester **13a** (10 g) and P₂O₅ (4 g) in benzene (150 ml) was refluxed for 2.5 h. The reaction mixture was filtered and the filtrate was concentrated to give 10 g of crude product which was purified by column chromatography on silica gel using hexane – ethylacetate as eluant to give 5.13 g (56% yield) of α,β -unsaturated ester **15a** as an oil.

Allylic alcohol 17a (formula 17, $R_1 = R_2 = X = H$)

[0030] To a stirred and ice-cooled mixture of $LiAlH_4$ (6 g) in dry ether (400 ml), a solution of α,β -unsaturated ester **15a** (12 g) in ether was added dropwise. The reaction mixture was stirred in an ice-bath for 5 h. and then quenched with water and 10% NaOH. The organic layer was separated, dried on Na_2SO_4 and concentrated to give 8.84 g. of crude product which was purified by column chromatography to furnish 5.67 g (59%) of allylic alcohol **17a**; m.p; 83-86°C.

3-[4-(2-Hydroxyethoxy)phenyl]-1-hydroxy-but-3-en-2-hydroperoxide (compound 19a, general formula 19, $R_1 = R_2 = H$, $X = H$)

[0031] (1) A solution of allylic alcohol **17a** and methylene blue (15 mg) in ethanol (60 ml) was irradiated with a 250-watt tungsten-halogen lamp at $-10^\circ C$ while a slow stream of oxygen was passed through the reaction mixture for 9.5 h. The reaction mixture was diluted with water and extracted with ether. The ether extract was concentrated and the crude product was chromatographed on silica gel using CH_2Cl_2 – ether as eluant to give 650 mg (28% yield) of β -hydroxyhydroperoxide **19a**.

[0032] (2) A solution of allylic alcohol **17a** (1 g), tetraphenylporphine (50 mg) in $CHCl_3$ (60 ml) was photooxygenated at r.t. for 6 h. β -hydroxyhydroperoxide **19a** separated as a solid. It was washed with ether to give 500 mg (44% yield) of TLC pure **19a**.

Trioxane 23a1 (formula 23, $R_1 = R_2 = X = H$, $R_3, R_4 = -CH_2CH_2CH_2CH_3$)

[0033] (1) **Two-pot procedure:** A mixture of β -hydroxyhydroperoxide **19a** (900 mg), cyclopentanone (2 ml) and p-toluene sulfonic acid (50 mg) in acetonitrile (10 ml) was stirred at room temperature for 3.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The ether extract was concentrated and the crude product was

purified by chromatography (elution with ethylacetate-hexane; 1:9) to furnish 310 mg (44% yield) of trioxane **23al**.

[0034] (2) **One-pot procedure:** A solution of alcohol **17a** (3.5 g) and methylene blue (10 mg) in CH₃CN (65 ml) was irradiated with a tungsten-halogen lamp at 0°C for 7.5 h when a slow stream of oxygen was passed through the reaction mixture to give β-hydroxyhydroperoxide **19a** as indicated by TLC. To the reaction mixture were added cyclopentanone (6 ml) and p-toluenesulfonic acid (50 mg) and the reaction mixture was stirred at r.t. for 2 days. Workup and purification by chromatography furnished 1.14 g (23% yield based on alcohol **17a**) of trioxane **23al**.

Acetate of trioxane 23al (compound 31al, formula 31, R₁ = R₂ = H; R₃, R₄ = CH₂CH₂CH₂CH₃; R₅ = CH₃; X = H)

[0035] A solution of trioxane **23al** (200 mg) in pyridine (6 ml) was treated with acetic anhydride (0.5 ml) and the resulting mixture was left in the refrigerator (~ 5°C) overnight. The reaction mixture was diluted with water and extracted with ether. Ether extract was washed sequentially with water, 10% HCl, water, and then dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography on silica gel to give 180 mg (91% yield) compound **31al** as an oil

EXAMPLE 2

Benzoate of trioxane 23al (compound 31a5, formula 31, R₁ = R₂ = H; R₃, R₄ = CH₂CH₂CH₂CH₃; R₅ = Ph; X = H)

[0036] A solution of trioxane **23al** (180 mg) and benzoyl chloride (0.5 ml) in pyridine (3 ml) was left at r.t. overnight. The reaction mixture was diluted with water and extracted with ether. Ether was extracted as usual processing followed by column chromatography on silica gel using hexane – ethylacetate as eluant and furnished 100 mg (42% yield) of benzoate **31a5** as an oil.

EXAMPLE 3

Trioxane 23a2 (formula 23, $R_1 = R_2 = X = H$, $R_3, R_4 = -CH_2CH_2CH_2CH_2CH_3$)

[0037] A solution of allylic alcohol **17a** (1 g) and methylene blue (15 mg) in acetonitrile was photooxygenated at 0°C for 6.5 h. as above and then reacted with cyclohexanone (2 ml) using p-toluenesulfonic acid as catalyst at r.t. for 5 h. The crude product obtained after workup as above was purified by chromatography to give 0.86 g (57% yield based on the alcohol **17a**) of 1,2,4-trioxane **23a2**.

EXAMPLE 4

Trioxane 23a3 (formula 23, $R_1 = R_2 = X = H$; $R_3 = R_4 = Me$)

[0038] (1) From β -hydroxyhydroperoxide 19a

To a solution of β -hydroxyhydroperoxide **19a** (100 mg) in acetone (5 ml) was added one drop of concentrated (conc.) HCl and the reaction mixture was stirred at r.t. for 30 minutes. The reaction mixture was concentrated under vacuum and the crude product was purified by chromatography on silica gel using hexane – ethylacetate as eluant to give 60 mg (52% yield) of trioxane **23a3**.

[0039] (2) From allylic alcohol 17a

A solution of allylic alcohol **17a** (1 g) and Rose Bengal (5 mg) in acetone (40 ml) was photooxygenated at –8°C for 6 h. To this reaction mixture were added 3 drops of conc. HCl and the reaction mixture was left overnight at r.t. The solvent was removed under vacuum and the crude product was chromatographed on silica gel as above to furnish 340 mg (26% yield based on allylic alcohol **17a**) of trioxane **23a3**.

EXAMPLE 5**Trioxane 27a (formula 27, $R_1 = R_2 = X = H$)**

[0040] A solution of allylic alcohol **17a** (2 g) and methylene blue (5 mg) in CH_3CN (60 ml) was photooxygenated at 0°C for 6 h to give β -hydroxyhydroperoxide **19a** as indicated by TLC. To this reaction mixture 2-adamantanone (2 g) was added and the reaction mixture was stirred for 1 h when p-toluenesulfonic acid (10 mg) was added and the reaction mixture was stirred for another 6 h at room temperature. The reaction was quenched with aqueous $NaHCO_3$, diluted with water and extracted with ether. Ether extract was washed with water, dried (Na_2SO_4) concentrated and the crude product was purified by chromatography on silica gel to furnish 1.9 g (57% yield based on alcohol **17a**) of trioxane **27a** as an oil.

Acetate of trioxane 27a (compound 35al, formula 35, $R_1 = R_2 = H$; $R_5 = CH_3$; $X = H$)

[0041] A mixture of trioxane **27a** (200 mg), acetic anhydride (1 ml) in pyridine (4 ml) was left at r.t. overnight. The reaction mixture was diluted with water and extracted with ether. Ether extract was washed with water, 10% aqueous HCl, water, dried (Na_2SO_4) and concentrated to give 200 mg of crude product which was purified by chromatography on silica gel (8 g, elution with 50% EtOAc in CH_2Cl_2) to give 178 mg (80% yield) of acetate **35al** as an oil.

Hemisuccinate of trioxane 27a (compound 41a, formula 41, $R_1 = R_2 = H$; $X = H$)

[0042] A mixture of trioxane **27a** (2 g) and succinic anhydride (3 g) in pyridine (20 ml) was left at r.t. overnight. The reaction mixture was diluted with water and extracted with ether. The extract was washed with water, 10% HCl, water, dried (Na_2SO_4) and concentrated to give 2.3 g of crude product which was purified by chromatography on silica gel (25 g, eluted with 50% ether in CH_2Cl_2) to give 1.5 g (60% yield) of hemisuccinate **41a** as a highly viscous material.

EXAMPLE 6

Trioxane 23a13 (formula 23, $R_1 = R_2 = X = H$; $R_3, R_4 = H$, 1-naphthyl)

[0043] A solution of allylic alcohol **17a** (1.0 g) and methylene blue (70 mg) in CH_3CN (50 ml) was photooxygenated at -10 to $0^\circ C$ for 6 h. To one-half of this reaction mixture were added 1-naphthaldehyde (1 ml) and p-toluene sulfonic acid (20 mg) and the reaction mixture was kept at $5^\circ C$ overnight. Usual workup followed by purification by chromatography furnished trioxane **17a13** in 32% yield.

Hemisuccinate of trioxane 23a13 compound 37a4, formula 37, $R_1 = R_2 = H$; $R_3, R_4 = H$, 1-naphthyl; $X = H$

[0044] To an ice-cooled mixture of **23a13** (120 mg) and succinic anhydride (200 mg) in CH_2Cl_2 (20 ml) were added triethylamine (0.2 ml) and 4-dimethylaminopyridine (30 mg) and the reaction mixture was left overnight at r.t. Workup as above followed by column chromatography in silica gel using CH_2Cl_2 – ether as eluant furnished hemisuccinate **37a4** as an oil (100 mg; 67% yield).

EXAMPLE 7

Ethyl 2-(4-acetylphenoxy) isobutyrate (compound 11b Formula 11, $R_1 = R_2 = Me$; $X=H$)

[0045] A mixture of p-hydroxyacetophenone (14 g), ethyl 2-bromoisobutyrate (21 g) and K_2CO_3 (40 g) in acetone (260 ml) was refluxed with stirring for 19 h. The reaction mixture was diluted with water and extracted with benzene. Usual processing of the benzene extract furnished 10.5 g (41% yield) of ketoester **11b** as an oil.

[0046] Compound **11b** was also prepared using the conditions as given in Table 3.

TABLE 3

α -Haloester	Solvent	Base	Temp.	Time	Yield(%)
Ethyl 2-bromoisobutyrate	Isobutyl methyl ketone	K ₂ CO ₃	Reflux	11 h	30
“	DMSO	K ₂ CO ₃	Room temp.	21 h	27
“	DMSO	K ₂ CO ₃	50 – 60°C	21 h	22
“	Neat	K ₂ CO ₃	120°C	14 h	49

 β -Hydroxyester 13b (formula 13, R₁ = R₂ = Me, X = H)

[0047] To a refluxing mixture of ketoester **11b** (12 g), zinc (6 g), I₂ (70 mg) in benzene (200 ml), ethyl bromoacetate (7 ml) was added dropwise and the reaction mixture was refluxed for 7 hr. Work up and purification by chromatography on silica gel (hexane – EtOAc on eluant) furnished 45% yield of β -hydroxyester **13b**.

 α , β - Unsaturated ester 15b (formula 15, R₁ = R₂ = Me, X = X)

[0048] To a refluxing mixture of ketoester **11b** (10.5 g), zinc (5 g), I₂ (40 mg) in benzene (200 ml), a solution of ethyl bromoacetate (5 ml) in benzene (50 ml) was added dropwise and the reaction mixture was refluxed for 7 h. The reaction mixture was cooled and acidified with 10% aqueous HCl. Benzene layer was separated and the aqueous layer was extracted with benzene (2 x 150 ml). The combined organic extract was washed with water and aqueous NaHCO₃ solution, dried (Na₂SO₄) and concentrated to give β -hydroxyester **13b** which was used in the next without isolation and purification.

[0049] The crude **13b** as obtained above was dissolved in benzene (200 ml). I₂ (50 mg) was added and the reaction mixture was refluxed for 1.75 h. The reaction mixture was cooled, washed with aqueous sodium thiosulphate and then with water, dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography to furnish 6.80 g (51% yield) of α , β -unsaturated ester **15b**

Allylic alcohol 17b (formula 17, R₁ = R₂ = Me; X = H)

[0050] To a stirred and ice-cooled mixture of LiAlH₄ (5 g) in dry ether (450 ml), a solution of α , β -unsaturated ester **15b** (6.2 g) in dry ether was added dropwise. The reaction mixture was stirred for 5 h. and then quenched with water and 10% aqueous NaOH. The organic layer was separated. The residue was washed with ether and the combined organic extract was dried (Na₂SO₄), concentrated and the crude product was purified to give 3.0 g (66% yield) of allylic alcohol **17b**, as an oil.

3-[4-(2-Hydroxy-1, 1-dimethyl-ethoxy)phenyl]-1-hydroxy-but-3-en-2-hydroperoxide (compound 19b, formula 19, R₁ = R₂ = Me, X = H)

[0051] A solution of allylic alcohol **17b** (1.40 g) and methylene blue (100 mg) in CH₃CN (45 ml) was irradiated with a 500 watt tungsten-halogen lamp at 0°C for 5 h while a slow stream of oxygen was passed through the reaction mixture. The reaction mixture was concentrated to 20 ml and then diluted with water (20ml) and extracted with ether (3 x 25 ml). The combined ether extract was washed with water, dried (Na₂SO₄), concentrated and purified by chromatography on silica gel to furnish 860 mg (61% yield) of β -hydroxyhydroperoxide **19b** as an oil.

Trioxane 23b1 (formula 23, R₁ = R₂ = Me, X = H ; R₃, R₄ = -CH₂CH₂CH₂CH₃)

[0052] A solution of allylic alcohol **17b** (680 mg) and methylene blue (15 mg) in CH₃CN (60 ml) was photooxygenated at 0°C for 3.25 h to give β -hydroxyhydroperoxide **19b** as indicated by TLC. This reaction mixture was divided into two equal parts. To one part were added cyclopentanone (2 ml) and PTSA (25 mg) and stirred at r.t. for 2.75 h. Usual workup followed by chromatography on silica gel furnished 240 mg (63% yield based on allylic alcohol **17b**) of trioxane **23b1**.

Hemisuccinate of trioxane 23b1 (compound 37b 1, formula 37, $R_1 = R_2 = \text{Me}$; $R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$; $X = \text{H}$)

[0053] A solution trioxane **23b1** (1 g) in CH_2Cl_2 (40 ml) was reacted with succinic anhydride as above and the product was purified by chromatography as above to furnish 1.23 g (93% yield) of hemisuccinate **37b1**.

EXAMPLE 8

Trioxane 23b2 (formula 23, $R_1 = R_2 = \text{Me}$, $X = \text{H}$; $R_3, R_4 = -\text{CH}_2- (\text{CH}_2)_3-\text{CH}_3$)

[0054] To one half of the photooxygenated mixture from the above example were added cyclohexanone (2 ml) and PTSA (25 mg) and the reaction mixture was stirred at r.t. for 2.75 h. Normal workup followed by purification by column chromatography on a silica gel gave 230 mg (46% yield based on the allylic alcohol **17b** used) of trioxane **23b2**.

EXAMPLE 9

Trioxane 27b (formula 27, $R_1 = R_2 = \text{Me}$, $X = \text{H}$)

[0055] A mixture of allylic alcohol **17b** (2.0 g) and methylene blue (100 mg) in CH_3CN (60 ml) was photooxygenated at 0°C for 6.5 h. To this reaction mixture were added 2-adamantanone (3.0 g) and p-toluenesulfonic acid (100 mg) and the reaction mixture was left at room temperature overnight. The reaction mixture was quenched with aqueous NaHCO_3 diluted with water and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on a silica gel and gave 1.61 g (59% yield based on allylic alcohol **17b**) of 1,2,4-trioxane **27b**, m.p. $100-102^\circ\text{C}$.

[0056] Trioxane **27b** was obtained in 44% yield when the condensation with 2-adamantanone was done using Amberlyst-15 as catalyst.

Acetate of trioxane 27b (compound 35b1, formula 35, $R_1 = R_2 = \text{Me}$; $R_5 = \text{CH}_3$; $X = \text{H}$)

[0057] A solution of trioxane **27b** (200 mg) and acetic anhydride (1 ml) in pyridine (4 ml) was reacted at r.t. overnight. Workup as above followed by column chromatography on silica gel furnished 0.21 g of acetate **35b1** as a viscous material.

EXAMPLE 10

Propionate of trioxane 27b (compound 35b2, formula 35, $R_1 = R_2 = \text{Me}$; $R_5 = \text{Et}$; $X = \text{H}$)

[0058] To an ice-cooled mixture of **27b** (300 mg) and propionic anhydride (1.3 ml) in CH_2Cl_2 (10 ml) were added triethylamine (0.8 ml) and 4-dimethylaminopyridine (20 mg) and left overnight at r.t. Usual workup as above followed by column chromatography on silica gel furnished 310 mg (91% yield) of propionate **35b2** as a colourless oil.

EXAMPLE 11

Hexanoate of trioxane 27b (compound 35b4, formula 35, $R_1 = R_2 = \text{Me}$; $R_5 = \text{n-pentyl}$; $X = \text{H}$)

[0059] A mixture of trioxane **27b** (300 mg) and hexanoic anhydride (1 ml) in CH_2Cl_2 (15 ml) was reacted in the presence of triethylamine (0.5 ml) and 4-dimethylamino pyridine (20 mg) at r.t. for 1 h. Workup as above followed by column chromatography on silica gel furnished 330 mg (89% yield) of hexanoate **35b4** as an oil.

EXAMPLE 12

Hemisuccinate of trioxane 27b (compound 41b, formula 41, $R_1 = R_2 = \text{Me}$; $X = \text{H}$)

[0060] To a stirred and ice-cooled mixture of trioxane **27b** (2.3 g) and succinic anhydride (2.5 g) in CH_2Cl_2 (100 ml) were added triethylamine (2.5 ml) and 4-dimethylamino pyridine (50 mg) and the reaction mixture was stirred at r.t. for 2h., concentrated under reduced pressure, acidified (50 ml of 10% HCl) and extracted with ether (3 x 150 ml). Ether extract was washed with water (3 x 100 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give 3.1 g of crude material which was

chromatographed on silica gel (50 g, eluted with 50% ether in hexane) to give 2.3 g solid which was crystallized from ether-hexane to give 1.91 g (68% yield) of hemisuccinate **41b** as white crystals, mp. 96-99°C.

[0061] Similar yields of **41b** were obtained when the reaction was done in the absence of 4-dimethylaminopyridine.

EXAMPLE 13

Ketoester 11f (formula 11, $R_1 = R_2 = H$, $X = OMe$)

[0062] Compound **11f** was prepared from 3-methoxy-4-hydroxyacetophenone (formula **9**, $X = OMe$) in 84% yield following the procedure used for the preparation of compound **11a** as given in example 1.

β -Hydroxyester 13f (formula 13, $R_1 = R_2 = H$; $X = OMe$)

[0063] To a refluxing mixture of ketoester **11f** (21 g), zinc (6 g), and catalytic amount of iodine in benzene (400 ml) was added dropwise ethyl bromoacetate (15 ml) and the reaction mixture was refluxed for 8 hr. Work up and purification as given in example 1 furnished 20 g (71% yield) of β -Hydroxyester **13f**.

α, β -Unsaturated ester 15f (formula 15, $R_1 = R_2 = H$; $X = OMe$)

[0064] β -Hydroxyester **13f** (20 g) was dehydrated with P_2O_5 in refluxing benzene as above and the crude product was purified by column chromatography on silica gel to furnish 10.5 g (55%) of α, β -unsaturated ester **15f**.

Allylic alcohol 17f (formula 17, $R_1 = R_2 = H$; $X = OMe$)

[0065] α, β -Unsaturated ester **15f** (1.2 g) was reduced with $LiAlH_4$ (240 mg) in dry ether (25 ml) at 0°C. Work and purification was done according to the procedure as given above to give 260 mg (29% yield) of allylic alcohol **17f**.

Trioxane 27f (formula 27, $R_1 = R_2 = H$; $X = OMe$)

[0066] A solution of allylic alcohol **17f** (550 mg), adamantanone (540 mg) and methylene blue (15 mg) in CH_3CN (40 ml) was photooxygenated as above for 6 h. to give β -hydroxyhydroperoxide **19f** (formula 19, $R_1 = R_2 = H$; $X = OMe$) as indicated by TLC. To this reaction mixture was added p-toluenesulfonic acid (20 mg) and was left at room temperature overnight. Workup as above followed by chromatography on silica gel furnished 180 mg (19% yield based on the allylic alcohol **17f** used) of 1,2,3-trioxane **27f**.

Hemisuccinate for trioxane 27f (compound 41f, formula 41, $R_1 = R_2 = H$; $X = OMe$)

[0067] Hemisuccinate **41f** was prepared from trioxane **27f** in 80% yield following the procedure used for preparation of compound **41a** as given in Example 5.

EXAMPLE 14**Ketoester 11g (formula 11, $R_1 = R_2 = Me$; $X = OMe$)**

[0068] A mixture of 4-hydroxy-3-methoxyacetophenone (15 g) ethyl 2-bromoisobutyrate (22 ml) and K_2CO_3 (45 g) in acetone (450 ml) was refluxed for 27 h. Most of the solvent was distilled off and the remainder was diluted with water and extracted with ether, ether extract dried on Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel (elution with 5% ethylacetate in hexane) to furnish 4.41 g (18% yield) of ketoester **11g** as an oil.

 β -Hydroxyester 13g (formula 13, $R_1 = R_2 = Me$; $X = OMe$)

[0069] A mixture of ketoester **11g** (4.4 g), zinc (3 g) and ethyl bromoacetate (2.5 g) in benzene was refluxed for 7 hr. Work up as above to give 6.0 g of crude product, which was used in the next step without purification.

 α , β -Unsaturated ester 15g (formula 15, $R_1 = R_2 = Me$, $X = OMe$)

[0070] β -Hydroxyester **13g** (crude product 6.0 g as obtained above) was dissolved in benzene (100 ml), I_2 (40 mg) was added the reaction mixture was refluxed for 6 hr.

Workup and purification effected as above furnished 2.7 g (49% yield, based on ketoester **11g**) of α , β -unsaturated ester **15g** as an oil.

Allylic alcohol 17g (formula 17, $R_1 = R_2 = \text{Me}$; $X = \text{OMe}$)

[0071] α , β -Unsaturated ester **15g** (1.9 g) was reduced with LiAlH_4 (1.8 g) in dry ether at 0°C as above. Normal workup followed by chromatography furnished 1.1 g (76% yield) of allylic alcohol **17g** as an oil.

Trioxane 27g (formula 27, $R_1 = R_2 = \text{Me}$; $X = \text{OMe}$)

[0072] A solution of allylic alcohol **17g** (1.1 g) and methylene blue (20 mg) in acetonitrile (50 ml) was photooxygenated as above at 0°C for 7 h. to give β -hydroxyhydroperoxide **19g** (formula 19, $R_1 = R_2 = \text{Me}$; $X = \text{OMe}$) as indicated by TLC. The reaction mixture was divided into two equal parts. One part was reacted with 2-adamantanone (500 mg) in the presence of conc. HCl (4 drops) at room temperature overnight. Usual workup followed by chromatography furnished 300 mg (34% yield based on the alcohol **17g** used) of trioxane **27g** as thick oil.

EXAMPLE 15

Trioxane 23g1 (formula 23, $R_1 = R_2 = \text{Me}$; $X = \text{OMe}$; $R_3, R_4 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0073] The other half of the reaction mixture as obtained in the above experiment was reacted with cyclopentanone (1 ml) in the presence of conc. HCl (5 drops) at r.t. overnight. Usual workup followed by purification furnished 210 mg (28% yield based on alcohol **17g**) of trioxane **23g1**.

EXAMPLE 16

Ketoester 12a (formula 12, $R_1 = R_2 = \text{H}$)

[0074] A mixture of 3-hydroxyacetophenone (5 g), ethyl chloroacetate (5.6 ml) and K_2CO_3 (7.5 g) was heated at 65°C with stirring for 13 h. It was cooled to room temperature, diluted with water (50 ml) and extracted with ether (2 x100 ml). Ether

extract was washed with water (3 x 50 ml), dried (Na_2SO_4), concentrated and chromatographed on silica gel using 50% ethylacetate – hexane as eluant to give 4.52 g (49% yield) of ketoester **12a** as an oil.

α , β –Unsaturated ester 16a (formula 16, $\text{R}_1 = \text{R}_2 = \text{H}$)

[0075] To a refluxing mixture of ketoester **12a** (15 g), zinc (6 g), iodine (70 mg) in benzene (350 ml), ethyl bromoacetate (8 ml) was added dropwise and the reaction mixture was refluxed for 9 hr. The reaction mixture was cooled, acidified with aqueous 10% HCl, benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene extract was washed with water, aqueous NaHCO_3 , dried (Na_2SO_4) and concentrated to give **14a** which was dehydrated with P_2O_5 (5 g) using the procedure as given in example 1, and the final product was purified by column chromatography on silica gel (hexane – ethylacetate as eluant) to furnish 14.75 g (45% based on **12a**) of **16a** as an oil.

Allylic alcohol 18a (formula 18, $\text{R}_1 = \text{R}_2 = \text{H}$)

[0076] To a stirred and ice-cooled mixture of LiAlH_4 (8 g) in dry ether (400 ml), a solution of α , β –unsaturated ester **16a** (11 g) in dry ether was added dropwise and the reaction mixture was stirred in an ice bath for 6 h. It was quenched with H_2O and 10% NaOH. The organic layer was separated and the residue was washed with ether. The combined ether extract was dried (Na_2SO_4), concentrated and purified by column chromatography on silica gel using hexane – ethylacetate as eluant to give 5.8 g (74% yield) of allylic alcohol **18a**.

Trioxane 24a1 (formula 24, $\text{R}_1 = \text{R}_2 = \text{H}$; $\text{R}_3, \text{R}_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0077] A solution of allylic alcohol **18a** (1.0 g) and Rose Bengal (5 mg) in acetonitrile (65 mg) was photooxygenated at 0°C for 7 h. to give β -hydroxyhydroperoxide **20a** (formula 20, $\text{R}_1 = \text{R}_2 = \text{H}$) as indicated by TLC. To this reaction mixture were added cyclopentanone (1.5 ml) and p-toluenesulfonic acid (15 mg) and the reaction mixture was

stirred at room temperature for 4h. Workup as above followed by column chromatography on silica gel furnished 600 mg (43% yield based on allylic alcohol **18a**) of trioxane **24a1**.

Hemisuccinate of trioxane 24a1 (compound 38a1, formula 38, $R_1 = R_2 = H$; $R_3 = R_4 = CH_2CH_2CH_2CH_3$)

[0078] A solution trioxane **24a1** (600 mg) and succinic anhydride (2.0 g) in pyridine (5 ml) was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water, 10% aqueous HCl, water, dried (Na_2SO_4) and concentrated. The crude product purified by column chromatography on silica gel using CH_2Cl_2 – ether as eluant furnished 780 mg (98% yield) of hemisuccinate **38a1**.

EXAMPLE 17

Trioxane 28a (formula 28, $R_1 = R_2 = H$)

[0079] A solution of allylic alcohol **18a** (1.0 g) and methylene blue (5 mg) in CH_2Cl_2 (65 mg) was photooxygenated as above at 0°C for 10 h. To the reaction mixture, were added 2-adamantanone (1 g) and p-toluenesulfonic acid (15 mg) and the reaction mixture was kept at room temperature overnight. Usual workup as above followed by purification by chromatography on silica gel column furnished 350 mg (21% yield based on allylic alcohol **18a**) of trioxane **28a** as a thick oil.

Hemisuccinate for trioxane 28a (compound 42a, formula 42, $R_1 = R_2 = H$)

[0080] Hemisuccinate **42a** was prepared in 91% yield by reacting trioxane **28a** with succinic anhydride following procedure as given in the above example.

EXAMPLE 18**Ketoester 12b (formula 12, $R_1 = R_2 = \text{Me}$)**

[0081] A mixture of 3-hydroxyacetophenone (5 g) ethyl 2-bromoisobutyrate (5.4 ml) and K_2CO_3 (7.5 g) was heated at 120°C for 6 h. The reaction mixture was diluted with water and extracted with ether. Ether extract was washed with water, dried, concentrated and chromatographed on silica gel to furnish 1.82 g (22% yield) of ketoester **12b** as an oil.

 α , β –Unsaturated ester 16b (formula 16, $R_1 = R_2 = \text{Me}$)

[0082] To a refluxing mixture of ketoester **12b** (14.6 g), zinc (7.3 g) and iodine (50 mg) in benzene (400 ml), a solution of ethyl bromoacetate (7.3 ml) in benzene (50 ml) was added dropwise and the reaction mixture was refluxed for 14.5 hr., cooled, and acidified with 10% aqueous HCl. Benzene layer was separated, washed with aqueous NaHCO_3 , dried and concentrated to give β -hydroxyester **14b**, which was used in the next step without purification.

[0083] The crude β -hydroxyester **14b** as obtained above was dissolved in benzene (500 ml), P_2O_5 (10 g) was added and the mixture was refluxed for 3 h. Usual workup followed by chromatography furnished α , β –unsaturated ester **16b** (7g, 42% yield based on **12b**).

Allylic alcohol 18b (formula 18, $R_1 = R_2 = \text{Me}$)

[0084] To a stirred and ice-cooled mixture of LiAlH_4 (3.2 g) in dry ether (450 ml), a solution of α , β –unsaturated **16b** (3.6 g) was added. The reaction mixture was stirred for 2.5 h. in an ice bath. It was quenched with water and 10% aqueous NaOH. The ether layer was separated and concentrated to give 2.6 g of residue which was chromatographed on silica gel to give 2.3 g (86% yield) of allylic alcohol **18b**.

Trioxane 24b 1 (formula 24, $R_1 = R_2 = \text{Me}$; $R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0085] A mixture of allylic alcohol **18b** (300 mg) and methylene blue (20 mg) in CH_3CN (40 ml) was photooxygenated at 0°C for 5.5 h. to give β -hydroxyhydroperoxide **20b** (formula 20, $R_1 = R_2 = \text{Me}$) as indicated by TLC. The reaction mixture was divided in two equal parts. To one-half of this reaction were added cyclopentanone of (1 ml) and PTSA (40 mg) and the reaction mixture was stirred at room temperature for 5 h. Usual workup followed by chromatography on silica gel furnished 170 mg (81% yield based on alcohol **18b**) of trioxane **24b 1**.

Hemisuccinate for trioxane 24b1 (compound 38b1, formula 38, $R_1 = R_2 = \text{Me}$; $R_3, R_4 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0086] To an ice-cooled solution of trioxane **24b1** (200 mg) and succinic anhydride (400 mg) in CH_2Cl_2 (20 ml) were added Et_3N (1 ml) and 4-dimethylamino-pyridine (DMAP, 20 mg) and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed under vacuum, acidified with 10% aq.HCl and extracted with ether. Ether extract was washed with water, concentrated and purified by chromatography on silica gel to give 230 mg (92% yield) of compound **38b1** as an oil.

Trioxane 24b2 (formula 24, $R_1 = R_2 = \text{Me}$; $R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0087] To the other half of the photooxygenated mixture obtained as in the above experiment were added cyclohexanone (1 ml) and PTSA (40 mg) and the reaction mixture was stirred at r.t. for 5 h. Workup and chromatography on silica gel column as above furnished 110 mg (50% yield based on alcohol **18b**) of trioxane **24b2**.

Hemisuccinate for trioxane 24b2 (compound 38b2, formula 38, $R_1 = R_2 = \text{Me}$; $R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0088] Trioxane **24b2** (250 mg) was reacted with succinic anhydride (350 mg) in CH_2Cl_2 (20 ml) as above and the crude product was purified by chromatography on silica gel using 25% ether in CH_2Cl_2 as eluant to give 280 mg (87% yield) of compound **38b2** as an oil.

EXAMPLE 19**Trioxane 28b (formula 28, $R_1 = R_2 = \text{Me}$)**

[0089] A solution of allylic alcohol **18b** (300 mg) and methylene blue (70 mg) in CH_3CN (30 ml) was photooxygenated at -8°C for 6 h. To the reaction mixture were added 2-adamantanone (300 mg) and p-toluenesulfonic acid (50 mg) and left at room temperature overnight. The solvent was removed under vacuum and the residue was diluted with aq. NaHCO_3 and water and extracted with ether. The ether extract was washed with water, dried, concentrated and chromatographed on silica gel to furnish 310 mg (62% yield) of trioxane **28b** as an oil.

Hemisuccinate of trioxane 28b [compound 42b, formula 42, $R_1 = R_2 = \text{Me}$]

[0090] To a stirred ice-cooled mixture of trioxane **28b** (100 mg) and succinic anhydride (200 mg) in CH_2Cl_2 (10 ml) were added triethylamine (0.5 ml) and 4-dimethylamino pyridine (20 mg) and the reaction mixture was stirred at r.t. for 3 h. The reaction mixture was concentrated under reduced pressure, acidified with 10% aqueous HCl and extracted with ether (2 x 20 ml). The ether extract was washed with water dried (Na_2SO_4), concentrated and purified by column chromatography on silica gel to give 100 mg (80% yield) of hemisuccinate **42b** as a thick oil.

EXAMPLE 20**Ketoester 11c (formula 11, $R_1 = \text{H}$, $R_2 = \text{Me}$, $\text{X} = \text{H}$)**

[0091] A mixture of 4-hydroxyacetophenone (5 g), ethyl 2-bromopropionate (5 ml) and K_2CO_3 (7.5 g) was heated at 120°C for 7.5 h. The reaction mixture was extracted with ether, washed with water, dried, concentrated and chromatographed on silica gel to furnish 1.8 g (21% yield) of **11c**, m.p. $64-72^\circ\text{C}$

α , β –Unsaturated ester 15c (formula 15, $R_1 = H$, $R_2 = Me$, $X = H$)

[0092] To a refluxing mixture of ketoester **11c** (25 g), Zn (6.5 g) and iodine (50 mg) in benzene (250 ml) was added dropwise ethyl bromoacetate (12 ml) and the reaction mixture was refluxed for 7 h. The crude product (**13c**) obtained after usual workup was dehydrated with iodine (2 g) in benzene (100 ml) by refluxing for 4 h. The reaction mixture was washed with a solution of sodium thiosulphate, concentrated and purified by chromatography on silica gel to give 14.6 g (47% yield) of **15c** as an oil.

Allylic alcohol 17c (formula 17, $R_1 = H$, $R_2 = Me$, $X = H$)

[0093] α , β –Unsaturated ester **15c** (5.0 g) was reduced with $LiAlH_4$ (3 g) in dry ether (250 ml) as above to give 2.7 g allylic alcohol **17c**.

Trioxane 25c (formula 25, $R_1 = Me$, $R_2 = X = H$)

[0094] A solution of allylic alcohol **17c** (1.5 g) and methylene blue (10 mg) in CH_2CN (45 ml) was photooxygenated as above for 6 h. to give β -hydroxyhydroperoxide **19c** (formula 19, $R_1 = Me$, $R_2 = X = H$). One third (corresponding to 500 mg of **17c**) was taken and reacted with norcomphor (1.0 g) in the presence of a catalytic amount of p-toluenesulfonic acid at r.t for 3 h. Usual workup followed by column chromatography on silica gel furnished 300 mg (38% yield based on the allylic alcohol **17c** used) of trioxane **25c**.

EXAMPLE 21**Ketoester 11d (formula 11, $R_1 = H$, $R_2 = Et$, $X = H$)**

[0095] A mixture of 4-hydroxyacetophenone (5.0 g) ethyl 2-bromobutyrate (5 ml) and K_2CO_3 (7.5 g) was heated at 120°C for 7.5 h. Workup followed by purification of the crude product as above (example 20) furnished 3.9 g (42% yield) of compound **11d** as an oil.

α , β –Unsaturated ester 15d (formula 15, $R_1 = H$, $R_2 = Et$, $X = H$)

[0096] To a refluxing mixture of ketoester **11d** (3.5 g), Zinc (2.0g), iodine (50 mg) in benzene (50 ml), ethyl bromoacetate (1.5 ml) was added and the reaction mixture was refluxed for 5 h. It was acidified with 10% HCl, benzene layer was separated and concentrated and the crude product was purified by chromatography to give 2.45 g (52% yield) of **13d**. Compound **13d** (2.4 g) was dehydrated in refluxing benzene using P_2O_5 as catalyst. Workup followed by column chromatography on silica gel as above furnished 2.0 g (88% yield) of ester **15d** as an oil.

Allylic alcohol 17d (formula 17, $R_1 = H$; $R_2 = Et$; $X = H$)

[0097] α , β –Unsaturated ester **15d** (2.7 g) was reduced with $LiAlH_4$ (1.5 g) in dry ether (150 ml) and the crude product was purified by chromatography on silica gel using hexane – ethylacetate as eluant to give 1.2 g of allylic alcohol **17d**.

Trioxane 27d (formula 27, $R_1 = Et$, $R_2 = X = H$)

[0098] A solution of allylic alcohol **17d** (1.2 g) and methylene blue (10 mg) in CH_3CN (40 ml) was photooxygenated as above for 7 h. to give β -hydroxyhydroperoxide **19d** (formula 19, $R_1 = Et$, $R_2 = X = H$) as indicated by TLC. To one half of this reaction mixture were added adamantanone (600 mg) and PTSA (10 mg) and the reaction mixture was stirred at r.t. for 2 h. Usual workup followed by chromatography on silica gel furnished 300 mg (30% yield based on the allylic alcohol **17d** used) of trioxane **27d** as oil.

EXAMPLE 22**Ketoester 11e (formula 11, $R_1 = H$, $R_2 = n$ -pentyl, $X = H$)**

[0099] A mixture of 4-hydroxyacetophenone (5.0 g) ethyl 2-bromoheptanoate (8.3 g) and K_2CO_3 was heated at $120^\circ C$ for 7.5 h. The reaction mixture was extracted with ether. Ether extract was washed with water, dried, concentrated and chromatographed on silica gel to furnish 9.1 g (89% yield) of compound **11e**, as an oil.

α , β –Unsaturated ester 15e (formula 15, $R_1 = H$, $R_2 = n\text{-pentyl}$, $X = H$)

[0100] To a refluxing mixture of ketoester **11e** (25 g), Zn (7.5 g), iodine (100 mg) in benzene (450 ml), ethyl bromoacetate (9 ml) was added dropwise and the resulting mixture was refluxed for 5.5 h. It was acidified with 10% HCl, benzene layer was separated, washed with aq. NaHCO_3 solution, dried and concentrated to give β -hydroxy-ester **13e** which was used without purification in the next step.

[0101] Crude product **13e** as obtained above was dissolved in benzene (350 ml), iodine (100 mg) was added and the mixture was refluxed for 2.5 h. The reaction mixture was washed with a solution of sodium thiosulphate, dried, concentrated and chromatographed on silica gel (elution with 5% ethyl acetate – hexane) to give 22.1 g (71% yield) of α , β –unsaturated ester **15e** as an oil.

Allylic alcohol 17e (formula 17, $R_1 = H$; $R_2 = n\text{-pentyl}$; $X = H$)

[0102] α , β –Unsaturated ester **15e** (12 g) was reduced with LiAlH_4 (10 g) in dry ether (600 ml) at 0°C as above to give 8.3 g of crude product which was purified by chromatography on silica gel to furnish 6.5 g (71% yield) of allylic alcohol **17e**.

Trioxane 23e1 (formula 23, $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$; $R_2 = X = H$; $R_3, R_4 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

[0103] A solution of alcohol **17e** (2 g) and methylene blue (100 mg) in CH_3CN (60 ml) was photooxygenated at 0°C for 4.5 h. to give β -hydroxyhydroperoxide **19e** (formula 19, $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$; $R_2 = X = H$) as indicated by TLC. One half of this photooxygenated reaction mixture was reacted with cyclopentanone (2 ml) in the presence of PTSA (50 mg) at r.t. for 5.5 h. Usual workup and column chromatography on silica gel furnished 610 mg (45% yield based on allylic alcohol **17e** used) of trioxane **23e1**.

Trioxane 27e (formula 27, $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$; $R_2 = X = \text{H}$)

[0104] To the other half of the photooxygenated mixture as obtained in the above example were added 2-adamantanone (1 g) and PTSA (50 mg) and the reaction mixture was stirred at r.t. for 5 h. Usual workup followed by column chromatography on silica gel using hexane – ethylacetate as eluant furnished 780 mg (76% yield based on allylic alcohol **17e** used) of trioxane **27e** as a thick oil.

Hemisuccinate of trioxane 27e (compound 41e, formula 41, $R_1 = \text{H}$, $R_2 = \text{n-pentyl}$; $X = \text{H}$)

[0105] To a stirred and ice-cooled mixture of trioxane **27e** (200 mg) and succinic anhydride (200 mg) in CH_2Cl_2 (20 ml) were added triethylamine (0.5 ml) and 4-dimethylamino pyridine (20 mg) and the reaction mixture was stirred at r.t. for 1.5 h. Workup as above followed by purification by column chromatography on silica gel furnished 200 mg (82% yield) of hemisuccinate **41e** as a colourless oil.

[0106] Using the above procedures, the following hydroxy-functionalized trioxane and their esters were also prepared

Trioxane 23a4 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = \text{Me, Et}$) ; 36% yield

Trioxane 23a5 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = \text{Me, CH}_2\text{CH}_2\text{CH}_3$) ; 43% yield

Trioxane 23a6 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = \text{Me, CH}_2\text{CHMe}_2$) ; 29% yield

Trioxane 23a7 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3 = R_4 = \text{n-propyl}$) ; 21% yield

Trioxane 23a8 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3 = R_4 = \text{n-butyl}$) ; 11% yield

Trioxane 23a9 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3 = R_4 = \text{n-pentyl}$) ; 16% yield

Trioxane 23a10 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = -\text{CH}_2(\text{CH}_2)_9-\text{CH}_3$) ; 16% yield

Trioxane 23a11 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = -\text{CH}_2-\text{CH}_2-\text{CO}-\text{CH}_2-\text{CH}_3$) ; 6% yield

Trioxane 23a12 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = \text{H, -C}_6\text{H}_5$) ; 45% yield

Trioxane 23a13 (formula 23, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = \text{H, 1-naphthyl}$) ; 38% yield

Trioxane 23b3 (formula **23**, $R_1 = R_2 = \text{Me}$, $X = \text{H}$, $R_3, R_4 = \text{H}$, 1-naphthyl) ; 7% yield

Trioxane 23b4 (formula **23**, $R_1 = R_2 = \text{Me}$, $X = \text{H}$; $R_3, R_4 = \text{CH}_2(\text{CH}_2)_4\text{-CH}_3$) ; 15% yield

Trioxane 23c1 (formula **23**, $R_1, R_2 = \text{H}$, Me ; $X = \text{H}$, $R_3, R_4 = \text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$) ; 42% yield

Trioxane 23c2 (formula **23**, $R_1, R_2 = \text{H}$, Me ; $X = \text{H}$, $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_3\text{-CH}_3$); 46% yield

Trioxane 23d1 (formula **23**, $R_1, R_2 = \text{H}$, Et ; $X = \text{H}$, $R_3, R_4 = \text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$); 33% yield

Trioxane 23e2 (formula **23**, $R_1, R_2 = \text{H}$, n-pentyl; $X = \text{H}$, $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_3\text{-CH}_3$); 54% yield

Trioxane 23e3 (formula **23**, $R_1, R_2 = \text{H}$, n-pentyl ; $X = \text{H}$, $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_4\text{-CH}_3$); 38% yield

Trioxane 23e4 (formula **23**, $R_1, R_2 = \text{H}$, n-pentyl ; $X = \text{H}$, $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_5\text{-CH}_3$); 15% yield

Trioxane 23e5 (formula **23**, $R_1, R_2 = \text{H}$, n-pentyl ; $X = \text{H}$, $R_3, R_4 = \text{Me}$) ; 54% yield

Trioxane 23f1 (formula **23**, $R_1 = R_2 = \text{H}$; $X = \text{OMe}$; $R_3, R_4 = \text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$); 27% yield

Trioxane 23f2 (formula **23**, $R_1 = R_2 = \text{H}$; $X = \text{OMe}$; $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_3\text{-CH}_3$); 16% yield

Trioxane 23g1 (formula **23**, $R_1 = R_2 = \text{Me}$; $X = \text{OMe}$; $R_3, R_4 = \text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$); 28% yield

Trioxane 24a2 (formula **24**, $R_1 = R_2 = \text{H}$; $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_3\text{-CH}_3$); 41% yield

Trioxane 24a3 (formula **24**, $R_1 = R_2 = \text{H}$; $R_3, R_4 = \text{-CH}_2\text{-(CH}_2)_4\text{-CH}_3$); 60% yield

Trioxane 24b3 (formula **24**, $R_1 = R_2 = \text{Me}$; $R_3, R_4 = \text{H}$, 1-naphthyl); 24% yield

Trioxane 25a (formula **25**, $R_1 = R_2 = \text{H}$) ; 34% yield

Trioxane 25c (formula **25**, $R_1, R_2 = \text{H}$, Me) ; 39% yield

Trioxane 25d (formula **25**, $R_1, R_2 = \text{H}$, Et) ; 15% yield

Trioxane 25e (formula **25**, $R_1, R_2 = H$, n-pentyl) ; 35% yield

Trioxane 26a (formula **26**, $R_1, R_2 = H$) ; 23% yield

Trioxane 26b (formula **26**, $R_1, R_2 = Me$) ; 53% yield

Trioxane 27c (formula **27**, $R_1, R_2 = H, Me$) ; 39% yield

Trioxane 28b (formula **28**, $R_1, R_2 = Me$); 27% yield

Compound 31a2 (formula **31**, $R_1 = R_2 = X = H$; $R_3, R_4 = -CH_2-CH_2-CH_2-CH_3$; $R_5 = Et$); 80% yield

Compound 31a3 (formula **31**, $R_1 = R_2 = X = H$; $R_3, R_4 = -CH_2-CH_2-CH_2-CH_3$; $R_5 = n-Pr$); 78% yield

Compound 31a4 (formula **31**, $R_1 = R_2 = X = H$; $R_3, R_4 = -CH_2-CH_2-CH_2-CH_3$; $R_5 = n-hexyl$) ; 75% yield

Compound 31a5 (formula **31**, $R_1 = R_2 = X = H$; $R_3, R_4 = -CH_2-CH_2-CH_2-CH_3$; $R_5 = phenyl$); 42% yield

Compound 31a6 (formula **31**, $R_1 = R_2 = X = H$; $R_3, R_4 = H$, 1-naphthyl; $R_5 = CH_3$); 36% yield

Compound 31b1 (formula **31**, $R_1 = R_2 = Me$, $X = H$; $R_3, R_4 = H$, 1-naphthyl; $R_5 = CH_3$) ; 90% yield

Compound 32b1 (formula **32**, $R_1 = R_2 = Me$; $R_3, R_4 = -CH_2-CH_2-CH_2-CH_3$; $R_5 = Me$); 89% yield

Compound 32b2 (formula **32**, $R_1 = R_2 = Me$; $R_3, R_4 = -CH_2-(CH_2)_3-CH_3$; $R_5 = Me$) ; 86% yield

Compound 32b3 (formula **32**, $R_1 = R_2 = Me$; $R_3, R_4 = H$, 1-naphthyl; $R_5 = Me$); 73% yield

Compound 33a1 (formula **33**, $R_1 = R_2 = X = H$; $R_5 = Me$); 82% yield

Compound 33a2 (formula **33**, $R_1 = R_2 = X = H$; $R_5 = Et$); 76% yield

Compound 33a3 (formula **33**, $R_1 = R_2 = X = H$; $R_5 = n-hexyl$); 83% yield

Compound 34b (formula **34**, $R_1 = R_2 = Me$; $R_5 = Me$); 94% yield

Compound 35b3 (formula **35**, $R_1 = R_2 = Me$; $X = H$; $R_5 = n-Pr$); 57% yield

Compound 35b5 (formula **35**, $R_1 = R_2 = Me$; $X = H$; $R_5 = n-hexyl$); 95% yield

Compound 36b (formula **36**, $R_1 = R_2 = R_5 = \text{Me}$); 91% yield

Compound 37a1 (formula **37**, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = -\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$); 87% yield

Compound 37a2 (formula **37**, $R_1 = R_2 = X = \text{H}$; $R_3, R_4 = -\text{CH}_2\text{-(CH}_2)_3\text{-CH}_3$); 40% yield

Compound 37a3 (formula **37**; $R_1 = R_2 = X = \text{H}$; $R_3 = R_4 = \text{Me}$); 70% yield

Compound 37a4 (formula **37**; $R_1 = R_2 = X = \text{H}$; $R_3 = R_4 = \text{H}$, 1-naphthyl); 66% yield

Compound 37b2 (formula **37**; $R_1 = R_2 = \text{Me}$; $X = \text{H}$; $R_3, R_4 = -\text{CH}_2\text{-(CH}_2)_3\text{-CH}_3$); 86% yield

Compound 37b3 (formula **37**; $R_1 = R_2 = \text{Me}$; $X = \text{H}$; $R_3, R_4 = \text{H}$, 1-naphthyl); 66% yield

Compound 37e1 (formula **37**; $R_1, R_2 = \text{H}$, n-pentyl; $X = \text{H}$; $R_3, R_4 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); 79% yield

Compound 37f1 (formula **37**; $R_1 = R_2 = \text{H}$; $X = \text{OMe}$; $R_3, R_4 = -\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$); 76% yield

Compound 38a2 (formula **38**; $R_1 = R_2 = \text{H}$; $R_3, R_4 = -\text{CH}_2(\text{CH}_2)_3\text{-CH}_3$); 90% yield

Compound 38b1 (formula **38**; $R_1 = R_2 = \text{Me}$; $R_3, R_4 = -\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$); 92% yield

Compound 38b2 (formula **38**; $R_1 = R_2 = \text{Me}$; $R_3, R_4 = -\text{CH}_2(\text{CH}_2)_3\text{-CH}_3$); 88% yield

Compound 38b3 (formula **38**; $R_1 = R_2 = \text{Me}$; $R_3, R_4 = \text{H}$, 1-naphthyl); 87% yield

Compound 39a (formula **39**; $R_1 = R_2 = X = \text{H}$); 97% yield

Compound 40b (formula **40**; $R_1 = R_2 = \text{Me}$); 96% yield

Compound 41f (formula **41**; $R_1 = R_2 = \text{H}$; $X = \text{OMe}$); 80% yield

Compound 41g (formula **41**; $R_1 = R_2 = \text{Me}$, $X = \text{OMe}$); 80% yield

Compound 42a (formula **42**; $R_1 = R_2 = \text{H}$); 91% yield

Anti-malarial Activity

[0107] The anti-malarial activity of the test compounds was evaluated in rodent using multidrug resistant strain of *Plasmodium yoelii Nigeriensis* in Swiss mice.

General Procedure

[0108] Random bred Swiss mice of either *sex* (20 ± 2 gm) were inoculated intraperitoneally with 1×10^5 *P. yoelii* (MDR) parasites on day zero. The treatment with test compounds was administered to groups of 6 mice each at different dose levels ranging between 24-96 mg/kg/day. The trioxanes were dissolved in groundnut oil (or 50% sodium bicarbonate solutions in case of hemisuccinate derivatives) and were administered via intramuscular or oral route for 4 consecutive days (day 0-3).

[0109] Blood smears from experimental *mice* were observed on day 4 and 7, day 10 and thereafter at regular intervals till day 28 or death of the animal. The parasitaemia level on day 4 was compared with the vehicle control group and the percent suppression of parasitaemia in treated groups was calculated.

[0110] For determining the curative dose of a compound the treated mice were observed till day 28. The dose at which no parasitaemia develop during the observation period has been recorded as the curative dose. The anti-malarial data is summarized in Table 4.

TABLE 4

Anti-malarial activity of substituted trioxanes against multi drug resistance strain of *Plasmodium yoelii* Nigeriensis in Swiss mice

Compd. No.	Route	Dose mg/kg	No. of animals	% Suppression on day 4	Cured/Treated
23a1	im	96	6	100	1/6
	im	48	5	100	0/5
23a2	im	96	5	100	0/5
	im	48	5	100	1/5
23a4	im	96	6	70	0/5
23b1	im	96	5	98	2/5
23b2	im	96	5	100	2/5
23c1	im	96	6	100	3/6
23c2	im	96	6	100	0/6
23e1	im	96	5	100	1/5
23e2	im	96	6	92	0/5

Compd. No.	Route	Dose mg/kg	No. of animals	% Suppression on day 4	Cured/Treated
23f1	im	96	5	100	0/5
	im	48	5	100	0/5
23f2	im	96	5	97	0/5
23g1	im	96	6	93	0/6
24a1	im	96	6	100	0/6
24a2	im	96	6	89	0/6
24a3	im	96	6	100	0/6
24b2	im	96	6	83	0/6
25a	im	96	6	100	6/6
25c	im	96	6	100	5/6
	im	48	6	100	1/6
25e	im	96	6	81	0/6
26a	im	96	6	100	-
	im	48	6	88	-
27a	im	96	6	100	6/6
	im	48	6	100	6/6
	im	24	6	100	1/6
	oral	96	6	100	2/6
	oral	48	5	100	0/6
27b	oral	96	6	100	6/6
	oral	72	6	100	6/6
	oral	48	6	100	1/6
	im	96	6	100	6/6
	im	72	6	100	6/6
27c	im	96	6	100	6/6
	im	48	6	100	3/6
27e	im	96	5	84	0/6
	im	48	6	15	0/6
27f	im	96	6	100	6/6
	im	48	6	100	1/6
27g	im	96	6	92	-
	im	48	6	85	-
28a	im	96	5	100	5/5
	im	48	5	100	3/5
28b	im	96	6	96	-
	im	48	6	66	-
31a1	im	96	6	100	6/6
	im	64	5	100	1/5

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Compd. No.	Route	Dose mg/kg	No. of animals	% Suppression on day 4	Cured/Treated
	im	48	6	100	2/6
31a2	im	96	6	97	0/6
	im	48	6	47	0/6
31a3	im	96	6	36	0/6
	im	48	6	26	0/6
31a4	im	96	6	22	0/6
	im	48	6	22	0/6
31a5	im	96	6	57	0/6
	im	48	6	41	0/6
31b2	im	96	6	20	0/6
	im	96	6	75	0/6
33a1	im	96	6	99.5	0/6
	im	48	6	96.8	0/6
33a2	im	96	6	52.5	0/6
	im	48	6	61.6	0/6
33a3	im	96	6	0	0/6
	im	48	6	14	0/6
35a1	im	96	6	100	6/6
	im	48	6	99	0/6
	oral	48	6	92	1/6
	im	96	6	100	6/6
35b1	oral	96	6	100	1/6
	im	96	5	99	1/5
35b2	im	96	5	94	0/6
	oral	96	5	100	0/6
35b4	im	96	5	0	0/6
	oral	96	5	35	0/6
35b5	im	96	5	67	0/6
	oral	96	5	80	0/6
37a1	im	128	6	0	0/6
37a2	im	128	6	91.6	0/6
37a3	im	128	6	83	0/6
	im	64	5	53	0/5
37b1	im	96	6	-	1/6
	im	48	6	-	2/6
37e1	im	96	6	100	1/6
	oral	96	6	82	0/6
38a1	im	96	6	82	0/6
	im	48	6	62	0/6

Compd. No.	Route	Dose mg/kg	No. of animals	% Suppression on day 4	Cured/Treated
38a2	im	96	6	59	0/6
	im	48	6	55	0/6
39a	im	96	5	94	0/5
	im	48	5	93	1/5
41a	im	64	6	100	6/6
	im	48	6	100	6/6
	oral	96	6	100	6/6
	oral	48	6	100	0/6
41b	im	64	6	100	6/6
	im	72	6	100	6/6
	im	48	6	100	5/6
	im	24	6	100	3/6
	oral	96	6	100	6/6
	oral	96	6	100	6/6
	oral	48	6	100	2/6
	oral	48	6	100	2/6
41e	im	96	6	100	0/6
	oral	96	6	97	0/6
42a	im	96	5	100	2/5
	im	48	5	78	0/5
42b	im	96	6	100	0/6
	oral	96	6	96	0/6

[0111] Trioxanes **27a** and **27b** and their hemisuccinates **41a** and **41b** were evaluated for blood schizontocidal activity against *Plasmodium cynomolgi* and *Plasmodium knowlesi* in Rhesus monkeys using the following protocol:

[0112] For activity against *P. cynomolgi*, rhesus monkeys were inoculated intravenously with 1×10^5 parasitized RBC and the treatment was initiated when the parasitaemia level reached above 0.5%. For activity against *P. knowlesi* the rhesus monkeys were inoculated intravenously with 1×10^4 parasitized RBC and the treatment was initiated at 0.1% parasitaemia level.

[0113] Compounds **27a** and **27b** were *dissolved* in groundnut oil and administered in various regimens for 3-5 days via oral or intramuscular (im) routes. Hemisuccinates **41a** and **41b** were dissolved in 5% bicarbonate solution and administered similarly by oral, im or iv routes.

[0114] The blood smears from the *treated* monkeys were examined once daily to record parasitaemia clearance time and subsequent recurrence of parasitaemia. The animals in which no recrudescence was observed up to day 60 were recorded as cured. The anti-malarial data are summarized in Table 5 and Table 6.

TABLE 5

**Anti-malarial activity of trioxanes against
Plasmodium cynomolgi in rhesus monkey model**

Compound	Route	Dose mg/kg x days	Regimen	Time for complete clearance of parasitaemia (hr)	Cure rate
27a	im	10.0 x 4	Divided	48	2/2
	im	10.0 x 4	Single	48	3/4
	im	7.5 x 4	Single	48	1/2
	im	5.0 x 4	Divided	48-72	1/2
	oral	20.0 x 5	Divided	72	2/2
	oral	20.5 x 5	Divided	48	3/3
	oral	15.0 x 5	Divided	48	3/3
	oral	10.0 x 5	Divided	48	0/2
27b	im	15.0 x 4	Divided	48	2/2
	im	10.0 x 4	Divided	72	2/2
	oral	20.0 x 5	Divided	48	2/2
	oral	20.0 x 5	Divided	72	2/2
	oral	15.0 x 5	Divided	72	2/2
41a	im	10.0 x 4	Divided	48	4/4
	im	10.0 x 4	Single	48	2/2
	im	7.5 x 4	Single	48	1/2
	oral	20.0 x 5	Divided	48	3/3
	oral	20.0 x 4	Divided	48	2/2
	oral	15.0 x 5	Divided	48	0/2

Compound	Route	Dose mg/kg x days	Regimen	Time for complete clearance of parasitaemia (hr)	Cure rate
41b	iv	10.0 x 4	Divided	48	2/2
	im	10.0 x 4	Divided	48	2/2
	im	10.0 x 4	Single	48-72	0/2
	oral	20.0 x 5	Divided	48-72	2/2
	oral	10.0 x 5	Divided	96	0/2
	oral	20.0 x 1 +	Divided	48-72	5/5
		10.0 x 4			

TABLE 6**Anti-malarial activity of trioxanes against *P. knowlesi* in rhesus monkey model**

Compound	Route	Dose mg/kg x days	Regimen	Time for complete clearance of parasitaemia (hr)	Cure rate
27a	im	20.0 x 4	Divided	48	2/2
	im	15.0 x 4	Divided	48	2/2
	im	10.0 x 4	Divided	48	0/2
	im	5.0 x 4	Divided	72	0/2
	oral	15.0 x 4	Divided	48-72	2/2
41a	im	20.0 x 4	Divided	48	2/2
	im	15.0 x 4	Divided	48	1/2
	oral	30.0 x 4	Divided	48	1/2
	oral	15.0 x 4	Divided	48	0/2

Gametocytocidal Activity

[0115] Compounds **27a** and **41a** were also tested for *gametocytocidal* activity according to the following protocol:

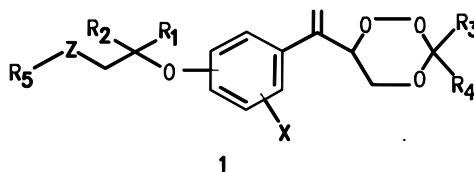
[0116] Different batches of 3 to 4 days old naïve *Anopheles stephensis* mosquitoes are allowed to engorge blood from gametocyte carrying infected host (rhesus monkey infected with *P. cynomolgi* or hamster infected with *P. yoelii*) at different time intervals

prior to and after administration with a single dose of the test compound. The blood-fed mosquitoes were maintained for the next 7–10 days in an insectarium to allow development of oocysts. A comparison of mosquito infectivity rate and oocyst numbers in pre-treatment versus post-treatment provided index for gametocytocidal potential of the test agent.

[0117] Compounds **27a** and **41a** showed complete loss of infectivity in mosquito batches fed 24 h. post-treatment with 50 mg/kg (im, single dose) in *P. yoelii* model and 20 mg/kg (im, single dose) or 30 mg/kg (oral, single dose) in *P. cynomolgi* model.

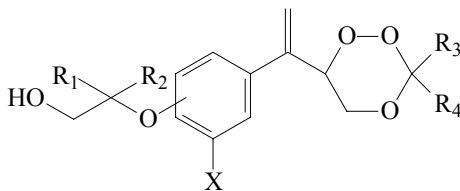
CLAIMS

1. Novel substituted 1,2,4-trioxanes of formula 1,



wherein R_1 and R_2 are selected from the group consisting of a hydrogen and a C_{1-11} alkyl group; R_3 and R_4 are selected from the group consisting of a hydrogen, a C_{1-11} alkyl group, and a C_{3-10} aryl group; R_5 is selected from the group consisting of a hydrogen, a C_{1-11} alkyl group, a C_{3-10} aryl group, a $C_{1-2}CO_2H$ carboxyalkyl group; Z is O or OCO; and X is hydrogen or a lower alkoxy group having 1 to 6 carbons.

2. Novel trioxanes as claimed in claim 1, wherein said compounds **23a1-23a3**, **23b1-23b4**, **23c1-23c2**, **23d1**, **23e1-23e5**, **23f1-23f2**, and **23g1** have structural formulae as shown below:



wherein,

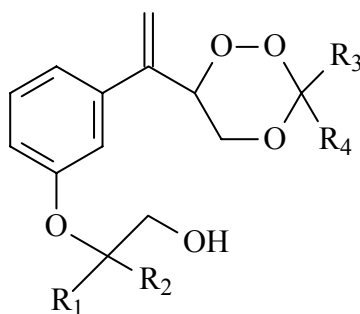
23a1 $R_1, R_2 = H, H; X = H; R_3, R_4 = CH_2CH_2CH_2CH_3$

23a2 $R_1, R_2 = H, H; X = H; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$

23a3	$R_1, R_2 = H, H; X = H; R_3, R_4 = Me, Me$
23a4	$R_1, R_2 = H, H; X = H; R_3, R_4 = Me, Et$
23a5	$R_1, R_2 = H, H; X = H; R_3, R_4 = Me, CH_2CH_2CH_3$
23a6	$R_1, R_2 = H, H; X = H; R_3, R_4 = Me, CH_2CHMe_2$
23a7	$R_1, R_2 = H, H; X = H; R_3, R_4 = n\text{-propyl}, n\text{-propyl}$
23a8	$R_1, R_2 = H, H; X = H; R_3, R_4 = n\text{-butyl}, n\text{-butyl}$
23a9	$R_1, R_2 = H, H; X = H; R_3, R_4 = n\text{-pentyl}, n\text{-pentyl}$
23a10	$R_1, R_2 = H, H; X = H; R_3, R_4 = -CH_2-(CH_2)_9-CH_3$
23a11	$R_1, R_2 = H, H; X = H; R_3, R_4 = CH_2CH_2-CO-CH_2-CH_3$
23a12	$R_1, R_2 = H, H; X = H; R_3, R_4 = H, \text{phenyl}$
23a13	$R_1, R_2 = H, H; X = H; R_3, R_4 = H, 1\text{-naphthyl}$
23b1	$R_1, R_2 = Me, Me; X = H; R_3, R_4 = CH_2CH_2CH_2CH_3$
23b2	$R_1, R_2 = Me, Me; X = H; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$
23b3	$R_1, R_2 = Me, Me; X = H; R_3, R_4 = H, 1\text{-naphthyl}$
23b4	$R_1, R_2 = Me, Me; X = H; R_3, R_4 = -CH_2-(CH_2)_4-CH_3$
23c1	$R_1, R_2 = H, Me; X = H; R_3, R_4 = CH_2CH_2CH_2CH_3$
23c2	$R_1, R_2 = H, Me; X = H; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$
23d1	$R_1, R_2 = H, Et; X = H; R_3, R_4 = CH_2CH_2CH_2CH_3$
23e1	$R_1, R_2 = H, n\text{-pentyl}; X = H; R_3, R_4 = CH_2CH_2CH_2CH_3$
23e2	$R_1, R_2 = H, n\text{-pentyl}; X = H; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$
23e3	$R_1, R_2 = H, n\text{-pentyl}; X = H; R_3, R_4 = CH_2(CH_2)_4CH_3$
23e4	$R_1, R_2 = H, n\text{-pentyl}; X = H; R_3, R_4 = CH_2(CH_2)_5CH_3$

- 23e5** $R_1, R_2 = H, n\text{-pentyl}; X = H; R_3, R_4 = Me, Me$
- 23f1** $R_1, R_2 = H, H; X = OMe; R_3, R_4 = CH_2CH_2CH_2CH_3$
- 23f2** $R_1, R_2 = H, H; X = OMe; R_3, R_4 = CH_2-(CH_2)_3-CH_3$
- 23g1** $R_1, R_2 = Me, Me; X = OMe; R_3, R_4 = CH_2CH_2CH_2CH_3.$

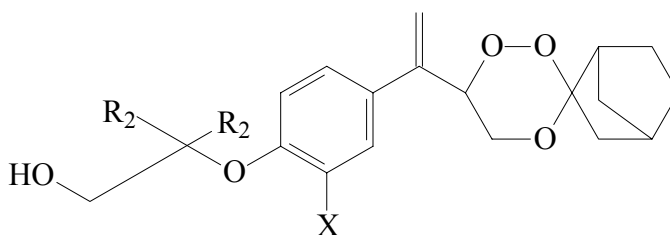
3. Novel trioxanes as claimed in claim 1, wherein said compounds **24a1-24a3** and **24b1-24b3** have the structural formulae as shown below:



wherein,

- 24a1** $R_1, R_2 = H, H; R_3, R_4 = CH_2CH_2CH_2CH_3$
- 24a2** $R_1, R_2 = H, H; R_3, R_4 = CH_2(CH_2)_3-CH_3$
- 24a3** $R_1, R_2 = H, H; R_3, R_4 = CH_2(CH_2)_4-CH_3$
- 24b1** $R_1, R_2 = Me, Me; R_3, R_4 = CH_2CH_2CH_2CH_3$
- 24b2** $R_1, R_2 = Me, Me; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$
- 24b3** $R_1, R_2 = Me, Me; R_3, R_4 = H, 1\text{-naphthyl}.$

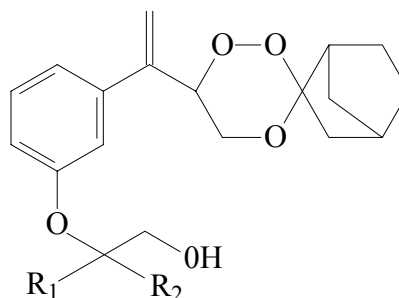
4. Novel trioxanes as claimed in claim 1, wherein said compounds **25a, 25c, 25d, and 25e** have the structural formulae as shown below:



wherein,

- 25a** $R_1, R_2 = H, H; X = H$
25c $R_1, R_2 = H, Me; X = H$
25d $R_1, R_2 = H, Et; X = H;$
25e $R_1, R_2 = H, n\text{-phenyl}; X = H.$

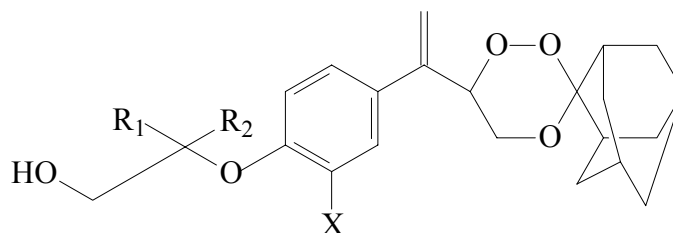
5. Novel trioxanes as claimed in claim 1, wherein said compounds **26a** and **26b** have the structural formulae as shown below:



wherein,

- 26a** $R_1, R_2 = H, H$
26b $R_1, R_2 = Me, Me.$

6. Novel trioxanes as claimed in claim 1, wherein said compounds **27a**, **27b**, **27c**, **27d**, **27e**, **27f**, and **27g** have the structural formulae as shown below:



wherein,

27a $R_1, R_2 = H, H; X = H$

27b $R_1, R_2 = Me, Me; X = H$

27c $R_1, R_2 = He, Me; X = H$

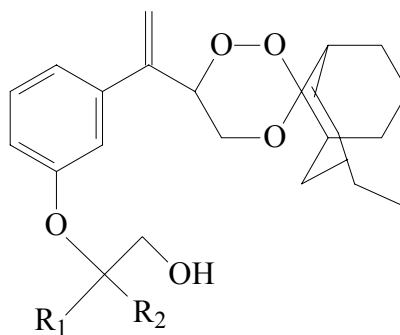
27d $R_1, R_2 = H, Et; X = H$

27e $R_1, R_2 = H, n\text{-pentyl}; X = H$

27f $R_1, R_2 = H, H; X = OMe$

27g $R_1, R_2 = Me, Me; X = OMe.$

7. Novel trioxanes as claimed in claim 1, wherein said compounds **28a** and **28b** have the structural formulae as shown below:



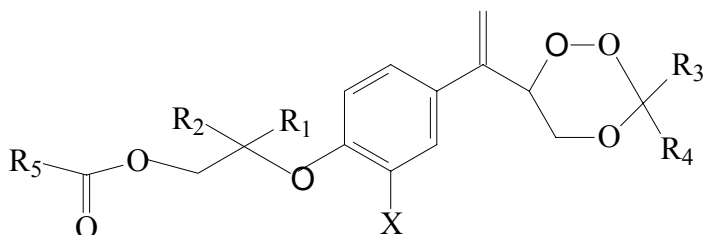
wherein,

28a $R_1, R_2 = H, H$

28b $R_1, R_2 = Me, Me.$

8. Novel trioxanes as claimed in claim 1, wherein said compounds **31a1-31a6** and **31b1** have the structural formulae as shown below:

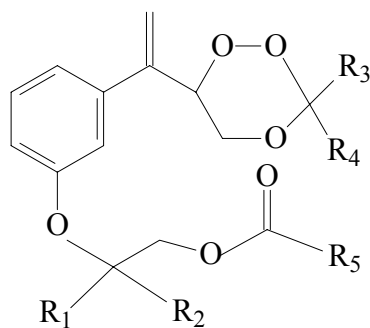
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wherein,

- 31a1** $R_1, R_2 = H, H$; $X = H$; $R_3, R_4 = CH_2CH_2CH_2CH_3$; $R_5 = CH_3$
- 31a2** $R_1, R_2 = H, H$; $X = H$; $R_3, R_4 = CH_2CH_2CH_2CH_3$; $R_5 = Et$
- 31a3** $R_1, R_2 = H, H$; $X = H$; $R_3, R_4 = CH_2CH_2CH_2CH_3$; $R_5 = n\text{-propyl}$
- 31a4** $R_1, R_2 = H, H$; $X = H$; $R_3, R_4 = CH_2CH_2CH_2CH_3$; $R_5 = n\text{-hexyl}$
- 31a5** $R_1, R_2 = H, H$; $X = H$; $R_3, R_4 = CH_2CH_2CH_2CH_3$; $R_5 = Phenyl$
- 31a6** $R_1, R_2 = H, H$; $X = H$; $R_3, R_4 = H, 1\text{-naphthyl}$; $R_5 = CH_3$
- 31b1** $R_1, R_2 = Me, Me$; $X = H$; $R_3, R_4 = H, 1\text{-naphthyl}$; $R_5 = Me$.

9. Novel trioxanes as claimed in claim 1, wherein said compounds **32b1-31b3** have the structural formulae as shown below:



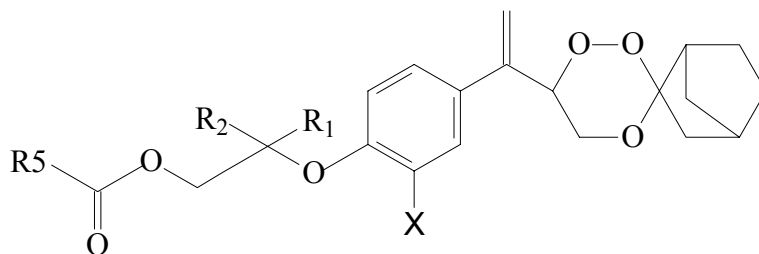
wherein,

32b1 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3; R_5 = \text{Me}$

32b2 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3; R_5 = \text{Me}$

32b3 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_4 = \text{H, 1-naphthyl}; R_5 = \text{Me}.$

10. Novel trioxanes as claimed in claim 1, wherein said compounds **33a1-33a3** have the structural formulae as shown below:



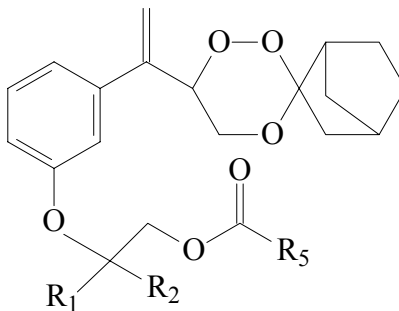
wherein,

33a1 $R_1, R_2 = \text{H, H}; X = \text{H}; R_5 = \text{Me}$

33a2 $R_1, R_2 = \text{H, H}; X = \text{H}; R_5 = \text{Et}$

33a3 $R_1, R_2 = \text{H, H}; X = \text{H}; R_5 = \text{n-hexyl}.$

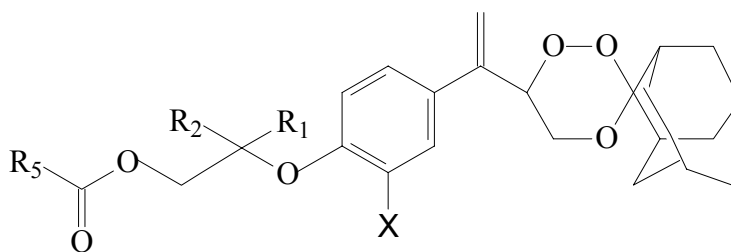
11. Novel trioxanes as claimed in claim 1, wherein said compound **34b** has the structural formula as shown below:



wherein,

34b $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_5 = \text{Me}.$

12. Novel trioxanes as claimed in claim 1, wherein said compounds **35a1**, **35b1-35b5** have the structural formulae as shown below:



wherein,

35a1 $R_1, R_2 = \text{H, H}; X = \text{H}; R_5 = \text{Me}$

35b1 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_5 = \text{Me}$

35b2 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_5 = \text{Et}$

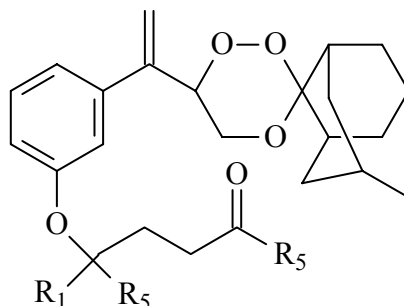
35b3 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_5 = \text{n-propyl}$

35b4 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_5 = \text{n-pentyl}$

35b5 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_5 = \text{n-hexyl}.$

13. Novel trioxanes as claimed in claim 1, wherein said compound **36b** has the structural formula as shown below:

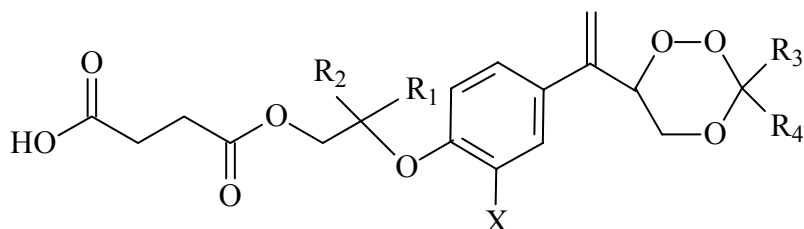
-50-



wherein,

36b $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_5 = \text{Me}.$

14. Novel trioxanes as claimed in claim 1, wherein said compounds **37a1-37a4**, **37b1-37b3**, **37e1**, and **37f1** have the structural formulae as shown below:



wherein,

37a1 $R_1, R_2 = \text{H, H}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

37a2 $R_1, R_2 = \text{H, H}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

37a3 $R_1, R_2 = \text{H, H}; X = \text{H}; R_3, R_4 = \text{Me, Me}$

37a4 $R_1, R_2 = \text{H, H}; X = \text{H}; R_3, R_4 = \text{H, 1-naphthyl}$

37b1 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

37b2 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

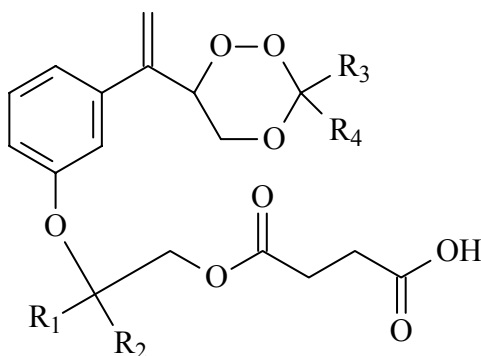
37b3 $R_1, R_2 = \text{Me, Me}; X = \text{H}; R_3, R_4 = \text{H, 1-naphthyl}$

37e1 $R_1, R_2 = \text{H, n-pentyl}; X = \text{H}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

37f1 $R_1, R_2 = \text{H, H}; X = \text{OMe}; R_3, R_4 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3.$

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15. Novel trioxanes as claimed in claim 1, wherein said compounds **38a1-38a2** and **38b1-38b3** have the structural formulae as shown below:



wherein,

38a1 $R_1, R_2 = H, H; R_3, R_4 = CH_2CH_2CH_2CH_3$

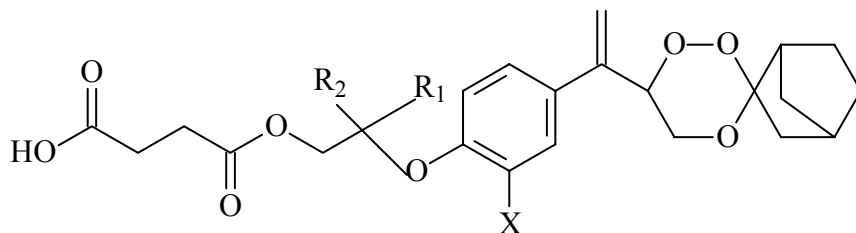
38a2 $R_1, R_2 = H, H; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$

38b1 $R_1, R_2 = Me, Me; R_3, R_4 = CH_2CH_2CH_2CH_3$

38b2 $R_1, R_2 = Me, Me; R_3, R_4 = CH_2CH_2CH_2CH_2CH_3$

38b3 $R_1, R_2 = Me, Me; R_3, R_4 = H, 1\text{-naphthyl}.$

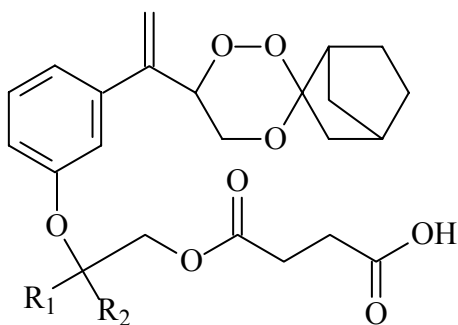
16. Novel trioxanes as claimed in claim 1, wherein said compound **39a** has the structural formula as shown below:



wherein,

39a $R_1, R_2 = H, H; X = H.$

17. Novel trioxanes as claimed in claim 1, wherein said compound **40b** has the structural formula as shown below:

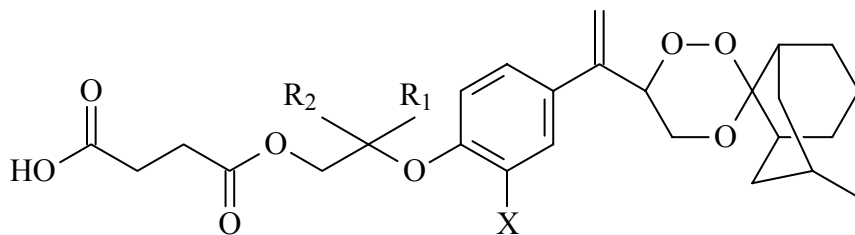


wherein,

40b $R_1, R_2 = \text{Me, Me.}$

18. Novel trioxanes as claimed in claim 1, wherein said compounds **41a**, **41b**, **41e**, **41f**, and **41g** have the structural formulae as shown below:

-53-



wherein,

41a $R_1, R_2 = H, H; X = H$

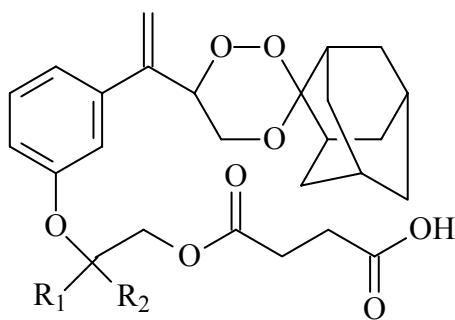
41b $R_1, R_2 = Me, Me; X = H$

41e $R_1, R_2 = H, n\text{-pentyl}; X = H$

41f $R_1, R_2 = H, H; X = OMe$

41g $R_1, R_2 = Me, Me; X = OMe.$

19. Novel trioxanes as claimed in claim 1, wherein said compounds **42a** and **42b** have the structural formulae as shown below:



wherein,

42a $R_1, R_2 = H, H$

42b $R_1, R_2 = Me, Me.$

20. A process for the preparation of novel substituted 1,2,4-trioxanes and their esters of general formula **1**, which comprises reacting hydroxyacetophenones of formula **2** wherein, X represents hydrogen or a lower alkoxy having 1 to 6 carbons, with α -haloesters of formula **3** wherein R_1 and R_2 are selected from the group consisting of a hydrogen, a C_{1-11} alkyl group and Y represents a halogen, in the presence of a base optionally in an organic solvent at a temperature in the range of room temperature to refluxing temperature to give ketoesters of general formula **4**, wherein R_1 , R_2 and X have the same meaning as above; reacting ketoesters of general formula **4** under Reformatsky condition in an aprotic organic solvent in the temperature range of room temperature to refluxing temperature to give β -hydroxyesters of general formula **5**, wherein R_1 , R_2 and X have the same meaning as above; dehydrating β -hydroxyesters of formula **5** using a catalyst in an organic solvent at a temperature in the range of room temperature to refluxing temperature to give α , β -unsaturated esters of general formula **6**, wherein R_1 , R_2 and X have the same meaning as above; reducing α , β -unsaturated esters of general formula **6** with a complex metal hydride in an ether solvent at a temperature in the range of 0°C to room temperature to give allylic alcohols of formula **7** wherein R_1 , R_2 and X have the same meaning as above; oxygenation of allylic alcohols of formula **7** in the presence of a sensitizer in an organic solvent at a temperature in the range of -10°C to room temperature to give β -hydroxyhydroperoxides of general formula **8** wherein R_1 , R_2 and X have the same meaning as above; isolating and then reacting or reacting *in situ* β -hydroxyhydroperoxides of formula **8** with compounds containing an aldehyde or ketone group in the presence of an acid catalyst in an organic solvent at a temperature in the range of 0°C to room temperature to give hydroxy-functionalized 1,2,4-trioxanes of general formula **1**, wherein R_1 , R_2 and X have the same meaning as above, R_3 and R_4 are selected from the group consisting of a hydrogen, a C_{1-11} alkyl group, a C_{3-10} aryl group, R_5 is H; and Z is O; reacting hydroxy-functionalized trioxanes of general formula **1**, wherein R_5 is H and Z is O with an acid chloride or anhydrides in the presence of a base in an organic solvent at a temperature in the range of 0°C to room temperature to give trioxane esters of general

formula **1**, wherein R_1 , R_2 , R_3 , R_4 and X have the same meaning as above, R_5 is selected from the group consisting of a C_{1-11} alkyl group, a C_{3-10} aryl group, a $C_{1-2}CO_2H$ carboxyalkyl group; and Z is OCO .

21. A process as claimed in claim 20, wherein the substituted acetophenones of formula **2** are reacted with α -haloesters of formula **3** in the presence of a base selected from the group consisting of $KaHCO_3$, Na_2CO_3 , and K_2CO_3 , and in an organic solvent selected from the group consisting of acetone, DMSO, and DMF.

22. A process as claimed in claim 20 wherein, Reformatsky reaction is carried out by reacting ketoesters of formula **4** with ethyl bromoacetate and Zn in an aprotic organic solvent selected from the group consisting of benzene, diethylether, and THF.

23. A process as claimed in claim 20 wherein dehydration of β -hydroxyesters of formula **5** is effected in a hydrocarbon solvent selected from the group consisting of benzene, toluene, and CH_2Cl_2 , using a catalyst selected from the group consisting of I_2 , P_2O_5 , *p*-toluene-sulfonic acid, and an acidic resin.

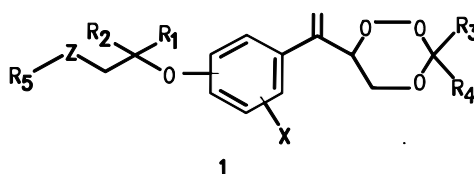
24. A process as claimed in claim 20 wherein the reduction of esters of formula **6** with $LiAlH_4$ is carried out in an ether solvent selected from the group consisting of diethyl ether and THF.

25. A process as claimed in claim 20 wherein the oxygenation is effected by photooxygenation of allylic alcohols of formula **7** in an organic solvent selected from the group consisting of acetone, CH_3CN , CH_2Cl_2 , methanol, and ethanol, using a dye sensitizer selected from the group consisting of methylene blue, Rose Bengal, and tetraphenyl porphine.

26. A process as claimed in claim 20 wherein condensation of β -hydroxyhydroperoxides of formula **8** with aldehydes and ketones of formulae **21-22** is done in an organic solvent selected from the group consisting of CH_2Cl_2 , CHCl_3 , benzene, and CH_3CN , using an acid catalyst selected from the group consisting of HCl , H_2SO_4 , p-toluene-sulfonic acid, BF_3OEt_2 , and acidic resin.
27. A process as claimed in claim 20 wherein esterification of hydroxy-functionalized trioxanes of formulae **23-28** with acid chlorides of formula **29** or an acid anhydride of formula **30** is done in an organic solvent selected from the group consisting of CH_2Cl_2 , CHCl_3 , THF, and CH_3CN in the presence of a base selected from the group consisting of Et_3N , pyridine, and dimethylaminopyridine.
28. A process as claimed in claim 20 wherein hemisuccinate derivatives of formulae **37-42** are prepared in an organic solvent selected from the group consisting of CH_2Cl_2 , CHCl_3 , CH_3CN , toluene, and THF, in the presence of a base selected from the group consisting of Et_3N , pyridine, and dimethylaminopyridine.
29. A process as claimed in claim 20 wherein the compounds containing aldehyde and ketonic groups are of formulae **21-22** wherein R_3 and R_4 are selected from the group consisting of a hydrogen, a C_{1-11} alkyl group, a C_{3-10} aryl group, and an araalkyl group, wherein said araalkyl is selected from the group consisting of said alkyl group and said aryl group.
30. A process as claimed in claim 20 wherein acid chlorides and acid anhydrides used have the formulae **29** and **30** wherein R_5 is selected from the group consisting of a C_{1-11} alkyl group and a C_{3-10} aryl group.

ABSTRACT

The present invention relates to novel substituted 1,2,4-trioxanes that are useful as anti-malarial agents, and have a general formula **1**,



wherein R₁ and R₂ are selected from the group consisting of a hydrogen, a C₁₋₁₁ alkyl group; R₃ and R₄ are selected from the group consisting of a hydrogen, a C₁₋₁₁ alkyl group, a C₃₋₁₀ aryl group, a C₁₋₂CO₂H carboxyalkyl group; and X represents hydrogen or a lower alkoxy group having 1 to 6 carbons.