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(54) Title: AMINO-FUNCTIONALIZED 1,2,4-TRIOXANES USEFUL AS ANTI-MALARIAL AGENTS AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: The present invention relates to a novel series of antimalarial amino functionalized 1,2,4-trioxane analogues of formula (4): wherein Ar represents aryl groups such as phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylaminophenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and the like.

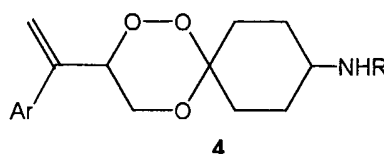


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AMINO-FUNCTIONALIZED 1,2,4-TRIOXANES USEFUL AS ANTI-MALARIAL AGENTS AND PROCESS FOR PREPARATION THEREOF

Field of the invention

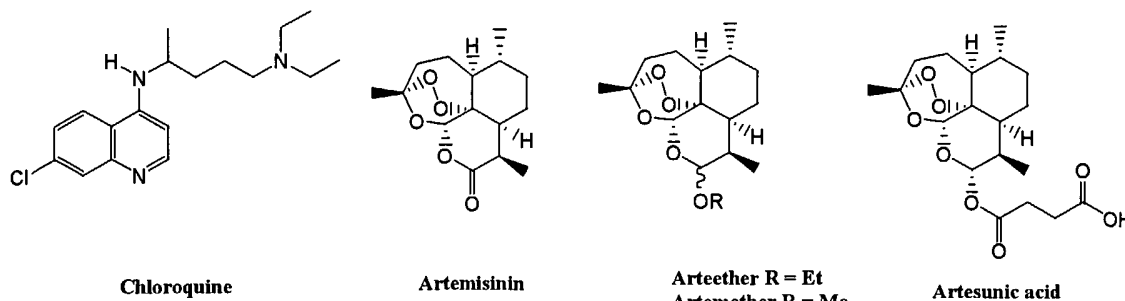
The present invention relates to a novel series of antimalarial amino functionalized 1,2,4-trioxane analogues of formula 4



wherein Ar represents aryl groups such as phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and the like. Several of these novel compounds show promising antimalarial activity against multidrug-resistant malaria in mice and thus hold promise as antimalarial agents against multidrug-resistant malaria.

Background of the invention

Malaria is one of the most deadly diseases affecting third world countries, claiming more than one million lives annually. While various classes of antimalarial agents are available, chloroquine remains the main stay of therapy against malaria. Increasing resistance of *Plasmodium falciparum*, the most dangerous of the four malaria parasites that infect humans, to the common drugs such as chloroquine has heightened concern about malaria. Extensive programs are underway to screen natural products and synthetic derivatives for new agents. Against this background, isolation of artemisinin as the active principle of Chinese herb *Artemisia annua* has opened new possibilities in malaria chemotherapy.



Semisynthetic derivatives of artemisinin such as arteether, artemether and artesunic acid, are currently the drugs of choice for the treatment of complicated cases of malaria such as cerebral malaria [For reviews on artemisinin and its analogues see: (a) Klayman, D. L

Science **1985**, 228, 1049. (b) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, 51, 1681. (c) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, 32, 1661. (d) Ploypradith, P. *Acta Trop.* **2004**, 89, 329. (e) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, 47, 2945].

5 The limited availability of artemisinin from natural sources and the fact that endoperoxide linkage present in the form of a 1,2,4-trioxane ring system is the antimalarial pharmacophore of these compounds, has led to the present efforts to develop structurally simple synthetic trioxanes. Several structurally simple synthetic 1,2,4-trioxanes have shown promising antimalarial activity [(a) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, 51, 1681. (b) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, 32, 1661. (c) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1995**, 5, 1913. (d) Singh, C.; Puri, S. K. U.S. Patent 6316493 B1, 2001. (e) Singh, C.; Gupta, N.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2003**, 13, 3445. (f) Singh, C.; Tiwari, P.; Puri, S. K. PCT Patent application No. PCT/IN02/00093, dated 28.3.2002].

15 Singh et al. have developed a novel photooxygenation route for the preparation of 1,2,4-trioxanes. β -Hydroxyhydroperoxide prepared by regiospecific photooxygenation of allylic alcohols on condensation with aldehydes or ketone in the presence of acid catalyst furnish 1,2,4-trioxane. [(a) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1992**, 2, 497. (b) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1995**, 5, 1913. (c) Singh, C.; Puri, S. K. U.S. Patent 6316493 B1, 2001. (d) Singh, C.; Gupta, N.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1913. (e) Singh, C.; Gupta, N.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2003**, 13, 3445. (f) Singh, C.; Tiwari, P.; Puri, S. K. PCT Patent application No. PCT/IN02/00093, dated 28.3.2002]. This method has been extended for the preparation of several amino functionalized 1,2,4-trioxanes, some of which have shown moderate antimalarial activity against multidrug resistant *P. yoelii* in mice [Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, 14, 459].

It is desirable to develop new compounds with show high degrees of anti-malarial activity in order to overcome the problems associated with the prior art compounds including the problem of drug-resistance in the malarial virus.

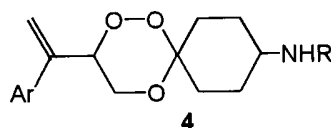
30 **Objects of the invention**

The main objective of the present invention is to provide novel amino functionalized 1,2,4-trioxanes with a potential to be used for the treatment of malaria.

It is another object of the invention to provide a process for the preparation of novel amino functionalized 1,2,4-trioxanes of formula 4, a new series of antimalarial agents.

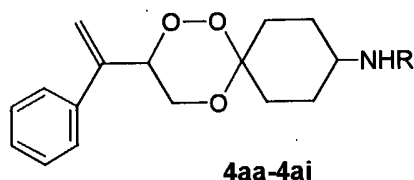
Summary of the invention

Accordingly the present invention provides substituted amino functionalized 1,2,4-trioxanes of formula 4



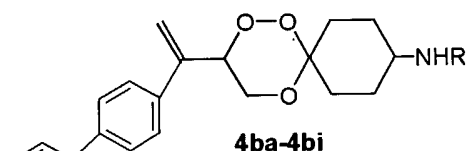
5 wherein Ar represents aryl groups selected from the groups consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and the like.

10 In one embodiment of the invention, the compound of formula 4 has structural formula **4aa-4ai** shown below:



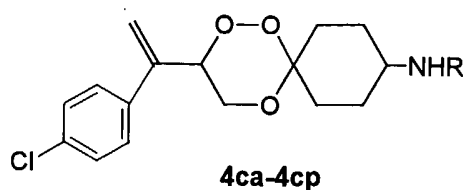
- 4aa** R = 4-chlorophenyl
- 4ab** R = 2-biphenyl (upper R_f)
- 4ac** R = 2-biphenyl (lower R_f)
- 4ad** R = 4-biphenyl
- 4ae** R = 2-fluorene
- 4af** R = 4-fluorophenyl
- 4ag** R = 2-trifluoromethylphenyl
- 4ah** R = 3-trifluoromethylphenyl
- 4ai** R = 4-trifluoromethylphenyl

In another embodiment of the invention, the compound of formula 4 has structural formulae **4ba-4bi** shown below:



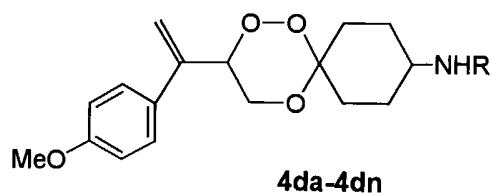
- 4ba** R = 4-chlorophenyl
- 4bb** R = 2-biphenyl (upper R_f)
- 4bc** R = 2-biphenyl (lower R_f)
- 4bd** R = 4-biphenyl
- 4be** R = 2-fluorene
- 4bf** R = 4-fluorophenyl
- 4bg** R = 2-trifluoromethylphenyl
- 4bh** R = 3-trifluoromethylphenyl
- 4bi** R = 4-trifluoromethylphenyl

In another embodiment of the invention, the compound of formula 4 has structural formulae **4ca-4cp** shown below:



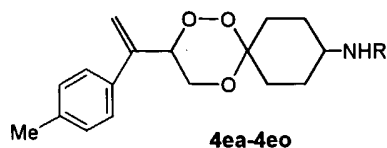
- 4ca** R = phenyl
- 4cb** R = 4-methoxyphenyl
- 4cc** R = 4-chlorophenyl (upper R_f)
- 4cd** R = 4-chlorophenyl (lower R_f)
- 4ce** R = 3,5-dichlorophenyl (upper R_f)
- 4cf** R = 3,5-dichlorophenyl (lower R_f)
- 4cg** R = 4-acetylamino phenyl
- 4ch** R = 1-naphthyl
- 4ci** R = 2-biphenyl (upper R_f)
- 4cj** R = 2-biphenyl (lower R_f)
- 4ck** R = 4-biphenyl
- 4cl** R = 2-fluorene
- 4cm** R = 4-fluorophenyl
- 4cn** R = 2-trifluoromethylphenyl
- 4co** R = 3-trifluoromethylphenyl
- 4cp** R = 4-trifluoromethylphenyl

5 In another embodiment of the invention, the compound of formula 4 has structural formulae **4da-4dn** shown below:



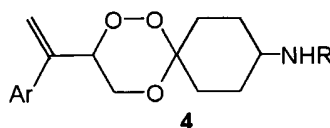
- 4da** R = phenyl
- 4db** R = 4-methoxyphenyl
- 4dc** R = 4-chlorophenyl
- 4dd** R = 3,5-dichlorophenyl
- 4de** R = 4-acetylamino phenyl
- 4df** R = 1-naphthyl
- 4dg** R = 2-biphenyl (upper R_f)
- 4dh** R = 2-biphenyl (lower R_f)
- 4di** R = 4-biphenyl
- 4dj** R = 2-fluorene
- 4dk** R = 4-fluorophenyl
- 4dl** R = 2-trifluoromethylphenyl
- 4dm** R = 3-trifluoromethylphenyl
- 4dn** R = 4-trifluoromethylphenyl

In another embodiment of the invention, the compound of formula 4 has structural formulae **4ea-4eo** shown below:

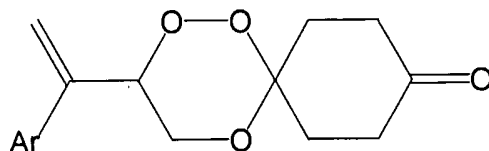


- 4ea** R = phenyl
- 4eb** R = 4-methoxyphenyl
- 4ec** R = 4-chlorophenyl
- 4ed** R = 3,5-dichlorophenyl (upper R_f)
- 4ee** R = 3,5-dichlorophenyl (lower R_f)
- 4ef** R = 4-acetylamino
- 4eg** R = 1-naphthyl
- 4eh** R = 2-biphenyl (upper R_f)
- 4ei** R = 2-biphenyl (lower R_f)
- 4ej** R = 4-biphenyl
- 4ek** R = 2-fluorene
- 4el** R = 4-fluorophenyl
- 4em** R = 2-trifluoromethylphenyl
- 4en** R = 3-trifluoromethylphenyl
- 4eo** R = 4-trifluoromethylphenyl

The present invention also provides a method for the preparation of a substituted
5 amino functionalized-1,2,4-trioxanes of formula 4



wherein Ar represents aryl groups selected from the groups consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and the like, the process comprising
10 reacting a keto trioxane of formula 3



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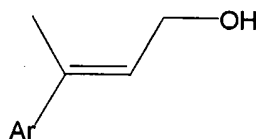
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with an aromatic amine in the presence of NaBH(OAc)₃ in CH₂Cl₂ to furnish amino functionalized 1,2,4-trioxanes of formula 4.

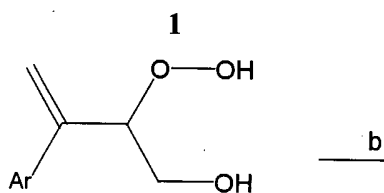
In one embodiment of the invention, the aromatic amine is selected from the group consisting of aniline, 4-methoxyaniline, 4-chloroaniline, 3,5-dichloroaniline, 4-aminoacetanilide, 1-naphthylamine, 2-aminobiphenyl, 4-aminobiphenyl, 2-aminofluorene, 4-fluoroaniline, 2-trifluoromethylaniline, 3-trifluoromethylaniline and 4-trifluoromethylaniline.

In another embodiment of the invention, the compound of formula 4 is obtained by:

- (i) Photooxygenating an allylic alcohol of formula 1 by passing oxygen gas or air in a solution of the alcohol in an organic solvent and in the presence of a dye and a light source which provides visible light, for a period of 4 h, to obtain a β -hydroxyhydroperoxide of formula 2



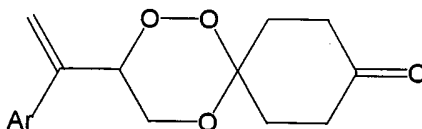
- 1a; Ar = Phenyl
1b; Ar = 4-Biphenyl
1c; Ar = 4-chlorophenyl
1d; Ar = 4-methoxyphenyl
1e; Ar = 4-methylphenyl



- 2a; Ar = Phenyl
2b; Ar = 4-Biphenyl
2c; Ar = 4-chlorophenyl
2d; Ar = 4-methoxyphenyl
2e; Ar = 4-methylphenyl

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- (ii) reacting the hydroperoxides of formula 2 in situ with 1,4-cyclohexanedione in the presence of an acid catalyst to give a trioxane of formula 3;

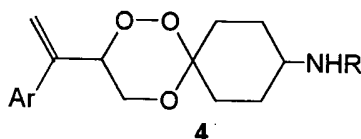


- 3a; Ar = Phenyl
3b; Ar = 4-Biphenyl
3c; Ar = 4-chlorophenyl
3d; Ar = 4-methoxyphenyl
3e; Ar = 4-methylphenyl

(iii) reacting the keto trioxane of formula 3 with an aromatic amine in the presence of $\text{NaBH}(\text{OAc})_3$ in CH_2Cl_2 to obtain amino functionalized 1,2,4-trioxane of formula 4.

In one embodiment of the invention, the aromatic amines is selected from the group consisting of aniline, 4-methoxyaniline, 4-chloroaniline, 3,5-dichloroaniline, 4-aminoacetanilide, 1-naphthylamine, 2-aminobiphenyl, 4-aminobiphenyl, 2-aminofluorene, 4-fluoroaniline, 2-trifluoromethylaniline, 3-trifluoromethylaniline and 4-trifluoromethylaniline.

The present invention also provides a method of treating a subject having malaria, comprising administering to the subject a pharmaceutically effective amount of a composition containing substituted amino functionalized-1,2,4-trioxanes of formula 4,



wherein Ar represents aryl groups selected from the groups consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and a pharmaceutically acceptable carrier.

In one embodiment of the invention, the composition is administered intramuscularly or orally.

In another embodiment of the invention, the pharmaceutically acceptable amount of compound of formula 4 is in the range of 12 to 96 mg of compound of formula 4 per kilogram of body weight of subject per day.

Detailed description of the invention

The present invention provides a process for the preparation of amino functionalized 1,2,4-trioxanes of formula 4 given above.

Our SAR studies on amino functionalized 1,2,4-trioxanes have resulted in several novel amino functionalized 1,2,4-trioxanes which show a very high order of antimalarial activity against rodent malaria and disclose here the structures and activity of these novel compounds. The order of activity of amino functionalized 1,2,4-trioxanes reported here is much higher than amino functionalized 1,2,4-trioxanes reported earlier by us [Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 459].

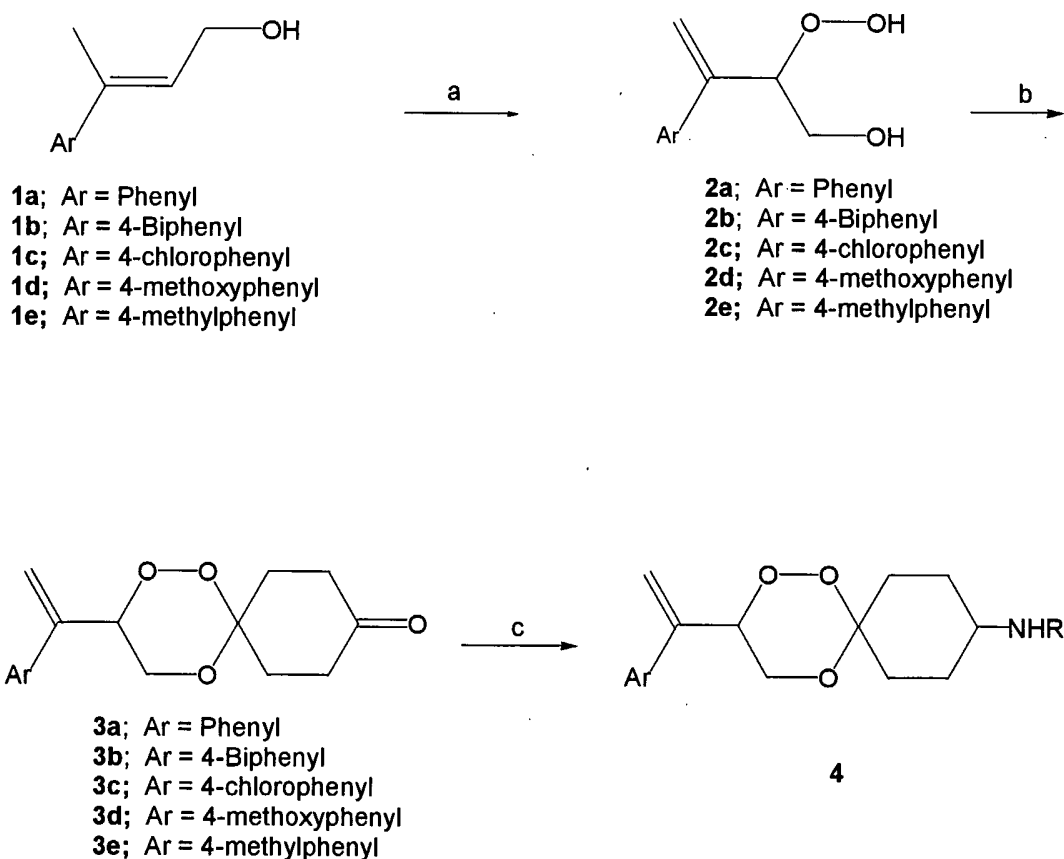
The present invention therefore also relates to the preparation of novel amino functionalized 1,2,4-trioxanes of formula 4 with high order of antimalarial activity. The present invention particularly relates to the preparation of amino functionalized 1,2,4-

trioxanes of formula **4** wherein Ar represents phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-methylphenyl and the like and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino-phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and the like. These trioxanes are new compounds and are useful as antimalarial agents. These compounds have been tested against multidrug-resistant malaria in mice and have shown high order of antimalarial activity.

These trioxanes, thus have a promise of use for the treatment of malaria, a highly prevalent parasitic disease. The invention thus relates to pharmaceutical industry.

The amino functionalized 1,2,4-trioxanes of formula **4** are new chemical entities and they have not been prepared earlier.

The process of the invention follows the general scheme shown below:



Scheme 1 Reagents and conditions: (a) $h\nu$, O_2 , methylene blue, MeCN, -10 to $0^\circ C$, 4 h. (b) 1,4-cyclohexanedione, concd HCl, $5^\circ C$, 18 h. (c) RNH_2 , $NaBH(OAc)_3$, CH_2Cl_2 , rt, 3.5 h.

In the process of the invention allylic alcohol of formula **1** were prepared by known procedure [(a) Singh, C. *Tetrahedron Lett.* **1990**, *31*, 6901. (b) Singh, C.; Tiwari, P.; Puri, S. K. PCT Patent application No. PCT/IN02/00093, dated 28.3.2002].

In the process photooxygenation of allylic alcohols of formula 1 is effected by passing oxygen gas or air in the solution of alcohol in an organic solvent and in the presence of a dye and a light source which provides visible light, for a period of 4 h, to furnish β -hydroxyhydroperoxide of formula 2. These hydroperoxides of formula 2 are known compounds and have been prepared by us earlier [(a) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1992**, 2, 497. (b) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1995**, 5, 1913. (c) Singh, C.; Tiwari, P.; Puri, S. K. PCT Patent application No. PCT/IN02/00093, dated 28.3.2002]. The dye acts as a sensitizer, i.e., converts $^3\text{O}_2$ to highly reactive $^1\text{O}_2$. Hydroperoxides of formula 2 are reacted in situ with 1,4-cyclohexanedione in the presence of an acid catalyst to give trioxanes of formula 3. These 1,2,4-trioxanes of formula 3 have been tested against malaria parasites in mice and show only moderate order of activity. Keto trioxanes **3a**, **3b** are known compounds as they have been prepared earlier by us [Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, 14, 459] while **3c**, **3d**, **3e** are new compounds and have not been prepared earlier.

The keto trioxanes of formula 3 are reacted with aromatic amines in the presence of $\text{NaBH}(\text{OAc})_3$ in CH_2Cl_2 to furnish amino functionalized 1,2,4-trioxanes of formula 4. Aromatic amines used may be aniline, 4-methoxyaniline, 4-chloroaniline, 3,5-dichloroaniline, 4-aminoacetanilide, 1-naphthylamine, 2-aminobiphenyl, 4-aminobiphenyl, 2-aminofluorene, 4-fluoroaniline, 2-trifluoromethylaniline, 3-trifluoromethylaniline and 4-trifluoromethylaniline and the like. All of these amino functionalized 1,2,4-trioxanes are new chemical entities and they have not been prepared earlier. These amino functionalized 1,2,4-trioxanes of formula 4 have been tested against malaria parasites in mice and have shown high order of antimalarial activity.

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

Example 1: 3-(1-Phenyl-vinyl)-1,2,5-trioxaspiro[5.5]undec-9-one (compound **3a**, Ar = phenyl).

Solution of allylic alcohol **1a** (1g, 6.75mmol) and methylene blue (30mg) in acetonitrile (100ml) maintained at 0°C , was irradiated with 500W tungsten-halogen lamp while oxygen was bubbled slowly into reaction mixture for 4h. 1,4-Cyclohexanedione (1.15 g, 10.13mmol) and concd. HCl (5 drops) were added and reaction mixture was left at 5°C overnight. Reaction mixture was concentrated under reduced pressure and residue taken up in ether (100ml) was washed with sat. aq NaHCO_3 (30ml). Aqueous layer was extracted with ether (2 x 75ml), combined ether layer dried over anhyd. Na_2SO_4 and concentrated. Crude

product was purified by column chromatography on silica gel using EtOAc-hexane (5:95) as eluant to furnish trioxane **3a** (0.94g, 51% yield, based on allylic alcohol **1a** used), m.p. 70-71°C.

Example 2: (4-chloro-phenyl)-[3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4aa**, Formula 4, Ar = phenyl, R = 4-chlorophenyl).

To a mixture of trioxane **3a** (0.40 g, 1.45 mmol) and 4-chloroaniline (0.23 g, 1.82 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.46 g, 3.63 mmol) was added slowly and was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4aa** as an inseparable mixture of diastereomers as oil (0.40 g, 71.7 % yield).

Example 3: Biphenyl-2-yl-[3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]amine (compound **4ab** and **4ac**, Formula 4, Ar = phenyl, R = 2-biphenyl).

To a mixture of trioxane **3a** (0.50 g, 1.82 mmol) and 2-aminobiphenyl (0.38 g, 2.27 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.58 g, 2.73 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ab** as oil (upper R_f, 0.17 g, 21.8 % yield) and **4ac** (lower R_f, 0.25 g, 32.6 % yield), m.p. 74-76°C.

Example 4: Biphenyl-4-yl-[3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]amine (compound **4ad**, Formula 4, Ar = phenyl, R = 4-biphenyl).

To a mixture of trioxane **3a** (0.40g, 1.45mmol) and 4-aminobiphenyl (0.30g, 1.82 mmol) in dichloromethane (20 ml) acetic acid (1ml) was added and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.46g, 3.63mmol) was added slowly and it was stirred for 3h at room temperature. Reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-

trioxane **4ad** as an inseparable mixture of diastereomers (0.44g, 70.5% yield), m.p. 118-120°C.

Example 5: (9H-Fluoren-3-yl)-[1-phenyl-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4ae**, Formula 4, Ar = phenyl, R = 2-fluorene).

To a mixture of trioxane **3a** (0.30 g, 1.09 mmol) and 2-aminofluorene (0.24 g, 1.36 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.35 g, 1.64 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ae** as an inseparable mixture of diastereomers (0.30 g, 63.5 % yield), m.p. 144-146°C.

Example 6: (4-Fluoro-phenyl)-[3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4af**, Formula 4, Ar = phenyl, R = 4-fluorophenyl).

To a mixture of trioxane **3a** (0.30 g, 1.09 mmol) and 4-fluoroaniline (0.15 g, 1.34 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.35 g, 1.65 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4af** as an inseparable mixture of diastereomers as oil (0.34 g, 84.1 % yield).

Example 7: [3-(1-Phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(3-trifluoromethyl-phenyl)-amine (compound **4ah**, Formula 4, Ar = phenyl, R = 3-trifluoromethylphenyl).

To a mixture of trioxane **3a** (0.50 g, 1.82 mmol) and 3-trifluoromethylaniline (0.37 g, 2.27 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.60 g, 2.73 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino

functionalized 1,2,4-trioxane **4ah** as an inseparable mixture of diastereomers as oil (0.49 g, 64.1 % yield).

Example 8: [3-(1-Phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(4-trifluoromethyl-phenyl)-amine (compound **4ai**, Formula 4, Ar = phenyl, R = 4-trifluoromethylphenyl).

5 To a mixture of trioxane **3a** (0.30 , 1.09 mmol) and 4-trifluoromethylaniline (0.22, 1.36 mmol) dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.34 g, 1.60 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried
10 over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ai** as an inseparable mixture of diastereomers as oil (0.26 g, 58.7 % yield).

Example 9: 3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxaspiro[5.5]undec-9-one (compound **3b**, Ar = biphenyl).

A solution of allylic alcohol **1b** (1 g, 6.75 mmol) and methylene blue (30 mg) in acetonitrile (100 ml) maintained at 0°C, was irradiated with a 500 W tungsten-halogen lamp while oxygen was bubbled slowly into the reaction mixture for 4 h. 1,4-Cyclohexanedione (1.15 g, 10.13 mmol) and concd HCl (5 drops) were added and the reaction mixture was left
20 at 5°C overnight. Reaction mixture was concentrated under reduced pressure and residue taken up in ether (100 ml) was washed with sat. aq NaHCO₃ (30 ml). The aqueous layer was extracted with ether (2 x 75 ml), combined ether layer dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (5:95) as eluant to furnish trioxane **3b** (0.65 g, 42 % yield, based on allylic
25 alcohol **1b** used), m.p. 104-105°C.

Example 10: [3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(4-chloro-phenyl)-amine (compound **4ba**, Formula 4, Ar = 4-biphenyl, R = 4-chlorophenyl).

To a mixture of trioxane **3b** (0.40 g, 1.14 mmol) and 4-chloroaniline (0.18 g, 1.42 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was
30 stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.36 g, 1.71 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino

functionalized 1,2,4-trioxane **4ba** as an inseparable mixture of diastereomers (0.38 g, 72.1 % yield), m.p. 148-150°C.

Example 11: Biphenyl-2-yl-[3-(1-biphenyl-4-yl-vinyl)-1,2,5-trioxaspiro[5.5]undec-9-yl]-amine (compound **4bb** and **4bc**, Formula 4, Ar = 4-biphenyl, R = 2-biphenyl).

5 To a mixture of trioxane **3b** (0.60 g, 1.71 mmol) and 2-aminobiphenyl (0.36 g, 2.14 mmol) in dichloromethane (25 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.54 g, 2.57 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 25 ml). Combined organic layer was dried
10 over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4bb** (upper R_f, 0.19 g, 21.7 % yield), m.p. 105-106°C and **4bc** (lower R_f, 0.28 g, 32.4 % yield), m.p. 148-150°C.

Example 12: Biphenyl-4-yl-[3-(1-biphenyl-4-yl-vinyl)-1,2,5-trioxaspiro[5.5]undec-9-yl]-amine (compound **4bd**, Formula 4, Ar = 4-biphenyl, R = 4-biphenyl).
15

To a mixture of trioxane **3b** (0.50 g, 1.42 mmol) and 4-aminobiphenyl (0.30 g, 1.78 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.45 g, 2.14 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then
20 poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4bd** as an inseparable mixture of diastereomers (0.53 g, 73.8 % yield), m.p. 158-160°C.

Example 13: [3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(9H-fluoren-3-yl)-amine (compound **4be**, Formula 4, Ar = 4-biphenyl, R = 2-fluorene).
25

To a mixture of trioxane **3b** (0.30 g, 0.85 mmol) and 2-aminofluorene (0.19 g, 1.07 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.27 g, 1.64 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then
30 poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino

functionalized 1,2,4-trioxane **4be** as an inseparable mixture of diastereomers (0.28 g, 65.04 % yield), m.p. 170-172°C.

Example 14: **3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecan-9-one** (compound **3c**, Ar = 4-chlorophenyl).

5 A solution of allylic alcohol **1c** (1 g, 5.47 mmol) and methylene blue (30 mg) in acetonitrile (100 ml) maintained at 0°C, was irradiated with a 500 W tungsten-halogen lamp while oxygen was bubbled slowly into the reaction mixture for 4 h. 1,4-Cyclohexanedione (1.22 g, 10.95 mmol) and concd HCl (5 drops) were added and the reaction mixture was left at 5°C overnight. Reaction mixture was concentrated under reduced pressure and residue
10 taken up in ether (100 ml) was washed with sat. aq NaHCO₃ (30 ml). The aqueous layer was extracted with ether (2 x 75 ml), combined ether layer dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (5:95) as eluant to furnish trioxane **3c** (0.64 g, 38 % yield, based on allylic alcohol **1c** used), m.p. 72-74°C.

15 **Example 15:** **{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-phenyl-amine** (compound **4ca**, Formula 4, Ar = 4-chlorophenyl, R = phenyl).

To a mixture of trioxane **3c** (0.50 g, 1.62 mmol) and aniline (0.19 g, 2.02 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.51 g, 2.43 mmol) was added
20 slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ca** as an inseparable mixture of diastereomers as oil (0.45 g, 73.4 % yield).

25 **Example 16:** **{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-p-tolyl-amine** (compound **4cb**, Formula 4, Ar = 4-chlorophenyl, R = 4-methoxyphenyl).

To a mixture of trioxane **3c** (0.50 g, 2.27 mmol) and 4-methoxyaniline (0.25 g, 2.02 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.51 g, 2.43 mmol) was
30 added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino

functionalized 1,2,4-trioxane as an inseparable mixture of diastereomers **4cb** (0.54 g, 80.2 % yield), m.p. 148-150°C.

Example 17: Biphenyl-2-yl-{3-[1-(4-chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound **4ci** and **4cj**, Formula 4, Ar = 4-chlorophenyl, R = 2-biphenyl).

5 To a mixture of trioxane **3c** (0.50 g, 1.62 mmol) and 2-aminobiphenyl (0.34 g, 2.02 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.51 g, 2.43 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried
10 over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ci** (upper R_f, 0.21 g, 28.8 % yield) and **4cj** (lower R_f, 0.32 g, 43.2 % yield) as oil.

Example 18: Biphenyl-4-yl-{3-[1-(4-chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound **4ck**, Formula 4, Ar = 4-chlorophenyl, R = 4-biphenyl).

To a mixture of trioxane **3c** (0.50 g, 1.62 mmol) and 4-aminobiphenyl (0.34 g, 2.02 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.51 g, 2.43 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then
20 poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ck** as an inseparable mixture of diastereomers as oil (0.37 g, 49.4 % yield).

25 **Example 19: {3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(9H-fluoren-3-yl)-amine** (compound **4cl**, Formula 4, Ar = 4-chlorophenyl, R = 2-fluorene).

To a mixture of trioxane **3c** (0.30 g, 0.97 mmol) and 2-aminofluorene (0.22 g, 1.21 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.30 g, 1.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then
30 poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino

functionalized 1,2,4-trioxane **4cl** as an inseparable mixture of diastereomers (0.19 g, 42.3 % yield), m.p. 162-164°C.

Example 20: {3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(4-trifluoromethyl-phenyl)-amine (compound **4cp**, Formula 4, Ar = 4-chlorophenyl, R = 4-trifluoromethylphenyl).

To a mixture of trioxane **3c** (0.30 g, 0.97 mmol) and 4-trifluoromethylaniline (0.19 g, 1.21 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.30 g, 1.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4cp** as an inseparable mixture of diastereomers as oil (0.21 g, 47.6 % yield).

Example 21: 3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecan-9-one (compound **3d**, Ar = 4-methoxyphenyl).

A solution of allylic alcohol **1d** (1 g, 5.61 mmol) and methylene blue (30 mg) in acetonitrile (100 ml) maintained at 0°C, was irradiated with a 500 W tungsten-halogen lamp while oxygen was bubbled slowly into the reaction mixture for 4 h. 1,4-Cyclohexanedione (1.25 g, 11.22 mmol) and concd HCl (5 drops) were added and the reaction mixture was left at 5°C overnight. Reaction mixture was concentrated under reduced pressure and residue taken up in ether (100 ml) was washed with sat. aq NaHCO₃ (30 ml). The aqueous layer was extracted with ether (2 x 75 ml), combined ether layer dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (5:95) as eluant to furnish trioxane **3d** as oil (0.48 g, 28.1 % yield, based on allylic alcohol **1d** used).

Example 22: {3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-phenyl-amine (compound **4da**, Formula 4, Ar = 4-methoxyphenyl, R = phenyl).

To a mixture of trioxane **3d** (0.50 g, 1.62 mmol) and aniline (0.19 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed

over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4da** as an inseparable mixture of diastereomers as oil (0.47 g, 74.9 % yield).

Example 23: (4-Methoxy-phenyl)-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxaspiro[5.5]undec-9-yl}-amine (compound **4db**, Formula 4, Ar = 4-methoxyphenyl, R = 4-methoxyphenyl).

To a mixture of trioxane **3d** (0.50 g, 1.64 mmol) and 4-methoxyaniline (0.25 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4db** as an inseparable mixture of diastereomers (0.53 g, 79.2 % yield), m.p. 126-128°C.

Example 24: (4-Chloro-phenyl)-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxaspiro[5.5]undec-9-yl}-amine (compound **4dc**, Formula 4, Ar = 4-methoxyphenyl, R = 4-chlorophenyl).

To a mixture of trioxane **3d** (0.50 g, 1.62 mmol) and 4-chloroaniline (0.19 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4dc** as an inseparable mixture of diastereomers (0.47 g, 74.9 % yield), m.p. 104-106°C.

Example 25: (3,5-Dichloro-phenyl)-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxaspiro[5.5]undec-9-yl}-amine (compound **4dd**, Formula 4, Ar = 4-methoxyphenyl, R = 3,5-dichlorophenyl).

To a mixture of trioxane **3d** (0.50 g, 1.64 mmol) and 3,5-dichloroaniline (0.33 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried

over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4dd** as an inseparable mixture of diastereomers (0.38 g, 51.3 % yield), m.p. 85-86°C.

5 **Example 26:** N-(4-{3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylamino}-phenyl)-acetamide (compound **4de**, Formula 4, Ar = 4-methoxyphenyl, R = 4-acetylamino-phenyl).

To a mixture of trioxane **3d** (0.50 g, 1.64 mmol) and 4-aminoacetanilide (0.30 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 20 ml). Combined organic layer was dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using EtOAc-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4de** as an inseparable mixture of diastereomers (0.60 g, 83.3 % yield), m.p. 70-72°C.

Example 27: {3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(3-trifluoromethyl-phenyl)-amine (compound **4dm**, Formula 4, Ar = 4-methoxyphenyl, R = 3-trifluoromethylphenyl).

20 To a mixture of trioxane **3d** (0.30 g, 0.98 mmol) and 3-trifluoromethylaniline (0.20 g, 1.21 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.31 g, 1.47 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 15 ml). Combined organic layer was dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using EtOAc-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4dm** as an inseparable mixture of diastereomers as oil (0.27 g, 60.9 % yield).

25 **Example 28:** 3-(1-p-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-one (compound **3e**, Ar = 4-methylphenyl).

30 A solution of allylic alcohol **1e** (1 g, 6.16 mmol) and methylene blue (30 mg) in acetonitrile (100 ml) maintained at 0°C was irradiated with a 500 W tungsten-halogen lamp while oxygen was bubbled slowly into the reaction mixture for 4 h. 1,4-Cyclohexanedione (1.15 g, 10.13 mmol) and concd HCl (5 drops) were added and the reaction mixture was left

at 5°C overnight. Reaction mixture was concentrated under reduced pressure and residue taken up in ether (100 ml) was washed with sat. aq NaHCO₃ (30 ml). The aqueous layer was extracted with ether (2 x 75 ml), combined ether layer dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (5:95) as eluant to furnish trioxane **3e** (0.58 g, 32.7 % yield, based on allylic alcohol **1e** used), m.p. 66-68°C.

Example 29: Phenyl-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4ea**, Formula 4, Ar = 4-methylphenyl, R = phenyl).

To a mixture of trioxane **3e** (0.30 g, 1.04 mmol) and aniline (0.12 g, 1.30 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.33 g, 1.56 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 20 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ea** as an inseparable mixture of diastereomers as oil (0.29 g, 76.3 % yield).

Example 30: (4-Methoxy-phenyl)-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4eb**, Formula 4, Ar = 4-methylphenyl, R = 4-methoxyphenyl).

To a mixture of trioxane **3e** (0.30 g, 1.04 mmol) and 4-methoxyaniline (0.16 g, 1.30 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.33 g, 1.56 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried over anhyd. Na₂SO₄, concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4eb** as an inseparable mixture of diastereomers as oil (0.33g, 80.2 % yield).

Example 31: (4-Chloro-phenyl)-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4ec** Formula 4, Ar = 4-methylphenyl, R = 4-chlorophenyl).

To a mixture of trioxane **3e** (0.30 g, 1.04 mmol) and 4-chloroaniline (0.16 g, 1.30 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxyborohydride (0.33 g, 1.56 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH₂Cl₂ (2 x 15 ml). Combined organic layer was dried

over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ec** as an inseparable mixture of diastereomers (0.26 g, 62.6 % yield), m.p. 110-112°C.

5 **Example 32: (3,5-Dichloro-phenyl)-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine** (compound **4ed** (upper R_f) and **4ee** (lower R_f), Formula 4, Ar = 4-methylphenyl, R = 3,5-dichlorophenyl).

To a mixture of trioxane **3e** (0.50 g, 1.62 mmol) and 3,5-dichloroaniline (0.19 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was
10 stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 20 ml). Combined organic layer was dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino
15 functionalized 1,2,4-trioxane **4ed** (upper R_f , 0.19 g, 25.20 % yield), m.p. 140-142°C and **4ee** (lower R_f , 0.28 g, 37.1 % yield), m.p. 112-114°C.

Example 33: N-{4-[3-(1-p-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylamino]-phenyl}-acetamide (compound **4ef**, Formula 4, Ar = 4-methylphenyl, R = 4-acetylaminophenyl).

To a mixture of trioxane **3e** (0.50 g, 1.62 mmol) and 4-aminoacetanilide (0.19 g, 2.05
20 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 20 ml). Combined organic layer was dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was
25 chromatographed over silica gel using EtOAc-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4ef** as an inseparable mixture of diastereomers (0.47 g, 76.2 % yield), m.p. 83-85°C.

Example 34: Naphthalen-1-yl-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound **4eg**, Formula 4, Ar = 4-methylphenyl, R = 1-naphthyl).

30 To a mixture of trioxane **3e** (0.50 g, 1.64 mmol) and 1-naphthylamine (0.30 g, 2.05 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.52 g, 2.46 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 20 ml). Combined organic layer was dried

over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4eg** as an inseparable mixture of diastereomers (0.52 g, 72.2 % yield), m.p. 70-72°C.

5 **Example 35: Biphenyl-2-yl-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine** (compound **4eh** and **4ei**, Formula 4, Ar = 4-methylphenyl, R = 2-biphenyl).

To a mixture of trioxane **3e** (0.80 g, 2.59 mmol) and 2-aminobiphenyl (0.41 g, 3.24 mmol) in dichloromethane (30 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.82 g, 3.89 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 25 ml). Combined organic layer was dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4eh** (upper R_f , 0.29 g, 26.60 % yield) and **4ei** (lower R_f , 0.44 g, 40.3 % yield) as oil.

15 **Example 36: (4-Fluoro-phenyl)-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine** (compound **4el**, Formula 4, Ar = 4-methylphenyl, R = 4-fluorophenyl).

To a mixture of trioxane **3e** (0.30 g, 1.04 mmol) and 4-fluoroaniline (0.14 g, 1.25 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.33 g, 1.55 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 20 ml). Combined organic layer was dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4el** as an inseparable mixture of diastereomers as oil (0.30 g, 75.1 % yield).

25 **Example 37: [3-(1-p-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(4-trifluoromethyl-phenyl)-amine** (compound **4eo**, Formula 4, Ar = 4-methylphenyl, R = 4-trifluoromethylphenyl).

30 To a mixture of trioxane **3e** (0.30 g, 1.04 mmol) and 4-trifluoromethylaniline (0.21 g, 1.30 mmol) in dichloromethane (20 ml) was added acetic acid (1 ml) and reaction mixture was stirred at room temp for half an hour. Sodium triacetoxymethylborohydride (0.33 g, 1.55 mmol) was added slowly and it was stirred for 3 h at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (2 x 20 ml). Combined organic layer was

dried over anhyd. Na_2SO_4 , concentrated under vacuum and the crude product was chromatographed over silica gel using benzene-hexane (50:50) as eluant to furnish amino functionalized 1,2,4-trioxane **4eo** as an inseparable mixture of diastereomers (0.22 g, 48.7 % yield), m.p. 104-106°C.

- 5 Following the above procedure the following amino functionalized 1,2,4-trioxanes **4ag**, **4bf**, **4bg**, **4bh**, **4bi**, **4cc**, **4cd**, **4ce**, **4cf**, **4cg**, **4ch**, **4cm**, **4cn**, **4co**, **4df**, **4dg**, **4dh**, **4di**, **4dj**, **4dk**, **4dl**, **4dn**, **4ej**, **4ek**, **4em** and **4en** were prepared (Scheme 1, Table1).

Table 1

S. No.	Amino Functionalized Trioxane	m.p.	% yield
1.	[3-(1-Phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(2-trifluoromethyl-phenyl)-amine (compound 4ag , Formula 4, Ar = phenyl, R = 2-trifluoromethylphenyl).	oil	43.6
2.	[3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(4-fluoro-phenyl)-amine (compound 4bf , Formula 4, Ar = 4-biphenyl, R = 4-fluorophenyl).	oil	78.7
3.	[3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(2-trifluoromethyl-phenyl)-amine (compound 4bg , Formula 4, Ar = 4-biphenyl, R = 2-trifluoromethylphenyl).	oil	43.5
4.	[3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(3-trifluoromethyl-phenyl)-amine (compound 4bh , Formula 4, Ar = 4-biphenyl, R = 3-trifluoromethylphenyl).	oil	58.1
5.	[3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(4-trifluoromethyl-phenyl)-amine (compound 4bi , Formula 4, Ar = 4-biphenyl, R = 4-trifluoromethylphenyl).	oil	44.8
6.	(4-chloro-phenyl-{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl})-amine (compound 4cc (upper R_f), Formula 4, Ar = 4-chlorophenyl, R = 4-chlorophenyl).	130-132°C	26.6

7.	(4-chloro-phenyl)-{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound 4cd (lower R_f), Formula 4, Ar = 4-chlorophenyl, R = 4-chlorophenyl).	138-140°C	40.3
8.	{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(3,5-dichloro-phenyl)-amine (compound 4ce (upper R_f), Formula 4, Ar = 4-chlorophenyl, R = 3,5-dichlorophenyl).	oil	30.9
9.	{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(3,5-dichloro-phenyl)-amine (compound 4cf (lower R_f), Formula 4, Ar = 4-chlorophenyl, R = 3,5-dichlorophenyl).	oil	47.4
10.	N-(4-{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylamino}-phenyl)-acetamide (compound 4cg , Formula 4, Ar = 4-chlorophenyl, R = 4-acetylamino-phenyl).	88-90°C	83.9
11.	{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-naphthalen-1-yl-amine (compound 4ch , Formula 4, Ar = 4-chlorophenyl, R = 1-naphthyl).	oil	77.7
12.	{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(4-fluoro-phenyl)-amine (compound 4cm , Formula 4, Ar = 4-chlorophenyl, R = 4-fluorophenyl).	oil	71.2
13.	{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(2-trifluoromethyl-phenyl)-amine (compound 4cn , Formula 4, Ar = 4-chlorophenyl, R = 2-trifluoromethylphenyl).	oil	37.4
14.	{3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(3-trifluoromethyl-phenyl)-amine (compound 4co , Formula 4, Ar = 4-chlorophenyl, R = 3-trifluoromethylphenyl).	oil	72.5
15.	{3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-	oil	73.4

	spiro[5.5]undec-9-yl}-naphthalen-1-yl-amine (compound 4df , Formula 4, Ar = 4-methoxyphenyl, R = 1-naphthyl).		
16.	Biphenyl-2-yl-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound 4dg (upper R _f), Formula 4, Ar = 4-methoxyphenyl, R = 2-biphenyl).	oil	35.4
17.	Biphenyl-2-yl-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound 4dh (lower R _f), Formula 4, Ar = 4-methoxyphenyl, R = 2-biphenyl).	oil	52.1
18.	Biphenyl-4-yl-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound 4di , Formula 4, Ar = 4-methoxyphenyl, R = 4-biphenyl).	124- 126°C	58.4
19.	9H-Fluoren-3-yl-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound 4dj , Formula 4, Ar = 4-methoxyphenyl, R = 2-fluorene).	166- 168°C	75.7
20.	(4-Fluoro-phenyl)-{3-[1-(4-methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-amine (compound 4dk , Formula 4, Ar = 4-methoxyphenyl, R = 4-fluorophenyl).	oil	60.2
21.	{3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(2-trifluoromethyl-phenyl)-amine (compound 4dl , Formula 4, Ar = 4-methoxyphenyl, R= 2-trifluoromethylphenyl).	oil	36.4
22.	{3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl}-(4-trifluoromethyl-phenyl)-amine (compound 4dn , Formula 4, Ar = 4-methoxyphenyl, R= 4-trifluoromethylphenyl).	oil	40.6
23.	Biphenyl-4-yl-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound 4ej ,	123- 124°C	70.5

	Formula 4, Ar = 4-methylphenyl, R = 4-biphenyl).		
24.	(9H-Fluoren-3-yl)-[3-(1-p-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-amine (compound 4ek, Formula 4, Ar = 4-methylphenyl, R = 2-fluorene).	152-154°C	85.8
25.	[3-(1-p-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(2-trifluoromethyl-phenyl)-amine (compound 4em, Formula 4, Ar = 4-methylphenyl, R = 2-trifluoromethylphenyl).	oil	40.8
26.	[3-(1-p-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-(3-trifluoromethyl-phenyl)-amine (compound 4en, Formula 4, Ar = 4-methylphenyl, R = 3-trifluoromethylphenyl).	oil	65.2

Antimalarial Activity

The antimalarial activity of the test compounds was evaluated in rodent using multidrug resistant strain of *Plasmodium yoelii* *Nigeriensis* in Swiss mice.

5 General Procedure

Random bred Swiss mice of either sex (20 ±2 gm) were inoculated intraperitoneally with 1 x 10⁵ *P. yoelii* (MDR) parasites on day zero. The treatments with test compounds were administered to group of 5 mice each at different dose levels ranging between 12–96 mg/kg/day. The treatment was administered in groundnut oil intramuscularly and orally for 4 consecutive days (day 0-3). 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 vehicle control group and percent suppression of parasitaemia in treated groups was calculated.

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 reported as the curative dose. The antimalarial data is summarized in Table 2.

Table 2: ANTIMALARIAL ACTIVITY OF TRIOXANES AGAINST *P. Yoelii* IN MICE.

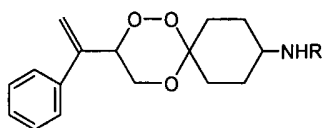
Compound	Dose (mg/kg/Day)	Route	% Suppression on Day 4 ^a	Mice alive on day- 28
3a	96	im	99	0/5
3b	96	im	100	1/5
3c	96	oral	100	0/5

	96	oral	100	5/5
4aa	96	im	71	2/5
	48	oral	100	3/5
4ab	96	oral	100	5/5
	48	oral	100	0/5
4ac	96	oral	100	5/5
	96	im	74	0/5
	48	oral	100	5/5
	24	oral	100	4/10
	12	oral	100	0/5
4ad	96	oral	100	5/5
	48	oral	100	5/5
	24	oral	100	6/10
	12	oral	99	0/5
4ae	96	oral	100	5/5
4ah	96	oral	100	5/5
	96	im	83	0/5
	48	oral	100	5/5
	24	oral	100	1/5
4ba	96	oral	100	5/5
4bg	96	oral	100	2/5
4cb	48	oral	100	5/5
4cc	48	oral	100	5/5
	24	oral	100	4/5
4cd	48	oral	100	5/5
	24	oral	100	4/5
4ce	48	oral	100	4/5
	24	oral	100	2/5
4cf	48	oral	100	2/5
	24	oral	100	1/5
4ch	96	oral	100	2/5
4cj	48	oral	100	5/5
	24	oral	100	2/5
4ck	96	oral	100	2/5

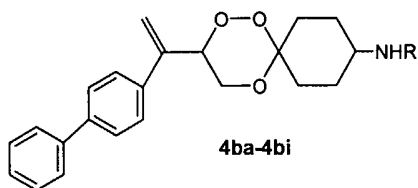
	96	oral	100	5/5
4co	96	im	73	0/5
	48	oral	100	5/5
	24	oral	100	3/5
4da	96	oral	100	0/5
	96	im	81	0/5
4dc	96	oral	100	5/5
	96	im	100	4/5
	48	oral	100	5/5
	24	oral	100	4/5
4dd	96	oral	100	4/5
4df	96	oral	100	5/5
	48	oral	100	2/5
4dg	48	oral	100	3/5
	24	oral	91	1/5
4dh	48	oral	100	5/5
	24	oral	100	5/5
4dm	96	oral	100	5/5
	96	im	100	0/5
	48	oral	100	5/5
	24	oral	100	5/5
4ea	96	oral	100	5/5
	96	im	96	0/5
4eb	96	oral	100	5/5
	96	im	93	0/5
4ec	96	oral	100	5/5
4ed	48	oral	100	4/5
	24	oral	95	0/5
4ee	48	oral	100	2/5
	24	oral	81	0/5
4eg	96	oral	100	5/5
4ej	96	oral	100	5/5
	96	im	69	0/5

	48	oral	100	2/5
4en	96	oral	100	3/5
β-Arteether	48	oral	100	5/5
	24	oral	100	1/5
Chloroquine	48	oral	100	2/5
	24	oral	100	0/5
Vehicle	-	-	-	0/15
Control	-	-	-	0/15

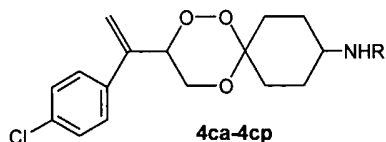
^aPercent suppression = [(C-T)/C]X100; where C = parasitaemia in control group, and T= parasitaemia in treated group.

**4aa-4ai**

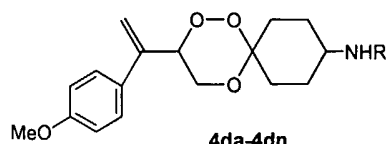
- 4aa** R = 4-chlorophenyl
4ab R = 2-biphenyl (upper R_f)
4ac R = 2-biphenyl (lower R_f)
4ad R = 4-biphenyl
4ae R = 2-fluorene
4af R = 4-fluorophenyl
4ag R = 2-trifluoromethylphenyl
4ah R = 3-trifluoromethylphenyl
4ai R = 4-trifluoromethylphenyl

**4ba-4bi**

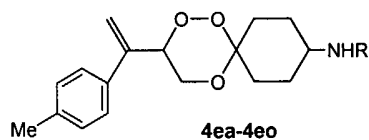
- 4ba** R = 4-chlorophenyl
4bb R = 2-biphenyl (upper R_f)
4bc R = 2-biphenyl (lower R_f)
4bd R = 4-biphenyl
4be R = 2-fluorene
4bf R = 4-fluorophenyl
4bg R = 2-trifluoromethylphenyl
4bh R = 3-trifluoromethylphenyl
4bi R = 4-trifluoromethylphenyl

**4ca-4cp**

- 4ca** R = phenyl
4cb R = 4-methoxyphenyl
4cc R = 4-chlorophenyl (upper R_f)
4cd R = 4-chlorophenyl (lower R_f)
4ce R = 3,5-dichlorophenyl (upper R_f)
4cf R = 3,5-dichlorophenyl (lower R_f)
4cg R = 4-acetylamino phenyl
4ch R = 1-naphthyl
4ci R = 2-biphenyl (upper R_f)
4cj R = 2-biphenyl (lower R_f)
4ck R = 4-biphenyl
4cl R = 2-fluorene
4cm R = 4-fluorophenyl
4cn R = 2-trifluoromethylphenyl
4co R = 3-trifluoromethylphenyl
4cp R = 4-trifluoromethylphenyl



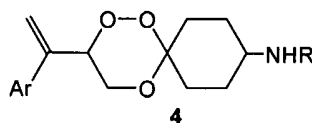
- 4da** R = phenyl
4db R = 4-methoxyphenyl
4dc R = 4-chlorophenyl
4dd R = 3,5-dichlorophenyl
4de R = 4-acetylamino-phenyl
4df R = 1-naphthyl
4dg R = 2-biphenyl (upper R_f)
4dh R = 2-biphenyl (lower R_f)
4di R = 4-biphenyl
4dj R = 2-fluorene
4dk R = 4-fluorophenyl
4dl R = 2-trifluoromethylphenyl
4dm R = 3-trifluoromethylphenyl
4dn R = 4-trifluoromethylphenyl



- 4ea** R = phenyl
4eb R = 4-methoxyphenyl
4ec R = 4-chlorophenyl
4ed R = 3,5-dichlorophenyl (upper R_f)
4ee R = 3,5-dichlorophenyl (lower R_f)
4ef R = 4-acetylamino-phenyl
4eg R = 1-naphthyl
4eh R = 2-biphenyl (upper R_f)
4ei R = 2-biphenyl (lower R_f)
4ej R = 4-biphenyl
4ek R = 2-fluorene
4el R = 4-fluorophenyl
4em R = 2-trifluoromethylphenyl
4en R = 3-trifluoromethylphenyl
4eo R = 4-trifluoromethylphenyl

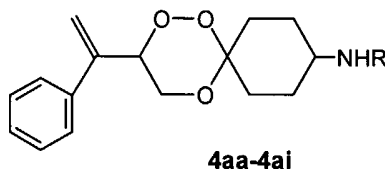
We claim:

1. A substituted amino functionalized 1,2,4-trioxane of formula 4



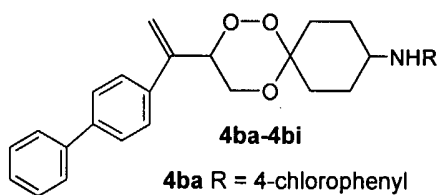
- 5 wherein Ar represents aryl groups selected from the groups consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl.

- 10 2. Compound of formula 4 with structural formula **4aa-4ai** shown below:



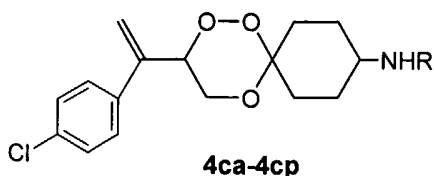
- 4aa** R = 4-chlorophenyl
4ab R = 2-biphenyl (upper R_f)
4ac R = 2-biphenyl (lower R_f)
4ad R = 4-biphenyl
4ae R = 2-fluorene
4af R = 4-fluorophenyl
4ag R = 2-trifluoromethylphenyl
4ah R = 3-trifluoromethylphenyl
4ai R = 4-trifluoromethylphenyl

3. Compound of formula 4 with structural formula **4ba-4bi** shown below:



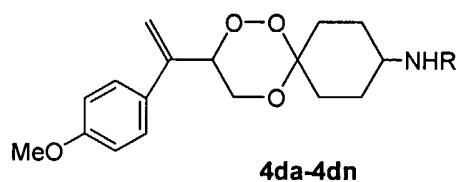
- 4ba** R = 4-chlorophenyl
4bb R = 2-biphenyl (upper R_f)
4bc R = 2-biphenyl (lower R_f)
4bd R = 4-biphenyl
4be R = 2-fluorene
4bf R = 4-fluorophenyl
4bg R = 2-trifluoromethylphenyl
4bh R = 3-trifluoromethylphenyl
4bi R = 4-trifluoromethylphenyl

4. Compound of formula 4 with structural formula **4ca-4cp** shown below:



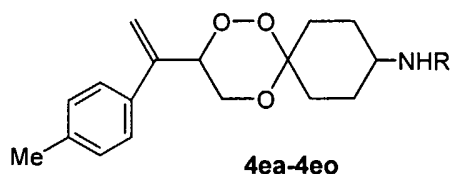
- 4ca** R = phenyl
4cb R = 4-methoxyphenyl
4cc R = 4-chlorophenyl (upper R_f)
4cd R = 4-chlorophenyl (lower R_f)
4ce R = 3,5-dichlorophenyl (upper R_f)
4cf R = 3,5-dichlorophenyl (lower R_f)
4cg R = 4-acetylamino phenyl
4ch R = 1-naphthyl
4ci R = 2-biphenyl (upper R_f)
4cj R = 2-biphenyl (lower R_f)
4ck R = 4-biphenyl
4cl R = 2-fluorene
4cm R = 4-fluorophenyl
4cn R = 2-trifluoromethylphenyl
4co R = 3-trifluoromethylphenyl
4cp R = 4-trifluoromethylphenyl

5. Compound of formula 4 with structural formula **4da-4dn** shown below:



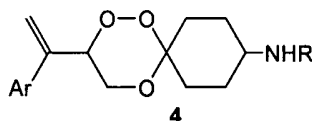
- 4da** R = phenyl
4db R = 4-methoxyphenyl
4dc R = 4-chlorophenyl
4dd R = 3,5-dichlorophenyl
4de R = 4-acetylamino phenyl
4df R = 1-naphthyl
4dg R = 2-biphenyl (upper R_f)
4dh R = 2-biphenyl (lower R_f)
4di R = 4-biphenyl
4dj R = 2-fluorene
4dk R = 4-fluorophenyl
4dl R = 2-trifluoromethylphenyl
4dm R = 3-trifluoromethylphenyl
4dn R = 4-trifluoromethylphenyl

6. Compound of formula 4 with structural formula **4ea-4eo** shown below:

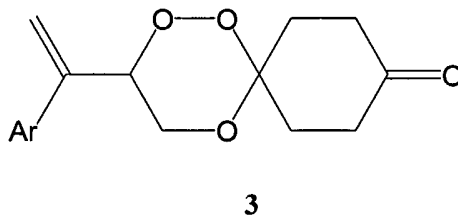


- 4ea** R = phenyl
4eb R = 4-methoxyphenyl
4ec R = 4-chlorophenyl
4ed R = 3,5-dichlorophenyl (upper R_f)
4ee R = 3,5-dichlorophenyl (lower R_f)
4ef R = 4-acetylamino phenyl
4eg R = 1-naphthyl
4eh R = 2-biphenyl (upper R_f)
4ei R = 2-biphenyl (lower R_f)
4ej R = 4-biphenyl
4ek R = 2-fluorene
4el R = 4-fluorophenyl
4em R = 2-trifluoromethylphenyl
4en R = 3-trifluoromethylphenyl
4eo R = 4-trifluoromethylphenyl

7. Method for the preparation of a substituted amino functionalized-1,2,4-trioxane of formula 4



- 5 wherein Ar represents aryl groups selected from the groups consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl, the
- 10 process comprising reacting a keto trioxane of formula 3

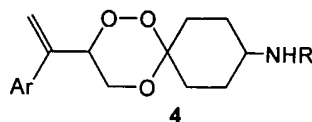


with an aromatic amine in the presence of NaBH(OAc)₃ in CH₂Cl₂ to furnish amino functionalized 1,2,4-trioxanes of formula 4.

- 15 8. A method as claimed in claim 7 wherein the aromatic amine is selected from the group consisting of aniline, 4-methoxyaniline, 4-chloroaniline, 3,5-dichloroaniline, 4-

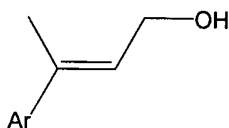
aminoacetanilide, 1-naphthylamine, 2-aminobiphenyl, 4-aminobiphenyl, 2-aminofluorene, 4-fluoroaniline, 2-trifluoromethylaniline, 3-trifluoromethylaniline and 4-trifluoromethylaniline.

9. A method for the preparation of substituted amino functionalized-1,2,4-trioxanes of formula 4



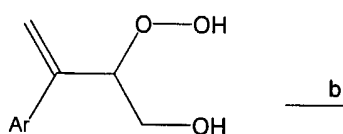
wherein Ar is an aryl group selected from the group consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl, the method comprising:

- (i) photooxygenating an allylic alcohol of formula 1 by passing oxygen gas or air in a solution of the alcohol in an organic solvent and in the presence of a dye and a light source which provides visible light, for a period of 4 h, to obtain a β -hydroxyhydroperoxide of formula 2



- 1a;** Ar = Phenyl
1b; Ar = 4-Biphenyl
1c; Ar = 4-chlorophenyl
1d; Ar = 4-methoxyphenyl
1e; Ar = 4-methylphenyl

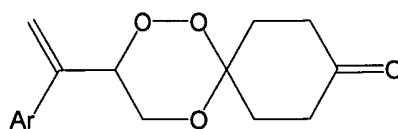
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- 2a;** Ar = Phenyl
2b; Ar = 4-Biphenyl
2c; Ar = 4-chlorophenyl
2d; Ar = 4-methoxyphenyl
2e; Ar = 4-methylphenyl

2

- (ii) reacting the hydroperoxides of formula 2 in situ with 1,4-cyclohexanedione in the presence of an acid catalyst to give a trioxane of formula 3;

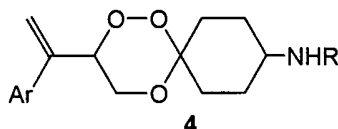


3a; Ar = Phenyl
 3b; Ar = 4-Biphenyl
 3c; Ar = 4-chlorophenyl
 3d; Ar = 4-methoxyphenyl
 3e; Ar = 4-methylphenyl

3

reacting the keto trioxane of formula 3 with an aromatic amine in the presence of $\text{NaBH}(\text{OAc})_3$ in CH_2Cl_2 to obtain amino functionalized 1,2,4-trioxane of formula 4.

10. A method as claimed in claim 9 wherein the aromatic amine is selected from the group consisting of aniline, 4-methoxyaniline, 4-chloroaniline, 3,5-dichloroaniline, 4-aminoacetanilide, 1-naphthylamine, 2-aminobiphenyl, 4-aminobiphenyl, 2-aminofluorene, 4-fluoroaniline, 2-trifluoromethylaniline, 3-trifluoromethylaniline and 4-trifluoromethylaniline.
11. A method of treating a subject having malaria, comprising administering to the subject a pharmaceutically effective amount of a composition containing substituted amino functionalized-1,2,4-trioxanes of formula 4,



4

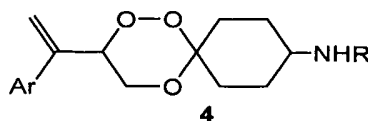
- wherein Ar represents aryl groups selected from the groups consisting of phenyl, 4-biphenyl, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl and R represents phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl and a pharmaceutically acceptable carrier.
12. A method as claimed in claim 11 wherein the composition is administered intramuscularly or orally.
13. A method as claimed in claim 11 wherein the pharmaceutically acceptable amount of compound of formula 4 is in the range of 12 to 96 mg of compound of formula 4 per kilogram of body weight of subject per day.
14. A method as claimed in claim 11 wherein the subject is a human being.

AMENDED CLAIMS

[(received by the International Bureau on 24 April 2006 (24.04.06))]

+ STATEMENT

1. A substituted amino functionalized 1,2,4-trioxane of formula 4

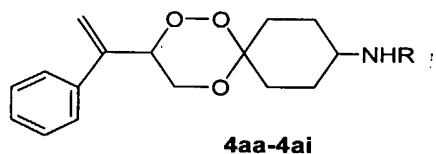


wherein, when Ar is phenyl, R is selected from the group comprising of 4-chlorophenyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl;

when Ar is biphenyl, R is selected from the group comprising of 4-chlorophenyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl;

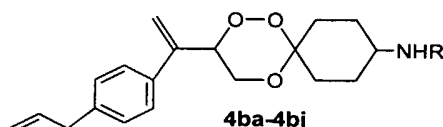
when Ar is selected from 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl, R is selected from the group comprising of phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylaminophenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl.

2. Compound of formula 4 with structural formula 4aa-4ai shown below:



- 4aa R = 4-chlorophenyl
 4ab R = 2-biphenyl (upper R_f)
 4ac R = 2-biphenyl (lower R_f)
 4ad R = 4-biphenyl
 4ae R = 2-fluorene
 4af R = 4-fluorophenyl
 4ag R = 2-trifluoromethylphenyl
 4ah R = 3-trifluoromethylphenyl
 4ai R = 4-trifluoromethylphenyl

3. Compound of formula 4 with structural formula 4ba-4bi shown below:



- 4ba R = 4-chlorophenyl
 4bb R = 2-biphenyl (upper R_f)
 4bc R = 2-biphenyl (lower R_f)
 4bd R = 4-biphenyl
 4be R = 2-fluorene
 4bf R = 4-fluorophenyl
 4bg R = 2-trifluoromethylphenyl
 4bh R = 3-trifluoromethylphenyl
 4bi R = 4-trifluoromethylphenyl

4. Compound of formula 4 with structural formula 4ca-4cp shown below:

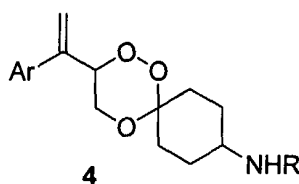
STATEMENT

The following point wise comments on the documents cited in the International Search Report are provided here as under:

D1: XP002340515

Document D1 which is closest prior art describes antimalarial 3-(1-aryl-vinyl)-9-arylamino-1, 2, 5-trioxa-spiro [5.5] undecanes, wherein 1-aryl group is selected from phenyl or biphenyl and 9-aryl group is selected from R=phenyl, 4-methoxyphenyl, 3,5-dichlorophenyl 4-acetylamino-phenyl, 1-naphthyl. The said compounds are tested for antimalarial activity against *Plasmodium yoelii*.

The present application describes the compounds of general formula 4, wherein the variations have been carried out at Ar and R level.

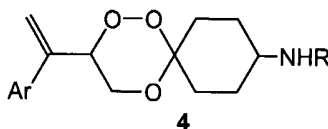


As can be seen from structure **4** there are two substituents Ar and R which are variable. Compounds claimed in claim **2-6** have general structure **4a**, **4b**, **4c**, **4d**, and **4e**.

Accordingly, in an attempt to overcome the objections of novelty and inventiveness encountered by the instant application in view of the cited document D1, **we are hereby amending claim 1 of the present invention to include only those novel compounds which are not available in the prior art.**

In this regard, it may kindly be noted that we are now restricting the substituents at the 'Ar' and 'R' position of the compound of claim 1 as follows:

1. A substituted amino functionalized 1,2,4-trioxane of formula 4



wherein, when Ar is phenyl, R is selected from the group comprising of 4-chlorophenyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl;

when Ar is biphenyl, R is selected from the group comprising of 4-chlorophenyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl;

when Ar is selected from the group comprising of 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl, R is selected from phenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-acetylamino phenyl, 1-naphthyl, 2-biphenyl, 4-biphenyl, 2-fluorene, 4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl and 4-trifluoromethylphenyl.

The above said combinations of Ar and R substituents are not disclosed in the cited document D1 as well as elsewhere in the prior art.

Further, with respect to the objections set forth by the learned Examiner as regards inventiveness it is humbly submitted that the compounds **4aa – 4ai**, **4ba** and **4bf** as claimed in claim 1 of the present application exhibit **100% protection** to the mice infected with *Plasmodium yoelii* at a dosage of **96mg/kg**. In addition,

the compounds **4ac**, **4ad**, **4ah**, also exhibit 100% protection even at doses as low as 48mg/kg.

It may also be observed that only one of the compounds [9a] cited in D1 provides 100% protection at 96mg/kg, which suggests that the cited compounds are less active than all the compounds claimed in the present application. The activity of the compounds claimed in the present application could not have been predicted by the activity data of the compounds published in D1. Therefore, all the compounds claimed in the present invention are novel and are more active than the related compounds published by us.

Hence, it is respectfully submitted that it is not merely a motivation for the person skilled in the art to synthesize the compounds of the present application merely by replacing the substituents at Ar and R positions coupled to the high biological activity.

In light of the arguments as proposed above, the learned Examiner is humbly requested to reconsider the application in totality.

INTERNATIONAL SEARCH REPORT

International Application No
P/IN2004/000413

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D323/06 A61K31/357 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SINGH C ET AL: "Orally active amino functionalized antimalarial 1,2,4-trioxanes" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 2, January 2004 (2004-01), pages 459-462, XP002340515 cited in the application the whole document -----	1-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

12 August 2005

Date of mailing of the international search report

26/08/2005

Name and mailing address of the ISA

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Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2004/000413

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.