Reduction of the Double Bond of 6-Arylvinyl-1,2,4-trioxanes Leads to a Remarkable Increase in Their Antimalarial Activity against Multidrug-Resistant *Plasmodium yoelii nigeriensis* in a Swiss Mice Model

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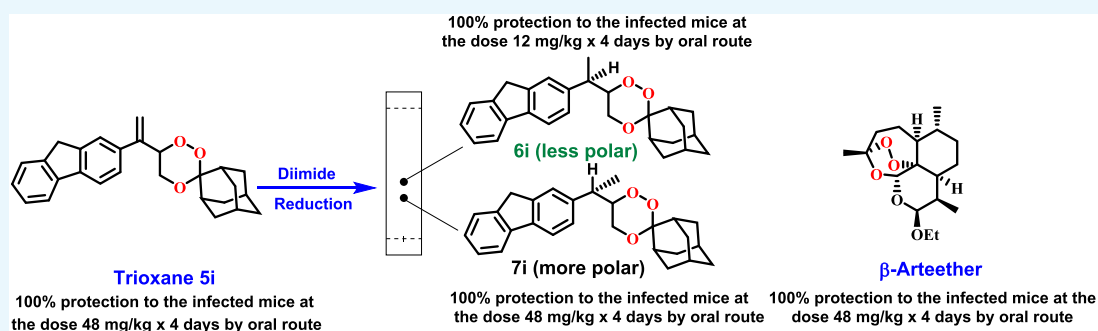
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ABSTRACT: Novel 6-arylethyl-1,2,4-trioxanes **6a−i** and **7a−i** are easily accessible in one step from the diimide reduction of 6-arylvinyl-1,2,4-trioxanes **5a−i**. All of these new trioxanes were assessed for their oral antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in a Swiss mice model. Most of the saturated trioxanes **6c**, **6f**, **6g**, **6h**, and **6i**, the active compounds of the series, provided 100% protection to the malaria-infected mice at a dose of 24 mg/kg × 4 days. Further, trioxane **6i**, the most active compound of the series, also showed 100% protection even at a dose of 12 mg/kg × 4 days and 20% protection at a dose of 6 mg/kg × 4 days. In this model, *β*-arteether provided 100% protection at a dose of 48 mg/kg × 4 days and only 20% protection at a dose of 24 mg/kg × 4 days via the oral route, which was found to exhibit 4-fold antimalarial activity compared with the currently used drug *β*-arteether.

INTRODUCTION

Since ancient times, humankind has had to struggle against the persistent onslaught of pathogenic microorganisms and is still suffering. Malaria, a vector-borne disease caused by *Plasmodium* sp., is still one of the world's most deadly diseases that threaten nearly 40% of the world's population, putting 3.2 billion people at risk in 107 countries, and infects approximately 300−500 million people annually worldwide, mainly in tropical and subtropical areas.[1] It is estimated that there are between 1 and 3 million deaths every year due to malaria. In Africa alone, more than 1 million people die because of malaria and most of them are children under 5 years of age.[2] The economic toll of malaria is tremendous, as it has been estimated that the African continent has suffered almost $100 billion loss in GDP over the last 35 years due to malaria alone.[3] Malaria ranks third among the major infectious diseases in causing deaths after pneumococcal acute respiratory infections and tuberculosis and accounts for approximately 2.6% of the total disease burden of the world.[4,5]

Indeed, the emergence of malaria as a worldwide epidemic can largely be attributed to the indiscriminate use of conventional drugs, due to which there has been a rapid development of resistant varieties of the malaria parasite. In that regard, the discovery of artemisinin **1**, a sesquiterpene lactone endoperoxide, isolated from the Chinese traditional medicinal herb *Artemisia annua*, has proven to be a milestone in malaria chemotherapy.[6−13] It was found to be active against both chloroquine-sensitive and chloroquine-resistant strains of malaria, and its semisynthetic derivatives artemether **2**, arteether **3**, and artesunic acid **4** (Figure 1) have shown tremendous potential and are presently the drugs of choice for
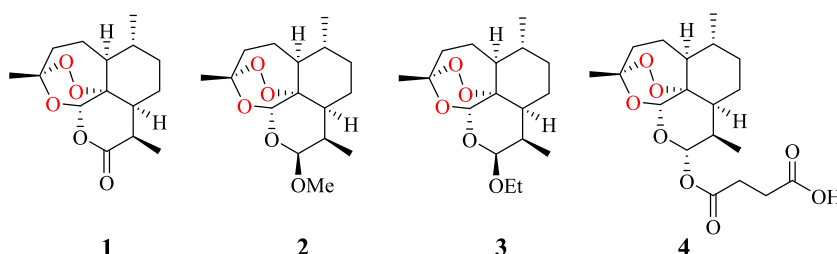
Figure 1. Artemisinin and its clinically used derivatives.

the treatment of multidrug-resistant malaria caused by *Plasmodium falciparum*.[14−19] Several analogues of artemisinin have been synthesized so far that have shown potential antimalarial activity.[20−24] The very fact that it is the endoperoxide linkage of artemisinin and its semisynthetic analogues in the form of a 1,2,4-trioxane ring system, which is responsible for its antimalarial activity, has led to the development of several synthetic trioxanes and various other related peroxides that have shown potent antimalarial activity both in vivo and in vitro.[25−37]

As part of an endeavor to develop synthetic substitutes for artemisinin and its derivatives, we had earlier reported a photooxygenation route for the preparation of 6-arylvinyl-1,2,4-trioxanes.[38,39] Preparation of β-hydroxyhydroperoxides by the photooxygenation of allylic alcohols and their acid-catalyzed condensation with ketones are the key steps of this method (Scheme 1). Several 1,2,4-trioxanes prepared by this route have shown promising activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in Swiss mice.[40−50]

Scheme 1. Preparation of 6-Arylvinyl-1,2,4-trioxanes
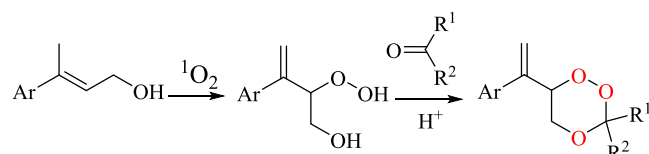
A unique feature of these 6-arylvinyl-substituted 1,2,4-trioxanes is that they undergo a highly facile fragmentation under basic conditions by the extraction of an acidic C-6 proton to furnish α,β-unsaturated keto alcohols, which react very efficiently with various amines and thiols to afford Michael adducts (Scheme 2).[51]

Based on these results, we had earlier suggested that this facile formation of α,β-unsaturated keto systems under mild basic conditions and their equally facile reaction with amines and thiols might have relevance to their mechanism of action

Scheme 2. Base-Catalyzed Fragmentation of 6-Arylvinyl-1,2,4-trioxanes
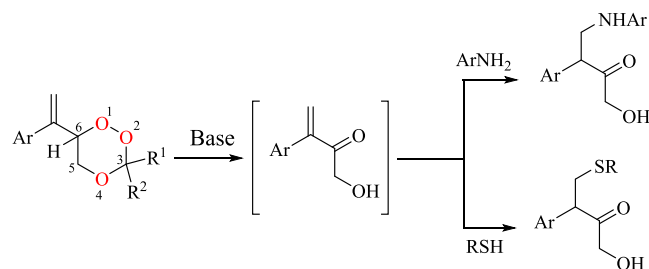

as antimalarials.[51] This suggestion naturally brings the role of the double bond as the key group for the activity of this group of 1,2,4-trioxanes and calls for the preparation and antimalarial assessment of corresponding saturated analogues as proof for their mechanism of action, as it is expected that they should be less active. Toward this end, we prepared several saturated analogues (6-arylethyl-1,2,4-trioxanes) and assessed them for their antimalarial efficacy. A graphical representation of the evolution of our work on trioxanes resulting in the current series of molecules is shown in Figure 2. In this article, we report details of this study.

■ CHEMISTRY

Diimide reduction[52−56] of the double bond of 6-arylvinyl-1,2,4-trioxanes **5a−i** using hydrazinium carbazate $(N_2H_3COON_2H_5)$ and 30% H_2O_2 as reported by us earlier[57] furnished 6-arylethyl-1,2,4-trioxanes **6a−i** (less polar or higher R_f) and **7a−i** (more polar or lower R_f) as a mixture of diastereomers in very good yields. (Scheme 3).
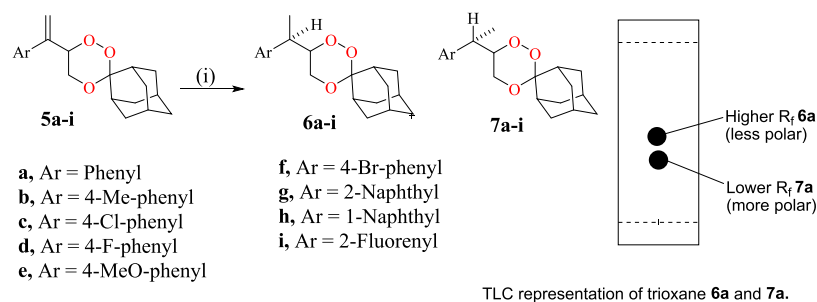
Thus, the reaction of trioxanes **5a−i** with $N_2H_3COON_2H_5$ and 30% H_2O_2 in a 1:1 mixture of THF/EtOH at rt furnished saturated trioxanes **6a−i** (less polar) and **7a−i** (more polar) as a mixture of diastereomers in a ratio of 2:3 in 35−97% yield. The two diastereomers were separated by repeated flash chromatography and characterized separately.

Antimalarial Activity. Parent 6-arylvinyl-1,2,4-trioxanes **5a−i** and their saturated derivatives **6a−i** (less polar) and **7a−i** (more polar) were assessed for their antimalarial activity against multidrug-resistant *P. yoelii nigeriensis* in mice by the oral route using Peter's procedure.[58−60] The activity data of trioxanes **5a−i** against *P. yoelii nigeriensis* have already been reported earlier, but it has been included in the present study just for the sake of comparison.[43,45] In this model, β-arteether **3** provides 100% protection to the mice infected with multidrug-resistant *P. yoelii nigeriensis* at a dose of 48 mg/kg × 4 days via the oral route as all of the treated mice survived beyond day 28. At a dose of 24 mg/kg × 4 days, β-arteether provides only 20% protection to the treated mice. Among the 6-arylvinyl-1,2,4-trioxanes **5a−i** that were initially tested at 96 mg/kg × 4 days orally, double the effective dose of β-arteether, only compounds **5h** and **5i** provided 100% protection and compound **5g** provided 80% protections at this dose. Compound **5i** also provided 100% protection at a dose of 48 mg/kg × 4 days but provided only 80% protection at a dose of 24 mg/kg × 4 days via the oral route. However, compounds **5g** and **5h** provided only 60% protection at a dose of 48 mg/kg × 4 days. Among the saturated trioxanes **6a−i** and **7a−i**, compounds **6a−i** (less polar) and **7i** (more polar) were found effective at a dose of 48 mg/kg × 4 days—the effective dose of β-arteether. Compounds **6c, 6f, 6g, 6h,** and **6i** were found 100% curative even at a dose of 24 mg/kg × 4 days, double the effective dose of β-arteether. Compound **6i** was
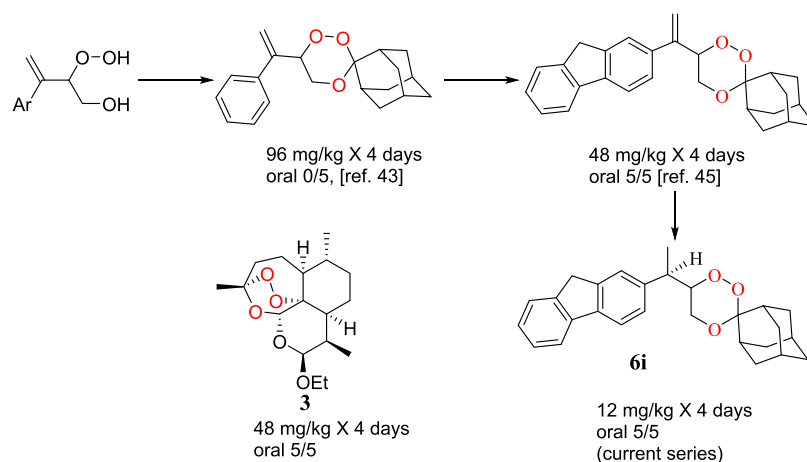
Figure 2. Graphical depiction of the evolution of our work on trioxanes leading to the current series of arylethyl trioxanes.

Scheme 3. Reagents and Reaction Conditions: $N_2H_3COON_2H_5$/30% H_2O_2, EtOH/THF, 0 °C-rt, 9 Days

a, Ar = Phenyl
b, Ar = 4-Me-phenyl
c, Ar = 4-Cl-phenyl
d, Ar = 4-F-phenyl
e, Ar = 4-MeO-phenyl

f, Ar = 4-Br-phenyl
g, Ar = 2-Naphthyl
h, Ar = 1-Naphthyl
i, Ar = 2-Fluorenyl

Higher R_f **6a** (less polar)
Lower R_f **7a** (more polar)

TLC representation of trioxane **6a** and **7a**.

found effective even at a dose of 12 mg/kg × 4 days. Compounds **7a–g** were found less effective at their respective doses at which they were screened. The results are summarized in Table 1.

RESULTS AND DISCUSSION

As seen in Table 1, although several 6-arylvinyl trioxanes **5a–i** prepared by the process as shown in Scheme 1 have shown promising antimalarial activity, a large number of such trioxanes were less effective than β-arteether. 6-Arylethyl-1,2,4-trioxanes showed very surprising results, as, contrary to our expectations, these trioxanes were found far more active than their parent counterparts. The interesting feature about their activity was that the less polar isomer (higher R_f) was far more active in comparison to the more polar isomer (lower R_f), which showed only moderate activity.

Among these 6-arylethyl 1,2,4-trioxanes compounds, **6i** was found to be the most active compound of the series, as it provided 100% clearance of parasitemia when administered at a dose of 48 mg/kg × 4 days, 24 mg/kg × 4 days, and 12 mg/kg × 4 days *via* the oral route. Compound **6i** also provided 20% protection at a dose of 6 mg/kg × 4 days. Its corresponding more polar isomer **7i** also provided 100% protection at a dose of 48 mg/kg × 4 days but showed no protection at a dose of 24 mg/kg × 4 days. Compounds **6c** and **6g–i** were the next most active compounds of the series, as they provided 100% protection to the treated mice at a dose of 24 mg/kg × 4 days. Compounds **6a,b** and **6d,e** showed 100% clearance of parasitemia at a dose of 48 mg/kg × 4 days. Compound **6a** also provided 20% protection to the treated mice at a dose of 24 mg/kg × 4 days.

The corresponding more polar isomers **7a–g** showed only partial to 100% suppression of parasitemia until day four, as compounds **7f** and **7h** provided 100% suppression, but none of the mice survived at a dose of 48 mg/kg × 4 days. Although compounds **7c** and **7g** provided 100 and 99% suppression of parasitemia, respectively, the rest of the compounds **7a,b**, and **7d,e** provided only partial suppression at a dose of 96 mg/kg × 4 days until day four, as none of the mice survived beyond day 28 in all of these cases.

A careful analysis of Table 1 reveals that there is a direct correlation between *in vivo* oral antimalarial activity and log p values in this new series of 6-arylethyl-1,2,4-trioxanes, and the compounds having log p values in the range of 6.74−5.56 are the most active. Recent reports on antimalarial activity have shown that compounds having high log p values are highly active by the oral route.[49] Compound **6i**, the most active compound of the series, having the highest log p value of 6.74 provided 100% protection at a dose of 12 mg/kg × 4 days, while the next best compounds **6g** and **6h** having a log p value of 6.00, compound **6f** having a log p value of 5.84, and compound **6c** having a log p value of 5.56 provided 100% protection at a dose of 24 mg/kg × 4 days.

Compounds that have relatively small log p values, for example, compound **6b** having a log p value of 5.49, compound **6d** having a log p value of 5.16, compound **6a** having a log p value of 5.01, and compound **6e** having a log p value of 4.88 exhibited 100% clearance of parasitemia only at a dose of 48 mg/kg × 4 days and none of the compounds provided 100% protection at a dose of 24 mg/kg × 4 days.

Analysis of Table 1 also shows that the saturated derivatives have log p values higher than that of their parent unsaturated counterparts; for example, compound **5a** has a log p value of

Table 1. Comparative Oral Antimalarial Activity of 6-Arylvinyl-1,2,4-trioxanes 5a−i versus 6-Arylethyl-1,2,4-trioxanes 6a−i and 7a−i against Multidrug-Resistant *P. yoelii nigeriensis* in Swiss Mice[a]
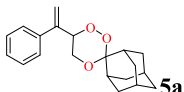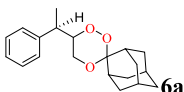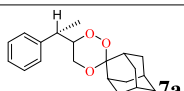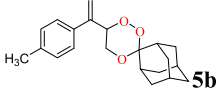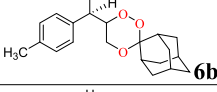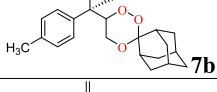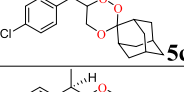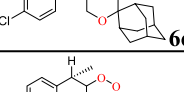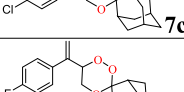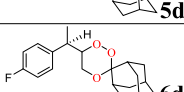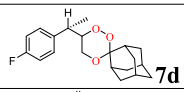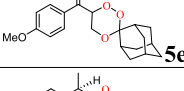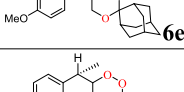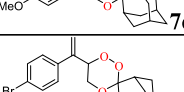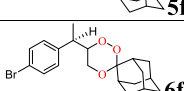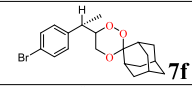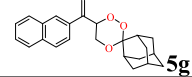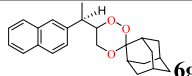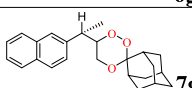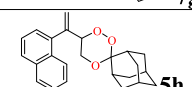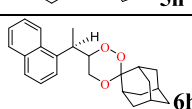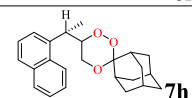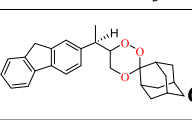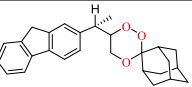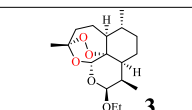
Compound	Log P	Dose mg/kg	% Suppression on day 4[a]	Mice alive on day 28
5a	4.65	96	96	0/5
6a	5.01	96 48 24 12	100 100 100 100	5/5 5/5 1/5 0/5
7a	5.01	96	40	0/5
5b	5.14	96	95	0/5
6b	5.49	48 24	100 96	5/5 0/5
7b	5.49	96	32	0/5
5c	5.21	96	100	0/5
6c	5.56	48 24 12	100 100 100	5/5 5/5 2/5
7c	5.56	96	100	0/5
5d	4.81	96	99	0/5
6d	5.16	48 24 12	100 100 100	5/5 0/5 0/5
7d	5.16	96	33	0/5
5e	4.53	96	99	0/5
6e	4.88	48 24 12	100 100 82	5/5 0/5 0/5
7e	4.88	96	11	0/5
5f	5.48	96	99	0/5
6f	5.84	48 24 12	100 100 100	5/5 5/5 0/5

Table 1. continued

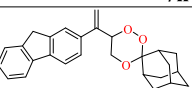| Compound	Log P	Dose mg/kg	% Suppression on day 4[a]	Mice alive on day 28
7f	5.84	48	100	0/5
5g	5.65	96 48	100 100	4/5 3/5
6g	6.00	48 24 12	100 100 100	5/5 5/5 3/5
7g	6.00	96	99	0/5
5h	5.65	96 48	100 100	5/5 3/5
6h	6.00	48 24 12	100 100 100	5/5 5/5 0/5
7h	6.00	48	100	0/5
5i	6.39	96 48 24	100 100 100	5/5 5/5 4/5
6i	6.74	48 24 12 6	100 100 100 100	5/5 5/5 5/5 1/5
7i	6.74	48 24	100 100	5/5 0/5
3	3.84	48 24	100 100	5/5 1/5

[a]Percent suppression = $[(C - T)/C] \times 100$, where C = parasitemia in the control group and T = parasitemia in the treated group. The drug dilutions of compounds were prepared in groundnut oil and administered to a group of mice at each dose, from day 0 to 3 in two divided doses daily. log p values have been calculated using ChemDraw Professional 15.1.

4.65, while its saturated derivatives **6a** and **7a** have a log p value of 5.01. A similar pattern is observed in the rest of the compounds as well. This could be one of the reasons for their increased activity in comparison to their parent trioxanes. The difference in activity of the two diastereomers is still uncertain and could be due to certain unknown stereochemical factors, as there are numerous reports in the literature where one isomer has been found active and the other less active or sometimes even toxic.[61]

These observations also indicated that the mechanism of action for antimalarial activity, certainly not in the case of 6-arylvinyl-1,2,4-trioxanes but at least in the case of 6-arylethyl 1,2,4-trioxanes, is not by the process as shown in Scheme 2.

■ CONCLUSIONS

In conclusion, in our efforts to assess the role of the double bond of 6-arylvinyl-1,2,4-trioxanes toward antimalarial activity, we have prepared a new series of saturated 1,2,4-trioxanes using the chemistry of the double bond and studied their structure–activity relationship. Several of these trioxanes (**6a–i**) have shown a better activity profile than the parent trioxanes **5a–i**. The trioxane **6i**, the most active compound of the series, has four times better oral antimalarial activity than that of the clinically used drug, β-arteether. Hopefully, the outcome of our finding, the antimalarial activity of current trioxanes by oral route, helps scientists in finding the better drug candidate in fighting against malaria.

■ EXPERIMENTAL SECTION

General. All glass apparatus were oven-dried prior to use. Melting points were determined in open capillaries on a complab melting-point apparatus and are uncorrected. Infrared spectra were recorded on a PerkinElmer Fourier transform infrared (FT-IR) RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Supercon Magnet DRX-300 spectrometer (operating at 300 MHz for ^{1}H and 75

MHz for ^{13}C) using CDCl$_3$ as the solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and CDCl$_3$ (δ 77.23 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). In NMR, the numbering of atoms is presented according to the usual numbering in artemisinin, as indicated in the text. Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as the matrix. Electrospray mass spectrometry (ES-MS) was performed on a Micromass Quattro II triple quadrupole mass spectrometer. High-resolution electron impact mass spectra (HR-EIMS) were obtained on a JEOL MS route 600H instrument. Elemental analyses were performed on a Vario EL-III CHNS analyzer (Germany) and values were within ±0.4% of the calculated values except where noted. Column chromatography was performed over Merck silica gel (particle size: 60−120 mesh) procured from Qualigens (India) and flash silica gel (particle size: 230−400 mesh). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. log *p* values of the compounds were calculated using ChemDraw Ultra 15.1 software. The purity of final tested compounds was typically determined to be >95% by elemental analysis.

Procedure for the Preparation of a Hydrazinium Carbazate Solution. In an ice-cooled hydrazine hydrate (N$_2$H$_4$·H$_2$O, 103 g, 2.06 mol), a slow stream of CO$_2$ gas was bubbled until the weight of the reaction mixture became constant (150 g, which corresponds to a 2:1 adduct of N$_2$H$_4$·H$_2$O and CO$_2$). One gram of this highly viscous material (density 1.45) was dissolved in 100 mL of water for the measurement of pH, which was found to be 7.51, while the pH value of 1% aqueous solution of N$_2$H$_4$·H$_2$O was found to be 9.79.

General Procedure for Diimide Reduction of 1,2,4-Trioxanes Using Hydrazinium Carbazate (N$_2$H$_3$COON$_2$H$_5$) and 30% H$_2$O$_2$. Reduction of 1,2,4-trioxane **5a** as a representative: to a stirred and ice-cooled solution of trioxane **5a** (3.00 g, 9.62 mmol) and hydrazinium carbazate (9.55 mL, 10 equiv) in a 1:1 mixture of EtOH/tetrahydrofuran (THF) (150 mL) was added 30% H$_2$O$_2$ (32.69 mL, 30 equiv) dropwise over 30 min, and the reaction mixture was allowed to stir at rt for 9 days. The reaction mixture was concentrated under vacuum, diluted with water (20 mL), and extracted with ether (2 × 150 mL). The combined organic extract was washed successively with 10% HCl (30 mL), water (30 mL), and with saturated aqueous NaHCO$_3$ (30 mL), dried over anhydrous Na$_2$SO$_4$, concentrated under vacuum, and the crude product was purified by column chromatography over silica gel to furnish saturated trioxanes **6a** and **7a** (2.92 g, 97% yield) as a mixture of diastereomers in approximately 2:3 ratio, which on flash chromatography using the eluent EtOAc/hexane (1:9) furnished the pure isomers **6a** (less polar, oil) and **7a** (more polar, white solid, mp 84−85 °C).

(1S,3S,5S,6′S,7S)-6′-((R)-1-Phenylethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6a). Yield (1.17 g, 39%) as an oil; FT-IR (neat cm^{-1}) 763, 1025, 1117, 1223, 1602, 2914; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.39 (d, 3H, *J* = 6.9 Hz), 1.59−2.05 (m, 13H), 2.76 (quin, 1H, *J* = 6.9 Hz), 2.81 (s, 1H), 3.34 (dd, 1H, *J* = 11.8 & 2.6 Hz), 3.62 (dd, 1H, *J* = 11.8 & 9.6

Hz), 4.35 (dt, 1H, *J*=9.6 & 2.6 Hz) 7.18−7.35 (m, 5H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.63 (CH$_3$), 27.38 (2 × CH), 30.10 (CH), 33.24 (CH$_2$), 33.48 (CH$_2$), 33.66 (2 × CH$_2$), 35.72 (CH), 37.44 (CH$_2$), 40.96 (CH), 61.22 (CH$_2$), 83.30 (CH), 104.52 (C), 127.25 (CH), 127.80 (2 × CH), 128.93 (2 × CH), 142.03 (C); FAB-MS (*m/z*) 315 [M + H]$^+$; EI-HRMS calcd for C$_{20}$H$_{26}$O$_3$ [M$^+$]: 314.1882. Found: 314.1829; Anal. Calcd for C$_{20}$H$_{26}$O$_3$: %C 76.40, %H 8.34. Found: %C 76.50, %H 8.40; purity 99.81%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-Phenylethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7a). Yield (1.75 g, 58%) as a white solid, mp 84−85 °C; FT-IR, (KBr cm^{-1}) 759, 1029, 1086, 1113, 1219, 1604, 2914; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.29 (d, 3H, *J* = 7.2 Hz), 1.55−2.08 (m, 13H), 2.77 (s, 1H), 2.87 (quin, 1H, *J* = 7.2 Hz), 3.77 (dd, 1H, *J* =11.6, 3.4 Hz), 3.83 (dd, 1H, *J* = 11.6 & 9.6 Hz), 4.35 (ddd, 1H, *J* = 9.6, 7.6, & 3.4 Hz) 7.23−7.35 (m, 5H, Ar); ^{13}C NMR (75 MHz,CDCl$_3$) δ 17.53 (CH$_3$), 27.29 (CH), 27.33 (CH), 29.69 (CH), 33.19 (CH$_2$), 33.34 (CH$_2$), 33.56 (CH$_2$), 33.67 (CH$_2$), 36.10 (CH), 37.39 (CH$_2$), 40.74 (CH), 60.88 (CH$_2$), 82.55 (CH), 104.60 (C), 126.92 (CH), 127.82 (2 × CH), 128.66 (2 × CH), 142.45 (C); FAB-MS (*m/z*) 315 [M + H]$^+$; EI-HRMS calcd for C$_{20}$H$_{26}$O$_3$ [M$^+$]: 314.1882. Found: 314.1839; Anal. Calcd for C$_{20}$H$_{26}$O$_3$: %C 76.40, %H 8.33. Found: %C 76.47, %H 8.45; purity 99.78%.

The unsaturated trioxanes **5b−i** were also reduced by the same procedure to furnish the corresponding saturated trioxanes **6b−i** and **7b−i** as a mixture of diastereomers, which were separated by flash chromatography.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(p-Tolyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6b). Yield (1.12 g, 37%) as an oil; FT-IR (neat cm^{-1}) 766, 1003, 1028, 1602, 2914; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.32 (d, 3H, *J* = 6.9 Hz), 1.54−1.97 (m, 13H), 2.29 (s, 3H), 2.70 (quin, 1H, *J* = 6.9 Hz), 2.76 (s, 1H), 3.30 (dd, 1H, *J* = 11.8, 2.8 Hz), 3.56 (dd, 1H, *J* = 11.8 & 9.5 Hz), 4.28 (dt, 1H, *J* = 9.5 & 2.8 Hz), 7.02 (dd, 2H, *J* = 8.1 Hz, Ar), 7.08 (dd, 2H, *J* = 8.1 Hz, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.82 (CH$_3$), 21.23 (CH$_3$), 27.35 (2 × CH), 29.99 (CH), 33.22 (CH$_2$), 33.46 (CH$_2$), 33.65 (2 × CH$_2$), 35.77 (CH), 37.41 (CH$_2$), 40.54 (CH), 61.29 (CH$_2$), 83.37 (CH), 104.47 (C), 127.64 (2 × CH), 129.60 (2 × CH), 136.83 (C), 138.92 (C); FAB-MS (*m/z*) 329 [M + H]$^+$; EI-HRMS calcd for C$_{21}$H$_{28}$O$_3$ [M$^+$]: 328.2039. Found: 328.2039; Anal. Calcd for C$_{21}$H$_{28}$O$_3$: %C 76.79, %H 8.59. Found: %C 76.88, %H 8.81; purity 99.63%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(p-Tolyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7b). Yield (1.68 g, 56%) as a white solid, mp 74−76 °C; FT-IR, (KBr cm^{-1}) 767, 1041, 1216, 1636, 2926; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.27 (d, 3H, *J* =7.3 Hz), 1.55−2.08 (m, 13H), 2.35 (s, 3H), 2.78 (s, 1H), 2.84 (quin, 1H, *J*=7.3 Hz), 3.76 (dd, 1H, *J* =11.6 & 3.4 Hz), 3.83 (dd, 1H, *J* =11.6 & 9.6 Hz), 4.47 (ddd, 1H, 9.6, 7.7, & 3.4 Hz) 7.13 (s, 4H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 17.62 (CH$_3$), 21.23 (CH$_3$), 27.38 (CH), 27.42 (CH), 29.80 (CH), 33.27 (CH$_2$), 33.40 (CH$_2$), 33.62 (CH$_2$), 33.74 (CH), 36.17 (CH), 37.48 (CH$_2$), 40.41 (CH), 60.95 (CH$_2$), 82.69 (CH), 104.59 (C), 127.71 (2 × CH), 129.40 (2 × CH), 136.42 (C), 139.47 (C); FAB-MS (*m/z*) 329 [M + H]$^+$; EI-HRMS calcd for C$_{21}$H$_{28}$O$_3$ [M$^+$]: 328.2039. Found: 328.2018; Anal. Calcd for C$_{21}$H$_{28}$O$_3$: %C 76.79, %H 8.59. Found: %C 76.82, %H 8.68; purity 99.85%.

(S,3S,5S,6′S,7S)-6′-((R)-1-(4-Chlorophenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6c). Yield (1.14 g, 38%)

as a white solid, mp 92−94 °C; FT-IR (KBr cm⁻¹) 768, 1091, 1112, 1217, 1655, 29117; ¹H NMR (300 MHz, CDCl₃) δ 1.36 (d, 3H, J = 6.9 Hz), 1.59−2.03 (m, 13H), 2.76 (s, 1H), 2.81 (quin, 1H, J = 6.9 Hz), 3.36 (dd, 1H, J = 11.8 & 2.5 Hz), 3.59 (dd,1H, J = 11.7 & 9.4 Hz), 4.28 (dt, 1H, J = 9.1 & 2.3 Hz), 7.13 (d, 2H, J = 8.4 Hz, Ar), 7.29 (d, 2H, J = 8.4 Hz, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 18.49 (CH₃), 27.31 (2 × CH), 30.19 (CH), 33.20 (CH₂), 33.42 (CH₂), 33.60 (2 × CH₂), 35.52 (CH), 37.36 (CH₂), 40.28 (CH), 60.90 (CH₂), 82.96 (CH), 104.62 (C), 129.08 (2 × CH), 129.14 (2 × CH), 132.95 (C), 140.56 (C); FAB-MS (m/z) 349 [M + H⁺]; EI-HRMS calcd for C₂₀H₂₅ClO₃ [M⁺]: 348.1492. Found: 348.1429; Anal. Calcd for C₂₀H₂₅ClO₃: %C 68.86, %H 7.22. Found: %C 68.99, %H 7.34; purity 99.67%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(4-Chlorophenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7c). Yield (1.72 g, 57%) as a white solid, mp 114−115 °C; FT-IR, (KBr cm⁻¹) 772, 1089, 1113, 1220, 1636, 2918; ¹H NMR (300 MHz, CDCl₃) δ 1.26 (d, 3H, J = 7.2 Hz), 1.55−2.06 (m, 13H), 2.72 (s, 1H), 2.85 (quin, 1H, J = 7.2 Hz), 3.78−3.80 (m, 2H), 4.41 (brddd, 1H), 7.16 (d, 2H, J = 8.3 Hz, Ar), 7.29 (d, 2H, J = 8.3 Hz, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 17.68 (CH₃), 27.31 (CH), 27.35 (CH), 29.90 (CH), 33.23 (CH₂), 33.35 (CH₂), 33.56 (CH₂), 33.68 (CH), 35.94 (CH), 37.40 (CH₂), 40.18 (CH), 60.87 (CH₂), 82.45 (CH), 104.72 (C), 128.81 (2 × CH), 129.22 (2 × CH), 132.66 (C), 141.06 (C); FAB-MS (m/z) 349 [M + H⁺]; EI-HRMS calcd for C₂₀H₂₅ClO₃ [M⁺]: 348.1492. Found: 348.1438; Anal. Calcd for C₂₀H₂₅ClO₃: %C 68.86, %H 7.22. Found: %C 68.98, %H 7.34; purity 99.68%.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(4-Fluorophenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6d). Yield (1.11 g, 37%) as an oil; FT-IR (neat cm⁻¹) 772, 1111, 1653, 2925; ¹H NMR (300 MHz, CDCl₃) δ 1.35 (d, 3H, J = 6.9 Hz), 1.57−2.02 (m, 13H), 2.75 (s, 1H), 2.78 (brquin, 1H), 3.32 (dd, 1H, J = 11.8 & 2.6 Hz), 3.58 (dd,1H, J = 11.8 & 9.3 Hz), 4.26 (dt, 1H, J = 9.3, 2.6 Hz) 6.96−7.16 (m, 4H, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 18.63 (CH₃), 27.36 (2 × CH), 30.15 (CH), 33.24 (CH₂), 33.47 (CH₂), 33.65 (2 × CH₂), 35.62 (CH), 37.41 (CH₂), 40.17 (CH), 61.01 (CH₂), 83.19 (CH), 104.62 (C), 115.76 (d, 2 × CH, J_{C-F} = 21 Hz), 129.24 (d, 2 × CH, J_{C-F} = 7.5 Hz), 137.79 (C), 162.04 (d, C, J_{C-F} = 244 Hz); FAB-MS (m/z) 333 [M + H⁺]; EI-HRMS calcd for C₂₀H₂₅O₃F [M⁺]: 332.1788. Found: 332.1786. Anal. Calcd for C₂₀H₂₅FO₃: %C 72.27, %H 7.58. Found: %C 72.47, %H 7.64; purity 99.67%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(4-Fluorophenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7d). Yield (1.66 g, 55%) as a white solid, mp 80−81 °C; FT-IR, (KBr cm⁻¹) 767, 1113, 1637, 2923; ¹H NMR (300 MHz, CDCl₃) δ 1.26 (d, 3H, J = 7.2 Hz), 1.55−2.07 (m, 13H), 2.73 (s, 1H), 2.86 (quin, 1H, J = 7.2 Hz) 3.73−3.85 (m, 2H,), 4.41 (brddd,1H), 6.98−7.21 (m, 4H, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 17.73 (CH₃), 27.26 (CH), 27.30 (CH), 29.76 (CH), 33.16 (CH₂), 33.30 (CH₂), 33.52 (CH₂), 33.64 (CH₂), 35.97 (CH), 37.35 (CH₂), 39.97 (CH), 60.85 (CH₂), 82.53 (CH), 104.64 (C), 115.42 (2 × CH, d, J_{C-F} = 21 Hz), 129.24 (d, 2 × CH, J_{C-F} = 7.5 Hz), 138.16 (d, C, J_{C-F} = 3 Hz), 161.84 (d, C, J_{C-F} = 242 Hz); FAB-MS (m/z) 333 [M + H]⁺; EI-HRMS calcd for C₂₀H₂₅O₃F [M⁺]: 332.1788. Found: 332.1781. Anal. Calcd for C₂₀H₂₅FO₃: %C 72.27, %H 7.58. Found: %C 72.48, %H 7.72; purity 99.78%.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(4-Methoxyphenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6e). Yield (1.13 g, 37%) as an oil; FT-IR (neat cm⁻¹) 772, 1115, 1635, 1602, 2928; ¹H

NMR (300 MHz, CDCl₃) δ 1.34 (d, 3H, J = 6.9 Hz), 1.53−2.03 (m, 13H), 2.72 (quin, 1H, J = 6.9 Hz), 2.76 (s, 1H), 3.32 (dd, 1H, J = 11.8 & 2.9 Hz), 3.58 (dd, 1H, J = 11.8 & 9.5 Hz), 3.78 (s, 3H), 4.26 (dt, 1H, J = 9.5 & 2.9 Hz), 6.83 (d, 2H, J = 8.6 Hz, Ar), 7.08 (d, 2H, J = 8.6 Hz, Ar); ¹³C NMR (75 MHz,CDCl₃) δ 18.82 (CH₃), 27.34 (2 × CH), 29.91 (CH), 33.21 (CH₂), 33.45 (CH₂), 33.64 (2 × CH₂), 35.82 (CH), 37.40 (CH₂), 40.08 (CH), 55.46 (CH₃), 61.26 (CH₂), 83.44 (CH), 104.45 (C), 114.28 (2 × CH), 128.70 (2 × CH), 133.97 (C), 158.75 (C); FAB-MS (m/z) 345 [M + H⁺]; EI-HRMS calcd for C₂₁H₂₈O₄ [M⁺]: 344.1988. Found: 344.1988; Anal. Calcd for C₂₁H₂₈O₄: %C 73.23, %H 8.19. Found: % C 73.30, %H 8.40; purity 99.65%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(4-Methoxyphenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7e). Yield (1.70 g, 57%) as a white solid, mp 60−62 °C; FT-IR, (KBr cm⁻¹) 757, 1033, 1113, 1612, 2913; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (d, 3H, J = 7.2 Hz), 1.52−2.04 (m, 13H), 2.73 (s, 1H), 2.80 (quin, 1H, J = 7.2 Hz), 3.71 (dd, 1H, J = 11.6, 3.4 Hz), 3.78 (s, 3H), 3.78−3.81 (dd merged, 1H), 4.41 (ddd, 1H, J = 10.6, 7.6, & 3.4 Hz), 6.84 (d, 2H, J = 8.7 Hz, Ar) 7.12 (d, 2H, J = 8.7 Hz, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 17.68 (CH₃), 27.34 (CH), 27.37 (CH), 29.73 (CH), 33.23 (CH₂), 33.37 (CH₂), 33.59 (CH₂), 33.71 (CH₂), 36.15 (CH), 37.44 (CH₂), 39.96 (CH), 55.43 (CH₃), 60.91 (CH₂), 82.72 (CH), 104.57 (C), 114.10 (2 × CH), 128.78 (2 × CH), 134.51 (C), 158.55 (C); FAB-MS (m/z) 345 [M + H⁺]; EI-HRMS calcd for C₂₁H₂₈O₄ [M⁺]: 344.1988. Found: 344.1988; Anal. Calcd for C₂₁H₂₈O₄: %C 73.23, %H 8.19. Found: % C 73.40, %H 8.52; purity 99.38%.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(4-Bromophenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6f). Yield (1.14 g, 38%) as a white solid, mp 115−116 °C; FT-IR (KBr cm⁻¹) 772, 1115, 1635, 1602, 2928; ¹H NMR (300 MHz, CDCl₃) δ 1.36 (d, 3H, J = 6.7 Hz), 1.58−2.02 (m, 13H), 2.76 (brm, 2H), 3.35 (dd, 1H, J = 11.7 & 1.9 Hz), 3.59 (dd, 1H, J = 11.7 & 9.3 Hz), 4.28 (dt, 1H, J = 9.3 & 1.9 Hz), 7.07 (d, 2H, J = 8.4 Hz, Ar), 7.44 (d, 2H, J = 8.4 Hz, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 18.43 (CH₃), 27.30 (2 × CH), 30.16 (CH), 33.20 (CH₂), 33.41 (CH₂), 33.59 (2 × CH₂), 35.55 (CH), 37.35 (CH₂), 40.33 (CH), 60.88 (CH₂), 82.87 (CH), 104.61 (C), 120.99 (C), 129.52 (2 × CH), 132.02 (2 × CH), 141.08 (C); ES-MS (m/z) 393 [M + H⁺]; EI-HRMS calcd for C₂₀H₂₅O₃Br [M⁺]: 392.0987. Found: 392.0947; Anal. Calcd for C₂₀H₂₅O₃Br: %C 61.07, %H 6.41. Found: %C 61.23, %H 6.61; purity 99.46%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(4-Bromophenyl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7f). Yield (1.72 g, 57%) as a white solid, mp 130−131 °C; FT-IR (KBr cm⁻¹) 782, 1074, 1112, 1594, 2930; ¹H NMR (300 MHz, CDCl₃) δ 1.25 (d, 3H, J = 7.2 Hz), 1.45−2.07 (m, 13H), 2.72 (s, 1H), 2.75 (quin, 1H, J = 7.2 Hz), 3.74−3.84 (m, 2H), 4.41 (brddd, 1H), 7.44 (d, 2H, J = 8.4 Hz, Ar), 7.44 (d, 2H, J = 8.4 Hz, Ar); ¹³C NMR (75 MHz, CDCl₃) δ 17.57 (CH₃), 27.28 (CH), 27.33 (CH), 29.91 (CH), 33.20 (CH₂), 33.32 (CH₂), 33.53 (CH₂), 33.64 (CH₂) 35.88 (CH), 37.37 (CH₂), 40.19 (CH), 60.79 (CH₂), 82.35 (CH), 104.65 (C), 120.70 (C), 129.58 (2 × CH), 131.70 (2 × CH), 141.58 (C); ES-MS (m/z) 393 [M + H]⁺; EI-HRMS calcd for C₂₀H₂₅O₃Br [M⁺]: 392.0987. Found: 392.0987; Anal. Calcd for C₂₀H₂₅O₃Br: % C 61.07, %H 6.41. Found: %C 61.26, %H 6.42; purity 99.70%.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(Naphthalen-2-yl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6g). Yield (1.09 g, 36%) as a white solid, mp 120−121 °C; FT-IR (KBr cm⁻¹) 761, 1109, 1624, 2921; ¹H NMR (300 MHz, CDCl₃) δ 1.48 (d, 3H,

J = 6.9 Hz), 1.61−2.08 (m, 13H), 2.83 (s, 1H), 2.83 (brquin, 1H), 3.36 (dd, 1H, J = 11.8 & 2.5 Hz), 3.66 (dd,1H, J = 11.8 & 9.4 Hz), 4.47 (dt, 1H, J = 9.4 & 2.5 Hz) 7.34 (dd, 1H, J = 8.5 & 1.6 Hz, Ar), 7.47−7.49 (m, 2H, Ar), 7.64 (s, 1H, Ar), 7.79-7.84 (m, 3H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.78 (CH$_3$), 27.37 (2 × CH), 30.18 (CH), 33.25 (CH$_2$), 33.49 (CH$_2$), 33.65 (2 × CH$_2$), 35.66 (CH), 37.42 (CH$_2$), 41.07 (CH), 61.22 (CH$_2$), 83.21 (CH), 104.58 (C), 125.75 (CH), 125.92 (CH), 126.41 (CH), 126.58 (CH), 127.80 (CH), 127.84 (CH), 128.73 (CH), 132.80 (C), 133.73 (C), 139.50 (C); FAB-MS (m/z) 365 [M + H$^+$]; EI-HRMS calcd for C$_{24}$H$_{28}$O$_3$ [M$^+$]: 364.2039. Found: 364.2007; Anal. Calcd for C$_{24}$H$_{28}$O$_3$: %C 79.09, %H 7.74. Found: %C 79.21, %H 7.81; purity 99.78%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(Naphthalen-2-yl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7g). Yield (1.64 g, 55%) as a white solid, mp 130−131 °C; FT-IR, (KBr cm^{-1}) 750, 1113, 1636, 2914; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.38 (d, 3H, J = 7.2 Hz), 1.54−2.07 (m, 13H), 2.77 (s, 1H), 3.05 (quin, 1H, J = 7.2 Hz), 3.80 (dd, 1H, J = 11.7 & 3.6 Hz), 3.87 (dd, 1H, J = 11.7 & 9.5 Hz), 4.60 (ddd, 1H, J = 9.5, 7.6, & 3.6 Hz) 7.41 (dd, 1H, J = 8.6 & 1.7 Hz), 7.44−7.50 (m, 2H, Ar), 7.66 (s, 1H, Ar), 7.79−7.83 (m, 3H, Ar); ^{13}C NMR (75 MHz,CDCl$_3$) δ 17.80 (CH$_3$), 27.32 (2 × CH), 29.70 (CH), 33.22 (CH$_2$), 33.34 (CH$_2$), 33.57 (CH$_2$), 33.69 (CH$_2$), 36.13 (CH), 37.38 (CH$_2$), 41.00 (CH), 61.04 (CH$_2$), 82.60 (CH), 104.68 (C), 125.70 (CH), 126.12 (CH), 126.16 (CH), 126.50 (CH), 127.80 (CH), 127.90 (CH), 128.40 (CH), 132.72 (C), 133.67 (C), 139.97 (C); FAB-MS (m/z) 365 [M + H$^+$]; EI-HRMS calcd for C$_{24}$H$_{28}$O$_3$ [M$^+$]: 364.2039. Found: 364.2046; Anal. Calcd for C$_{24}$H$_{28}$O$_3$: %C 79.09, %H 7.74. Found: %C 79.29, %H 7.87; purity 99.62%.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(Naphthalen-1-yl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6h). Yield (0.422 g, 14%) as an oil; FT-IR (neat cm^{-1}) 776, 1122, 1655, 2917; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.54 (d, 3H, J = 6.8 Hz), 1.61−2.12 (m, 13H), 2.87 (s, 1H), 3.42 (brdd, 1H), 3.62 (dd, 1H, J = 11.8 & 9.8 Hz), 3.76 (brquin, 1H) 4.63 (brdt, 1H) 7.46−7.59 (m, 4H, Ar), 7.75−7.79 (m, 1H, Ar), 7.88 (d, 1H, J = 1.5 Hz, Ar), 8.01 (d, 1H, J = 6.5 Hz, Ar), ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.98 (CH$_3$), 27.30 (CH), 27.35, (CH), 30.29 (CH), 33.21 (CH$_2$), 33.46 (CH$_2$), 33.59 (CH$_2$), 33.62 (CH$_2$), 33.62 (CH), 35.49 (CH), 37.38 (CH$_2$), 60.92 (CH$_2$), 83.91 (CH), 104.61 (C), 122.96 (CH), 124.46 (CH), 125.78 (2 × CH), 126.39 (CH), 127.52 (CH), 129.27 (CH), 131.75 (C), 134.20 (C), 138.66 (C); ESI-MS (m/z) 365 [M + H$^+$]; EI-HRMS calcd for C$_{24}$H$_{28}$O$_3$ [M$^+$]: 364.2039. Found: 364.2038; Anal. Calcd for C$_{24}$H$_{28}$O$_3$: %C 79.09, %H 7.74. Found: %C 79.29, %H 7.77; purity 99.73%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(Naphthalen-1-yl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7h). Yield (0.633 g, 21%) as a white solid, mp 120−122 °C; FT-IR, (KBr cm^{-1}) 776, 1029, 1113, 1597, 2915; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.42 (d, 3H, J = 7.2 Hz), 1.56−2.08 (m, 13H), 2.85 (s, 1H), 3.75 (dd, 1H, J = 11.6 & 2.9 Hz), 3.88 (quin, 1H, J = 7.2 Hz) 3.98 (dd, 1H, J = 11.6 & 10.1 Hz), 4.77 (ddd, 1H, J = 10.1, 7.3, & 2.9 Hz) 7.46−8.11 (m, 7H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.87 (CH$_3$), 27.33 (CH), 27.38, (CH), 29.83 (CH), 33.25 (CH$_2$), 33.39 (CH$_2$), 33.60 (CH$_2$), 33.72 (CH$_2$), 34.70 (CH), 36.15 (CH), 37.43 (CH$_2$), 60.53 (CH$_2$), 81.90 (CH), 104.66 (C), 123.06 (CH), 124.05 (CH), 125.62 (CH), 125.68 (CH), 126.25 (CH), 127.47 (CH), 129.23 (CH), 131.90 (C), 134.23 (C), 138.11 (C); ESI-MS (m/z) 365 [M + H$^+$]; EI-HRMS

calcd for C$_{24}$H$_{28}$O$_3$ [M$^+$]: 364.2039. Found: 364.2042; Anal. Calcd for C$_{24}$H$_{28}$O$_3$: %C 79.09, %H 7.74. Found: %C 79.30, %H 7.85; purity 99.63%.

(1S,3S,5S,6′S,7S)-6′-((R)-1-(9H-Fluoren-2-yl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (6i). Yield (1.08 g, 36%) as a white solid, mp 133−135 °C; FT-IR (KBr cm^{-1}) 768, 1091, 1115, 1599, 2910; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.45 (d, 3H, J = 6.9 Hz), 1.61−2.09 (m, 13H), 2.84 (s, 1H), 2.87 (brquin, 1H), 3.40 (dd, 1H, J = 11.9, 2.7 Hz), 3.66 (dd, 1H, J = 11.9 & 9.5 Hz), 3.89 (s, 2H) 4.41 (dt, 1H, J = 9.5 & 2.7 Hz), 7.19−7.14 (m, 4H, Ar), 7.56−7.54 (m, 1H, Ar), 7.79−7.71 (m, 2H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.94 (CH$_3$), 27.41 (2 × CH), 30.15 (CH), 33.28 (CH$_2$), 33.52 (CH$_2$), 33.69 (2 × CH$_2$), 35.77 (CH), 37.07 (CH$_2$), 37.46 (CH$_2$) 41.09 (CH), 61.29 (CH$_2$), 83.45 (CH), 104.56 (C), 119.99 (CH), 120.24 (CH), 124.36 (CH), 125.25 (CH), 126.55 (CH), 126.87 (CH), 126.99 (CH), 140.74 (C), 140.98 (C), 141.61 (C), 143.41 (C), 144.06 (C); ESI-MS (m/z) 425 [M + Na$^+$]; EI-HRMS calcd for C$_{27}$H$_{30}$O$_3$ [M$^+$]: 402.2195. Found: 402.2194; Anal. Calcd for C$_{27}$H$_{30}$O$_3$: %C 80.56, %H 7.51. Found: %C 80.76, %H 7.90; purity 99.33%.

(1S,3S,5S,6′S,7S)-6′-((S)-1-(9H-Fluoren-2-yl)ethyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (7i). Yield (1.62 g, 54%) as a white solid, mp 136−138 °C; FT-IR (KBr cm^{-1}) 739, 1086, 1113, 1596, 2912; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34 (d, 3H, J = 7.3 Hz), 1.59−2.03 (m, 13H), 2.77 (s, 1H), 2.95 (quin, 1H, J = 7.3 Hz), 3.79 (dd, 1H, J = 11.7 & 3.6 Hz), 3.85 (dd merged, 1H), 3.89 (s, 2H), 4.54 (ddd, 1H, J = 9.4, 7.7, & 3.6 Hz) 7.23−7.42 (m, 4H, Ar), 7.53−7.55 (m, 1H, Ar), 7.57−7.78 (m, 2H, Ar); ^{13}C NMR (75 MHz, CDCl$_3$) δ 17.89 (CH$_3$), 27.38 (2 × CH), 29.82 (CH), 33.28 (CH$_2$), 33.41 (CH$_2$), 33.63 (CH$_2$), 33.75 (CH$_2$), 36.19 (CH), 37.12 (CH$_2$), 37.47 (CH$_2$) 41.02 (CH), 61.03 (CH$_2$), 82.76 (CH), 104.67 (C), 119.94 (CH), 120.04 (CH), 124.51 (CH), 125.20 (CH), 126.60 (CH), 126.68 (CH), 126.91 (CH), 140.72 (C), 141.24 (C), 141.84 (C), 143.49 (C), 143.79 (C); ESI-MS (m/z) 403 [M + H$^+$]; EI-HRMS calcd for C$_{27}$H$_{30}$O$_3$ [M$^+$]: 402.2195. Found: 402.2196; Anal. Calcd for C$_{27}$H$_{30}$O$_3$: %C 80.56, %H 7.51. Found: %C 80.92, %H 7.81; purity 99.25%.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05041.

^{1}H NMR and ^{13}C NMR spectra of compounds **6a−i** and **7a−i** (PDF)

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Notes

The authors declare no competing financial interest.

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(58) (a) Peters, W. Techniques for the Study of Drug Response in Experimental Malaria. In *Chemotherapy and Drug Resistance in Malaria*; Academic Press, London, 1970; pp 64−136. (b) *In vivo* test procedure: The colony bred Swiss mice (25 ± 1 g) were inoculated with 1×10^6 parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0 to 3, in two divided doses daily. The drug dilutions of compounds **5a-i**, **6a-i** and **7a-i** were prepared in groundnut oil so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg, 0.6 mg for a dose of 48 mg/kg, 0.3 mg for a dose of 24 mg/kg, 0.15 mg for a dose of 12 mg/kg and 0.075 mg for a dose of 6 mg/kg) in 0.1 ml and administered orally for each dose. Parasitemia level were recorded from thin blood smears between day 4-28. The treated mice surviving beyond day 28 were recorded as the mice protected by the drug. Mice treated with β-Arteether served as positive controls.

(59) (a) 100% suppression of parasitemia means, number of parasites if at all present, is below the detection limit. The parasites present below the detection limit can multiply and eventually can be detected. In such cases though the drug is providing near 100% suppression of the parasitaemia but will not provide full protection to the treated mice. Multi-drug resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine. (b) 100% protection means all the treated mice survive till day 28. Similarly 50% and 20% protection means only 50% and 20% of the treated mice survive till day 28.

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