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Synthesis and Antimalarial Assessment of a New Series of Orally Active Amino-Functionalized Spiro 1,2,4-Trioxanes[1]

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Keto-trioxanes **7a–d**, easily accessible in two steps from allylic alcohols **5a–d**, underwent reductive amination with substituted anilines to furnish amino-functionalized trioxanes **8a–i**, **9a–i**, **10a–i**, and **11a–i**. All these new trioxanes were assessed for their oral antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in Swiss mice. 2-Naphthalene-based trioxanes **9c** and **9i**, the most active compounds of the series, provided 100% protection to the malaria-infected mice at 24 mg/kg × 4 days, while the related trioxane **9b** and phenanthrene-based trioxane **11e** provided a similar level of protection at 48 mg/kg × 4 days. All other trioxanes, except **10c**, **10d**, and **10g**, provided 100% protection at 96 mg/kg × 4 days. In this model, β-arteether provided 100% protection at 48 mg/kg × 4 days and 20% protection at 24 mg/kg × 4 days.

Introduction

Malaria affects around 300–500 million people in the tropical and subtropical areas of the world, with an annual death toll of around two million.[1,2] The malaria situation is getting worse with the rapid spread of multidrug-resistant *Plasmodium falciparum*. Against this background, isolation of artemisinin **1** as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, was a major breakthrough in malaria chemotherapy.[3] Artemisinin owes its antimalarial activity to the presence of 1,2,4-trioxane system and is active against both chloroquinine-sensitive and chloroquinine-resistant malaria. Artemisinin derivatives, e.g. artemether **2** and arteether **3** (Figure 1), are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *P. falciparum*.[4]

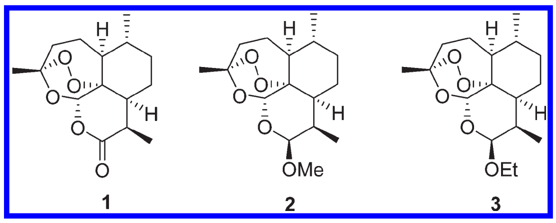


Figure 1. Artemisinin and its derivatives.

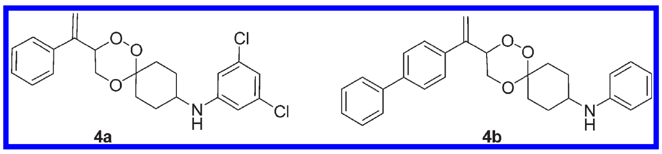
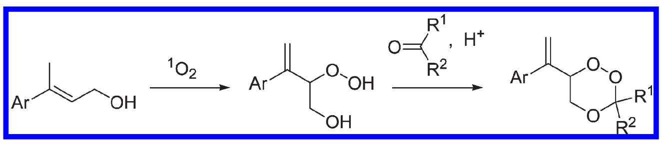


Figure 2. Amino-functionalized trioxanes **4a** and **4b**.

As a part of our endeavor to develop synthetic substitutes for artemisinin derivatives, we have earlier reported a photooxygenation route for the synthesis of 1,2,4-trioxanes. Preparation of β-hydroxyhydroperoxides by photooxygenation of allylic alcohols and their acid-catalyzed reaction with aldehydes/ketones are the key steps of this method (Scheme 1).[5] Several of the 1,2,4-trioxanes prepared by this method had shown significant antimalarial activity in vivo.[6,7]

Scheme 1



We had also extended the methodology for the preparation of a series of amino-functionalized 1,2,4-trioxanes, i.e. **4a** and **4b** (Figure 2), which exhibited moderate level of oral antimalarial activity against multidrug-resistant *P. yoelii nigeriensis*.[8] In another series of adamantane-based trioxanes, we have also observed that the substitution of phenyl ring in the aryl-vinyl moiety with naphthyl, phenanthren-3-yl, and fluoren-2-yl leads to major improvement in oral antimalarial activity.[9] On the basis of these observations, we have synthesized and screened a new series of amino-functionalized trioxanes **8a–i**, **9a–i**, **10a–i**, and **11a–i**, several of which showed superior oral antimalarial activity profile than that of β-arteether. A graphical representation of the evolution of our work on trioxanes resulting in the current series of molecules is shown in Figure 3. In this communication, we describe the details of this study.

Chemistry

Allylic alcohols **5a–d** were prepared and photooxygenated using our published procedure[9,10] to give β-hydroxyhydroperoxides **6a–d**, which were condensed in situ with 1,4-cyclohexanedione to furnish keto-trioxanes **7a–d** in

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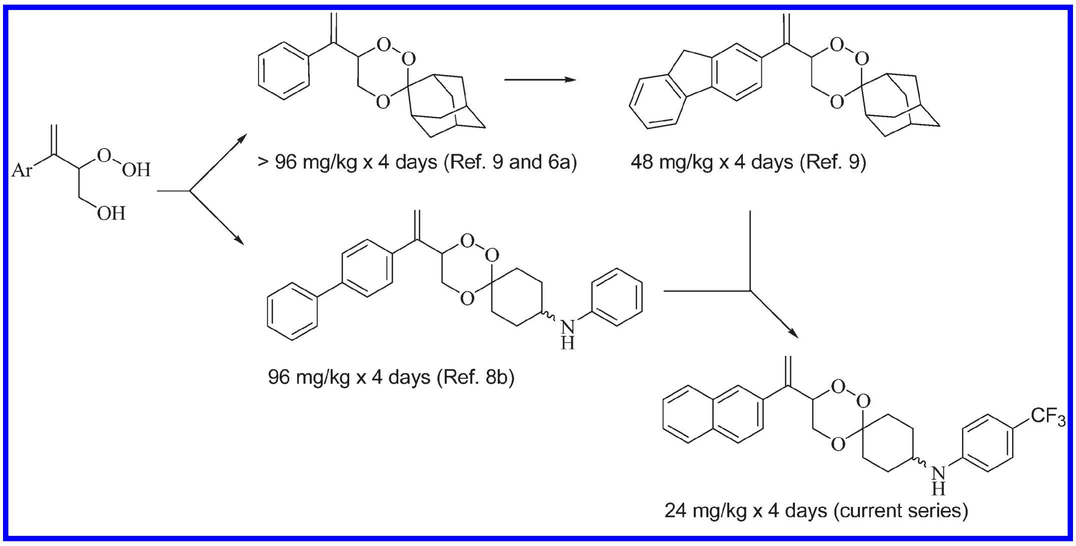


Figure 3. Graphical depiction of the evolution of our work on trioxanes leading to the current series of amino-trioxanes.

Table 1. Yields of Amino-Functionalized Trioxanes

compd	Ar	R	yield (%)
8a	1-naphthyl	phenyl	87
8b	1-naphthyl	4-fluorophenyl	78
8c	1-naphthyl	4-chlorophenyl	58
8d	1-naphthyl	3,5-dichlorophenyl	54
8e	1-naphthyl	4-methylphenyl	64
8f	1-naphthyl	4-methoxyphenyl	55
8g	1-naphthyl	2-biphenyl	61
8h	1-naphthyl	3-trifluoromethyl phenyl	48
8i	1-naphthyl	4-trifluoromethyl phenyl	81
9a	2-naphthyl	phenyl	87
9b	2-naphthyl	4-fluorophenyl	66
9c	2-naphthyl	4-chlorophenyl	46
9d	2-naphthyl	3,5-dichlorophenyl	46
9e	2-naphthyl	4-methylphenyl	62
9f	2-naphthyl	4-methoxyphenyl	47
9g	2-naphthyl	2-biphenyl	55
9h	2-naphthyl	3-trifluoromethyl phenyl	60
9i	2-naphthyl	4-trifluoromethyl phenyl	68
10a	2-fluorenyl	phenyl	54
10b	2-fluorenyl	4-fluorophenyl	66
10c	2-fluorenyl	4-chlorophenyl	58
10d	2-fluorenyl	3,5-dichlorophenyl	65
10e	2-fluorenyl	4-methylphenyl	72
10f	2-fluorenyl	4-methoxyphenyl	59
10g	2-fluorenyl	2-biphenyl	64
10h	2-fluorenyl	3-trifluoromethyl phenyl	65
10i	2-fluorenyl	4-trifluoromethyl phenyl	58
11a	3-phenanthrenyl	phenyl	67
11b	3-phenanthrenyl	4-fluorophenyl	82
11c	3-phenanthrenyl	4-chlorophenyl	63
11d	3-phenanthrenyl	3,5-dichlorophenyl	78
11e	3-phenanthrenyl	4-methylphenyl	74
11f	3-phenanthrenyl	4-methoxyphenyl	65
11g	3-phenanthrenyl	2-biphenyl	54
11h	3-phenanthrenyl	3-trifluoromethyl phenyl	72
11i	3-phenanthrenyl	4-trifluoromethyl phenyl	56

48–68% yields. Reductive amination of **7a–d** with substituted anilines using $NaBH(OAc)_3$ furnished the amino-functionalized trioxanes **8a–i**, **9a–i**, **10a–i**, and **11a–i** as mixture of diastereomers in 46–87% yields (Table 1). All the reductive amination reactions also furnished the corresponding hydroxy-functionalized trioxanes **12a–d** as mixture of diastereomers in 10–14% yields (Scheme 2).

Most of these diastereomers could not be separated by chromatography, and activity data was measured on mixture of diastereomers. The amino-trioxane **9i** was separated into pure diastereomers **9im** (more polar) and **9il** (less polar), which were separately evaluated for their antimalarial activity. Also, trioxanes **8g**, **9g**, **10g**, **10i**, **11g**, and **11i** were separated into pure diastereomers. However, the pure isomers in these cases were obtained in very small amounts, and hence the antimalarial activity was measured on the mixture of diastereomers.

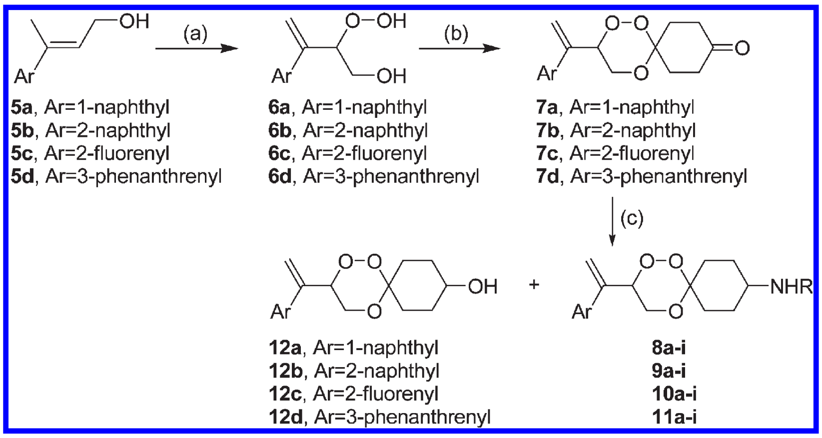
Antimalarial Activity

Amino-functionalized trioxanes **8a–i**, **9a–i**, **10a–i**, and **11a–i** were initially screened for oral antimalarial activity against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice at a dose of 96 mg/kg × 4 days using Peter's procedure.[11] Trioxanes which showed 100% protection at 96 mg/kg × 4 days were further screened at lower doses.[12] In this model, β-arteether provided 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively, by oral route. The results are summarized in Table 2.

Results and Discussion

In our efforts to develop synthetic substitutes for artemisinin derivatives, we had earlier reported a series of phenyl-vinyl substituted amino-trioxanes, i.e. **4a** and **4b**.[8] These trioxanes had shown only moderate order of oral antimalarial activity. In another series of adamantane-based 1,2,4-trioxanes, we had observed that the replacement of the phenyl group of the aryl-vinyl moiety with naphthyl, phenanthrenyl, and fluorenyl had a major improvement on oral antimalarial activity.[9] On the basis of this experience, we first prepared 1- and 2-naphthalene-based trioxanes **8a–i** and **9a–i** and evaluated their oral antimalarial activity against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice at dose ranging from 24 mg/kg × 4 days to 96 mg/kg × 4 days. As can be seen from Table 2, all these trioxanes showed 100% protection to the malaria-infected mice at 96 mg/kg × 4 days. None of the 1-naphthalene-based trioxanes showed 100% protection at 48 mg/kg × 4 days. On the other hand, several of the 2-naphthalene-based trioxanes showed a better activity profile than that of β-arteether. Trioxanes **9c** and **9i** (both the isomers **9im** and

Scheme 2[a]



[a] Reagents and conditions: (a) *hν*, O_2, methylene blue, CH_3CN, −10 to 0 °C, 4−6 h; (b) 1,4-cyclohexadione, *p*-TSA, CH_3CN, rt, 6−8 h; (c) RNH_2, $NaBH(OAc)_3$ C_6H_6, 0 °C, 1 h.

9il), the most active compounds of the series, provided 100% protection at 24 mg/kg × 4 days. Because both the diastereomers of **9i** (**9im** and **9il**) are equipotent, it appears that the stereochemical outcome of reductive amination may not be important for antimalarial activity.[14]

Trioxane **9b** provided 100% protection at 48 mg/kg × 4 days and 80% protection at 24 mg/kg × 4 days. Thus, trioxanes **9b**, **9c**, and **9i** were more active than *β*-arteether. Log *p* values of these highly active trioxanes lie in the range of 5.75−6.51.

Encouraged by these results, we prepared 2-fluorene and 3-phenanthrene-based trioxanes **10a**−**i** and **11a**−**i** and evaluated them for oral antimalarial activity. These trioxanes, however, were found to be less active than 2-naphthalene-based trioxanes. None of the fluorene-based trioxanes showed 100% protection at 48 mg/kg × 4 days. Phenanthrene-based trioxane **11e** provided 100% protection at 48 mg/kg × 4 days; related trioxane **11a** showed 80% protection at this dose. The remainder of the trioxanes, with the exception of **10c**, **10d**, and **10g**, showed 100% protection at 96 mg/kg × 4 days and partial protection at 48 mg/kg × 4 days.

Thus, looking across the series, 2-naphthalene-based trioxanes were found to be more promising than 1-naphthalene and 3-phenanthrene-based compounds, fluorene-based trioxanes being the least promising. 2-Naphthalene-based trioxanes **9c** and **9i**, the most active compounds of the series, have been identified for further studies in simian malaria.

Conclusion

Using keto-trioxanes **7a**−**d**, readily accessible from allylic alcohols **5a**−**d** in two steps, we have prepared a new series of amino-functionalized trioxanes **8a**−**i**, **9a**−**i**, **10a**−**i**, and **11a**−**i** in good yields. Several of these novel trioxanes showed activity profiles comparable with or better than that of *β*-arteether by oral route. Trioxanes **9c** and **9i**, the two most active compounds of the series, are twice as active as *β*-arteether. Because both the diastereomers of **9i** (**9im** and **9il**) are equipotent, it appears that the stereochemical outcome of reductive amination is not important for antimalarial activity.[14]

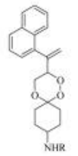
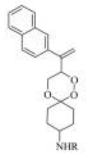
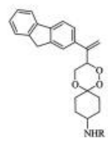
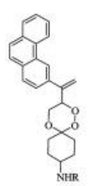
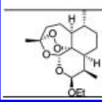
Experimental Section

General. All glass apparatus were oven-dried prior to use. Melting points were determined on COMPLAB melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-200 (operating at 200 MHz for ^1H and at 50 MHz for ^{13}C) or DRX-300 (operating at 300 MHz for ^1H and at 75 MHz for ^{13}C) spectrometers using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in part per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). Fast atom bombardment mass spectra (FAB-MS) were obtained on JEOL SX 102 spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck). Detecting agents used (for TLC) were: iodine vapors and/or spraying with an aq solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (60−120 Mesh) procured from Qualigens (India) and flash silica gel (230−400 Mesh) procured from Spectrochem (India). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (England), or Spectrochem (India) and were used without further purification. Log *p* values of the compounds were calculated using ChemDraw Ultra 7.0 software.

Elemental analyses of all the new compounds were recorded on Vario EL-III C H N S analyzer (Germany), and values were within 0.5% of the calculated values for all compounds except **8b**, **8i**, and **8g**, and therefore these compounds meet the criteria of ≥95% purity. Compounds **8b**, **8i**, and **9g** did not furnish acceptable elemental analysis. These compounds, however, were TLC homogeneous and furnished acceptable ^1H NMR, ^{13}C NMR, and HRMS data.

General Procedure for Preparation of Keto-trioxanes: Preparation of Trioxane 7a. A slow stream of oxygen was bubbled into a solution of **5a** (1 g, 5.05 mmol) and methylene blue (10 mg) in CH_3CN (50 mL) in a 100 mL double-jacketed round-bottom flask, maintained below 0 °C by circulating cold ethanol. The reaction mixture was irradiated with visible light by means of a tungsten-halogen lamp (500 W). Reaction was complete in 4 h as observed on TLC. *β*-Hydroxyhydroperoxide **6a** formed in the reaction was not isolated and reacted in situ with 1,4-cyclohexanedione (1.13 g, 10.08 mmol) in the presence of *p*-TSA (100 mg, 0.58 mmol) for 6 h at rt. Saturated aq $NaHCO_3$ (30 mL) was added. The aqueous layer was extracted with diethyl ether (2 × 100 mL), and the combined organic layer was dried over anhyd Na_2SO_4 and concentrated under vacuum at rt. The crude product was purified by column chromatography over silica gel using EtOAc/hexane (5:95) as eluent to furnish keto-trioxane **7a** (0.84 g, 52% yield, based on allylic alcohol **5a** as starting material).

Table 2. In Vivo Oral Antimalarial Activity of Compounds **8a−i**, **9a−i**, **10a−i**, and **11a−i** against Multidrug-Resistant *P. yoelii nigeriensis* in Swiss Mice

General structure	Compd. no.	R	Log *p*	Dose	%Suppression of parasitaemia on day 4[a,b]	Cured**/Treated
	**8a**	phenyl	5.59	96	100	5/5
				48	100	4/5
	8b	4–fluorophenyl	5.75	96	100	5/5
				48	100	1/5
	8c	4–chlorophenyl	6.15	96	100	5/5
				48	100	4/5
	8d	3,5–dichlorophenyl	6.71	96	100	5/5
				48	100	1/5
	8e	4–methylphenyl	6.08	96	100	5/5
				48	100	3/5
	8f	4–methoxyphenyl	5.46	96	100	5/5
				48	100	3/5
	8g	2–biphenyl	7.26	96	100	5/5
				48	100	3/5
	8h	3–trifluoromethyl phenyl	6.51	96	100	5/5
				48	100	1/5
	8i	4–trifluoromethyl phenyl	6.51	96	100	5/5
				48	100	3/5
	**9a**	phenyl	5.59	96	100	5/5
				48	100	3/5
	9b	4–fluorophenyl	5.75	96	100	5/5
				48	100	5/5
				24	100	4/5
	9c	4–chlorophenyl	6.15	96	100	5/5
				48	100	5/5
				24	100	5/5
				12	60.00	0/5
	9d	3,5–dichlorophenyl	6.71	96	100	5/5
				48	100	1/5
	9e	4–methylphenyl	6.08	96	100	5/5
				48	100	3/5
	9f	4–methoxyphenyl	5.46	96	100	5/5
				48	100	1/5
	9g	2–biphenyl	7.26	96	100	5/5
				48	100	1/5
	9h	3–trifluoromethyl phenyl	6.51	96	100	5/5
				48	100	4/5
	9il (less polar isomer)	4–trifluoromethyl phenyl	6.51	96	100	5/5
				48	100	5/5
				24	100	5/5
				12	6.25	0/5
	9im (more polar isomer)	4–trifluoromethyl phenyl	6.51	96	100	5/5
				48	100	5/5
				24	100	5/5
				12	100	1/5
	**10a**	Phenyl	6.33	96	100	5/5
				48	100	1/5
	10b	4–fluorophenyl	6.48	96	100	5/5
				48	100	1/5
	10c	4–chlorophenyl	6.88	96	100	1/5
	10d	3,5–dichlorophenyl	7.44	96	100	0/5
	10e	4–methylphenyl	6.81	96	100	5/5
				48	100	2/5
	10f	4–methoxyphenyl	6.20	96	100	5/5
				48	100	0/5
	10g	2–biphenyl	8.00	96	100	0/5
	10h	3–trifluoromethyl phenyl	7.25	96	100	5/5
				48	100	0/5
	10i	4–trifluoromethyl phenyl	7.25	96	100	5/5
				48	100	1/5
	**11a**	phenyl	6.59	96	100	5/5
				48	100	4/5
				24	100	3/5
	11b	4–fluorophenyl	6.74	96	100	5/5
				48	100	1/5
	11c	4–chlorophenyl	7.14	96	100	5/5
				48	76.90	0/5
	11d	3,5–dichlorophenyl	7.70	96	100	5/5
				48	62.50	0/5
	11e	4–methylphenyl	7.07	96	100	5/5
				48	100	5/5
				24	100	1/5
	11f	4–methoxyphenyl	6.46	96	100	5/5
				48	100	1/5
	11g	2–biphenyl	8.26	96	100	5/5
				48	74.36	0/5
	11h	3–trifluoromethyl phenyl	7.51	96	100	5/5
				48	100	0/5
	11i	4–trifluoromethyl phenyl	7.51	96	100	5/5
				48	82.22	0/5
	**3**	–	3.84	48	100	5/5
				24	100	1/5

[a] Percent suppression = $[(C - T)/C] \times 100$; where C = parasitaemia in control group, and T = parasitaemia in treated group. [b] 100% suppression of parasitaemia means, number of parasites if present, are below the detection limit.[12] (**) Mice that did not develop patent infection until day 28 were recorded as cured.

Trioxane 7a. Yield 52%, white solid; mp 82−83 °C. IR (KBr, cm^{-1}) 1598, 1717. ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (t, 2H, J = 7.1 Hz), 2.36−2.52 (m, 6H), 3.79 (dd, 1H, J = 11.6 and 2.8 Hz), 3.96 (dd, 1H, J = 11.66 and 10.2 Hz), 5.23 (dd, 1H, J = 10.2 and 2.8 Hz), 5.46 (s, 1H), 5.75 (s, 1H), 7.28−7.31 (m, 1H, Ar), 7.43−7.55 (m, 3H, Ar), 7.83−7.90 (m, 2H, Ar), 8.00−8.03 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.49 (CH_2), 33.20 (CH_2), 36.50 (CH_2), 36.68 (CH_2), 63.25 (CH_2), 81.80 (CH), 101.12 (C), 120.23 (CH_2), 125.28 (CH), 125.33 (CH), 126.09 (CH), 126.20 (CH), 126.62 (CH), 128.60 (2 × CH), 131.44 (C), 133.83 (C), 137.02 (C), 143.05 (C), 209.82 (C). FAB-MS (m/z) 324 $[M]^+$; Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06%, H 6.21%. Found: C 74.47%, H 6.66%.

Keto-trioxanes **7b−d** were prepared from allylic alcohols **5b−d**, respectively, by the above procedure.

Trioxane 7b. Yield 54%, white solid; mp 80−81 °C. IR (KBr, cm^{-1}) 1596, 1720. ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (t, 2H, J = 7.1 Hz), 2.35−2.70 (m, 6H), 3.89−4.09 (m, 2H), 5.45−5.52 (m, 2H), 5.68 (s, 1H), 7.48−7.56 (m, 3H, Ar), 7.82−7.86 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.60 (CH_2), 33.40 (CH_2), 36.62 (CH_2), 36.78 (CH_2), 63.64 (CH_2), 80.63 (CH), 101.35 (C), 117.31 (CH_2), 124.54 (CH), 125.56 (CH), 126.63 (CH), 126.72 (CH), 127.81 (CH), 128.41 (CH), 128.58 (CH), 133.26 (C), 133.44 (C), 135.83 (C), 143.24 (C), 209.92 (C). FAB-MS (m/z) 324 $[M]^+$. Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06%, H 6.21%. Found: C 74.01%, H 6.54%.

Trioxane 7c. Yield 48%, white solid; mp 87−88 °C. IR (KBr, cm^{-1}) 1598, 1717. ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (t, 2H, J = 7.1 Hz), 2.35−2.67 (m, 6H), 3.88 (s, 2H), 3.90 (dd, 1H, J = 11.6 and 2.8 Hz), 3.99 (dd, 1H, J = 11.9 and 10.2 Hz), 5.35 (s, 1H), 5.39 (dd, 1H, J = 10.2 and 2.9 Hz), 5.58 (s, 1H), 7.28−7.41 (m, 3H, Ar), 7.52−7.56 (m, 2H, Ar), 7.75 (t, 2H, J = 8.2 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.54 (CH_2), 33.38 (CH_2), 36.60 (CH_2), 36.77 (CH_2), 37.07 (CH_2), 63.60 (CH_2), 80.69 (CH), 101.27 (C), 116.40 (CH_2), 120.11 (CH), 120.23 (CH), 123.17 (CH), 125.25 (CH), 125.35 (CH), 127.05 (CH), 127.21 (CH), 137.05 (C), 141.20 (C), 142.13 (C), 143.47 (C), 143.61 (C), 143.84 (C), 209.99 (C). FAB-MS (m/z) 362 $[M]^+$. Anal. Calcd for $C_{23}H_{22}O_4$: C 76.22%, H 6.12%. Found: C 76.13%, H 6.56%.

Trioxane 7d. Yield 68%, white solid; mp 92−93 °C. IR (KBr, cm^{-1}) 1633, 1714. ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (t, 2H, J = 7.1 Hz), 2.38−2.54 (m, 6H), 3.93 (dd, 1H, J = 11.9 and 2.9 Hz), 4.04 (dd, 1H, J = 11.9 and 10.2 Hz), 5.50−5.55 (m, 2H), 5.71 (s, 1H), 7.61−7.74 (m, 5H, Ar), 7.86−7.91 (m, 2H, Ar), 8.63−8.71 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.64 (CH_2), 33.42 (CH_2), 36.66 (CH_2), 36.81 (CH_2), 63.58 (CH_2), 81.04 (CH), 101.36 (C), 117.92 (CH_2), 120.78 (CH), 122.76 (CH), 125.18 (CH), 126.58 (CH), 126.99 (CH), 127.12 (CH), 127.76 (CH), 128.95 (CH), 129.14 (CH), 130.34 (C), 130.43 (C), 132.02 (C), 132.46 (C), 136.71 (C) 143.73 (C), 210.00 (C). FAB-MS (m/z) 374 $[M]^+$. Anal. Calcd for $C_{24}H_{22}O_4$: C 76.99%, H 5.92%. Found: C 76.53%, H 5.98%.

General Procedure for Reductive Amination of Keto-1,2,4-trioxanes. Preparation of 8a. To a stirred slurry of sodium borohydride (0.057 g, 1.5 mmol) in benzene (15 mL) at 0 °C was added acetic acid (0.88 mL, 15.38 mmol) dropwise over 10 min. The contents were stirred for 3 h at rt to generate sodium triacetoxyborohydride. The contents were further cooled to 0 °C. Imine generated by the acid-catalyzed (acetic acid) reaction of aniline (0.35 mL, 3.86 mmol) with the keto-trioxane **7a** (0.50 g, 1.54 mmol) in benzene (5 mL) was added dropwise over 20 min to the flask containing sodium triacetoxyborohydride, and the reaction mixture was stirred at 0 °C for 1 h. Water (10 mL) was added to the reaction mixtrure. The aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 × 25 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum at rt. The crude compound was purified by column chromatography over silica gel using EtOAc/hexane (4:96) as eluent to furnish amino-functionlized 1,2,4-trioxane **8a** as an inseparable mixture of diastereomers (0.54 g, 87% yield).

Trioxane 8a. Yield 87%, oil; IR (neat, cm^{-1}) 1598, 3423. ^1H NMR (300 MHz, $CDCl_3$) δ 1.38−2.03 (m, 8H), 2.55−2.60 (bm, 1H), 3.37−3.43 (m, 1H), 3.68 (dd, 1H, J = 11.6 and 2.8 Hz), 3.88 (dd, 1H, J = 11.6 and 10.3 Hz), 5.13 (dd, 1H, J = 10.3 and 2.8 Hz), 5.40 (s, 1H), 5.70 (s, 1H), 6.57 (d, 2H, J = 7.7 Hz, Ar), 6.67 (t, 1H, J = 7.3 Hz, Ar), 7.14 (t, 2H, J = 8.5 Hz, Ar), 7.24−7.27 (m, 1H, Ar), 7.35−7.51 (m, 3H, Ar), 7.79−7.86 (m, 2H, Ar), 7.96−7.99 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.80 (CH_2), 28.26 (CH_2), 28.53 (CH_2), 34.34 (CH_2), 50.67 (CH), 62.83 (CH_2), 81.87 (CH), 102.10 (C), 113.55 (2 × CH), 117.59 (CH), 120.03 (CH_2), 125.38 (CH), 125.57 (CH), 126.17 (CH), 126.26 (CH), 126.66 (CH), 128.64 (2 × CH), 129.58 (2 × CH), 131.59 (C), 133.93 (C), 137.36 (C), 143.45 (C), 147.32 (C). FAB-MS (m/z) 401 $[M]^+$. HRMS calcd for $C_{26}H_{27}NO_3$, 401.1991; found, 401.1995; Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78%, H, 6.78%, N, 3.49%. Found: C, 77.42%, H, 6.94%, N, 3.38.

Amino-trioxanes **8b−i**, **9a−i**, **10a−i**, and **11a−i** were prepared by the above procedure.

Trioxane 8b. Yield 78%, oil. IR (neat, cm^{-1}) 1587, 3432. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21−1.96 (m, 8H), 2.54−2.58 and 2.73−2.78 (2 × bm, together integrating for 1H), 3.23−3.34 (m, 1H), 3.67 (dd, 1H, J = 11.8 and 2.7 Hz), 3.86 and 3.93 (2 × dd, J = 11.8 and 10.3 Hz respectively, together integrating for 1H,), 5.11 (dd, 1H, J = 10.3 and 2.7 Hz), 5.38 (s, 1H), 5.68 (s, 1H), 6.47−6.52 (m, 2H, Ar), 6.82−6.87 (m, 2H, Ar), 7.22−7.26 (m, 1H, Ar), 7.38−7.51 (m, 3H, Ar), 7.78−7.85 (m, 2H, Ar), 7.94−7.98 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.70 (CH_2), 27.25 (CH_2), 28.10 (CH_2), 28.37 (CH_2), 28.63 (CH_2), 28.74 (CH_2), 32.22 (CH_2), 33.12 (CH_2), 51.26 (CH), 51.57 (CH), 62.69 (CH_2), 63.04 (CH_2), 81.78 (CH), 101.92 (C), 114.37 (CH), 114.47 (CH), 115.71 (CH), 116.01 (CH), 120.00 (CH_2), 120.04 (CH_2), 125.30 (CH), 125.45 (CH), 126.08 (CH), 126.18 (CH), 126.58 (CH), 128.53 (CH), 128.57 (CH), 131.47 (C), 133.82 (C), 137.26 (C), 143.34 (C), 143.63 (C), 155.85 (C, J_{C-F} = 234.9 Hz). FAB-MS (m/z) 419 $[M]^+$. HRMS calcd for $C_{26}H_{26}FNO_3$, 419.1897; found, 419.1888.

Trioxane 8c. Yield 58%, white solid; mp 55−56 °C. IR (KBr, cm^{-1}) 1598, 3406. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34−1.99 (m, 8H), 2.55−2.59 and 2.75−2.79 (2 × bm, together integrating for 1H), 3.26−3.33 (m, 1H), 3.67 (dd, 1H, J = 11.5 and 2.6 Hz), 3.87 and 3.94 (2 × dd, J = 11.5 and 10.4 Hz, respectively, together integrating for 1H,), 5.10−5.14 (m, 1H), 5.40 (s, 1H), 5.69 (s, 1H), 6.47 (d, 2H, J = 8.3 Hz, Ar), 7.07 (d, 2H, J = 8.3 Hz, Ar), 7.22−7.25 (m, 1H, Ar), 7.38−7.50 (m, 3H, Ar), 7.78−7.85 (m, 2H, Ar), 7.95−7.98 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.71 (CH_2), 27.28 (CH_2), 28.05 (CH_2), 28.32 (CH_2), 28.59 (CH_2), 28.71 (CH_2), 32.25 (CH_2), 33.16 (CH_2), 50.73 (CH), 51.06 (CH), 62.79 (CH_2), 63.14 (CH_2), 81.83 (CH), 101.88 (C), 114.51 (2 × CH), 120.13 (CH_2), 121.92 (C), 125.36 (CH), 125.50 (CH), 126.14 (CH), 126.24 (CH), 126.64 (CH), 128.61 (2 × CH), 129.34 (2 × CH), 131.52 (C), 133.88 (C), 137.29 (C), 143.38 (C), 145.89 (C). FAB-MS (m/z) 435 $[M]^+$. HRMS calcd for $C_{26}H_{26}ClNO_3$, 435.1601; found, 435.1601. Anal. Calcd for $C_{26}H_{26}ClNO_3$: C, 71.63%, H, 6.01%, N, 3.21%. Found: C, 71.48%, H, 6.07%, N, 3.04.

Trioxane 8d. Yield 54%, white solid; mp 63−65 °C. IR (KBr, cm^{-1}) 1590, 3401. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35−1.94 (m, 8H), 2.55−2.60 and 2.76−2.80 (2 × bm, together integrating for 1H), 3.28−3.31 (m, 1H), 3.69 (dd, 1H, J = 11.6 and 2.3 Hz), 3.87 and 3.95 (2 × dd, J = 11.6 and 10.4 Hz respectively, together integrating for 1H), 5.11−5.15 (m 1H), 5.41 (s, 1H), 5.70 (s, 1H), 6.40 (s, 2H, Ar), 6.62 (s, 1H, Ar), 7.23−7.26 (m, 1H, Ar), 7.41 (t, 1H, J = 7.5 Hz, Ar), 7.48−7.51 (m, 2H, Ar), 7.79−7.87 (m, 2H, Ar), 7.95−7.98 (m 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.68 (CH_2), 27.24 (CH_2), 27.94 (CH_2), 28.24 (CH_2), 28.48 (CH_2), 28.61 (CH_2), 32.19 (CH_2), 33.09 (CH_2), 50.45 (CH), 50.75 (CH), 62.80 (CH_2), 63.14 (CH_2), 81.86 (CH), 101.72 (C), 111.32 (2 × CH), 116.98 (CH), 120.20 (CH_2), 125.37 (CH), 125.49 (CH), 126.16 (CH), 126.26 (CH), 126.66 (CH), 128.63 (2 × CH), 131.52 (C), 133.89 (C), 135.74 (2 × C), 137.27 (C), 143.35 (C), 148.96 (C). ESI-MS (*m*/*z*) 470 $[M + H]^+$. HRMS calcd for $C_{26}H_{25}Cl_2NO_3$, 469.1211; found, 469.1214. Anal. Calcd for $C_{26}H_{25}Cl_2NO_3$: C, 66.39%, H, 5.36%, N, 2.98%. Found: C, 66.22%, H, 5.66%, N, 3.16.

Trioxane 8e. Yield 64%, white solid; mp 49−50 °C. IR (KBr, cm^{-1}) 1590, 3401. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35−1.98 (m, 8H), 2.22 (s, 3H), 2.55−2.59 and 2.75−2.79 (2 × bm, together integrating for 1H), 3.29−3.36 (m, 1H), 3.67 (dd, 1H, *J* = 11.7 and 2.3 Hz), 3.88 and 3.94 (2 × dd, *J* = 11.5 and 10.4 Hz, respectively, together integrating for 1H), 5.10−5.13 (m, 1H), 5.40 (s, 1H), 5.69 (s, 1H), 6.50 (d, 2H, *J* = 8.1 Hz, Ar), 6.96 (d, 2H, *J* = 8.1 Hz, Ar), 7.21−7.26 (m, 1H, Ar), 7.40 (t, 1H, *J* = 7.4 Hz, Ar), 7.47−7.50 (m, 2H, Ar), 7.78−7.85 (m, 2H, Ar), 7.95−7.98 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.59 (CH_3), 26.75 (CH_2), 27.33 (CH_2), 28.23 (CH_2), 28.51 (CH_2), 28.77 (CH_2), 28.89 (CH_2), 32.31 (CH_2), 33.23 (CH_2), 50.91 (CH), 51.25 (CH), 62.79 (CH_2), 63.14 (CH_2), 81.82 (CH), 102.05 (C), 113.81 (2 × CH), 120.09 (CH_2), 125.35 (CH), 125.52 (CH), 126.13 (CH), 126.22 (CH), 126.63 (CH), 126.75 (C), 128.58 (CH), 130.02 (2 × CH), 131.52 (C), 133.87 (C), 137.33 (C), 143.42 (C), 145.05 (C). ESI-MS (*m*/*z*) 416 $[M + H]^+$. HRMS calcd for $C_{27}H_{29}NO_3$, 415.2147; found, 415.2148. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04%, H, 7.03%, N, 3.37%. Found: C, 78.19%, H, 6.54%, N, 3.27%.

Trioxane 8f. Yield 55%, white solid; mp 50−51 °C. IR (KBr, cm^{-1}) 1510, 3431. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33−1.97 (m, 8H), 2.56−2.60 and 2.75−2.79 (2 × bm, together integrating for 1H), 3.24−3.30 (m, 1H), 3.65−3.72 (m, 4H), 3.88 and 3.95 (2 × dd, *J* = 11.5 and 10.4 Hz respectively, together integrating for 1H,), 5.11−5.14 (m, 1H), 5.39 (s, 1H), 5.69 (s, 1H), 6.55 (d, 2H, *J* = 8.5 Hz, Ar), 6.75 (d, 2H, *J* = 8.5 Hz, Ar), 7.22−7.26 (m, 1H, Ar), 7.40 (t, 1H, *J* = 7.6 Hz, Ar), 7.45−7.52 (m, 2H, Ar), 7.78−7.85 (m, 2H, Ar), 7.96−7.98 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.76 (CH_2), 27.33 (CH_2), 28.30 (CH_2), 28.58 (CH_2), 28.85 (CH_2), 28.96 (CH_2), 32.32 (CH_2), 33.24 (CH_2), 51.71 (CH), 52.05 (CH), 55.98 (CH_3), 62.76 (CH_2), 63.13 (CH_2), 81.81 (CH), 102.06 (C), 115.16 (2 × CH), 115.25 (2 × CH), 120.08 (CH_2), 125.34 (CH), 125.51 (CH), 126.12 (CH), 126.21 (CH), 126.62 (CH), 128.57 (2 × CH), 131.51 (C), 133.86 (C), 137.32 (C), 141.48 (C), 143.41 (C), 152.36 (C). ESI-MS (*m*/*z*) 432 $[M + H]^+$. HRMS calcd for $C_{27}H_{29}NO_4$, 431.2097; found, 431.2127; Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15%, H, 6.77%, N, 3.25%. Found: C, 75.62%, H, 7.02%, N, 3.70.

Trioxane 8g. This was obtained as oil in 61% yield as a mixture of diastereomers **8gl** and **8gm**, which were separated by column chromatography.

Trioxane (8gl, Less Polar). Oil; IR (neat, cm^{-1}) 1584, 3430. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20−1.92 (m, 8H), 2.42−2.47 (bm, 1H), 3.38−3.44 (m, 1H), 3.64 (dd, 1H, *J* = 11.9 and 2.9 Hz), 3.84 (dd, 1H, *J* = 11.6 and 10.4 Hz), 5.10 (dd, 1H, *J* = 10.2 and 2.6 Hz), 5.38 (s, 1H), 5.68 (s, 1H), 6.69−6.76 (m, 2H, Ar), 7.05−7.08 (m, 1H, Ar), 7.18−7.50 (m, 10H, Ar), 7.78−7.86 (m, 2H, Ar), 7.94−7.97 (m, 1H, Ar)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.73 (CH_2), 28.08 (CH_2), 28.39 (CH_2), 32.22 (CH_2), 50.54 (CH), 63.75 (CH_2), 81.81 (CH), 102.03 (C), 111.21 (CH), 117.04 (CH), 120.08 (CH_2), 125.34 (CH), 125.52 (CH), 126.14 (CH), 126.22 (CH), 126.62 (CH), 127.42 (CH), 128.03 (C), 128.57 (CH), 128.61 (CH), 128.92 (CH), 129.14 (2 × CH), 129.51 (2 × CH), 130.69 (CH), 131.55 (C), 133.88 (C), 137.28 (C), 139.67 (C), 143.39 (C), 144.11 (C). FAB-MS (*m*/*z*) 477 $[M]^+$. Anal. Calcd for $C_{32}H_{31}NO_3$: C, 80.47%, H, 6.54%, N, 2.93%. Found: C, 80.59%, H, 6.89%, N, 2.84.

Trioxane (8gm, More Polar). Oil; IR (neat, cm^{-1}) 1584, 3430. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31−1.99 (m, 8H), 2.65−2.70 (bm, 1H), 3.36−3.42 (m, 1H), 3.66 (dd, 1H, *J* = 11.6 and 2.4 Hz), 3.93 (dd, 1H, *J* = 11.3 and 10.3 Hz), 5.09 (dd, 1H, *J* = 10.3 and 2.4 Hz), 5.39 (s, 1H), 5.67 (s, 1H), 6.69−6.76 (m, 2H, Ar), 7.07−7.09 (m, 1H, Ar), 7.18−7.25 (m, 2H, Ar), 7.34−7.50 (m, 8H, Ar), 7.78−7.85 (m, 2H, Ar), 7.94−7.96 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.20 (CH_2), 28.53 (CH_2), 28.69 (CH_2), 33.07 (CH_2), 50.72 (CH), 63.12 (CH_2), 81.82 (CH), 101.99 (C), 111.26 (CH), 117.04 (CH), 120.13 (CH_2), 125.36 (CH), 125.49 (CH), 126.12 (CH), 126.23 (CH), 126.65 (CH), 127.50 (CH), 128.18 (C), 128.59 (CH), 128.61 (CH), 128.86 (CH), 129.20 (2 × CH), 129.50 (2 × CH), 130.70 (CH), 131.51 (C), 133.87 (C), 137.31 (C), 139.56 (C), 143.40 (C), 144.09 (C). FAB-MS (*m*/*z*) 477 $[M]^+$. HRMS calcd for $C_{32}H_{31}NO_3$, 477.2309; found, 477.2303; Anal. Calcd for $C_{32}H_{31}NO_3$: C, 80.47%, H, 6.54%, N, 2.93%. Found: C, 80.46%, H, 6.92%, N, 2.80.

Trioxane 8h. Yield 48%, oil. IR (neat, cm^{-1}) 1587, 3432. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37−2.01 (m, 8H), 2.56−2.61 and 2.77−2.81 (2 × bm, together integrating for 1H), 3.38−3.41 (m, 1H), 3.68 (dd, 1H, *J* = 11.7 and 2.5 Hz), 3.87 and 3.95 (2 × dd, *J* = 11.7 and 10.3 Hz, respectively, together integrating for 1H), 5.11−5.15 (m, 1H), 5.40 (s, 1H), 5.70 (s, 1H), 6.68 (d, 1H, *J* = 7.8 Hz, Ar), 6.75 (s, 1H, Ar), 6.88 (d, 1H, *J* = 7.8 Hz, Ar), 7.18−7.26 (m, 2H, Ar), 7.41 (t, 1H, *J* = 7.7 Hz, Ar), 7.48−7.51 (m, 2H, Ar), 7.79−7.86 (m, 2H, Ar), 7.96−7.98 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.71 (CH_2), 27.28 (CH_2), 28.04 (CH_2), 28.32 (CH_2), 28.58 (CH_2), 28.70 (CH_2), 32.23 (CH_2), 33.12 (CH_2) 50.45 (CH), 50.76 (CH), 62.82 (CH_2), 63.16 (CH_2), 81.89 (CH), 101.85 (C), 109.42 (CH), 113.78 (CH), 116.32 (CH), 120.15 (CH_2), 125.38 (CH), 125.53 (CH), 126.17 (CH), 126.26 (CH), 126.66 (CH), 128.62 (2 × CH), 129.94 (CH), 131.56 (C), 131.88 (C, J_{C-F} = 31.7 Hz), 133.93 (2 × C), 137.33 (C), 143.43 (C), 147.55 (C). ESI-MS (*m*/*z*) 470 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}F_3NO_3$, 469.1865; found, 469.1871. Anal. Calcd for $C_{27}H_{26}F_3NO_3$: C, 69.07%, H, 5.58%, N, 2.98%. Found: C, 69.41%, H, 5.78%, N, 2.73.

Trioxane 8i. Yield 81%, oil. IR (neat, cm^{-1}) 1591, 3413. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32−1.99 (m, 8H), 2.56−2.61 and 2.76−2.80 (2 × bm, together integrating for 1H), 3.36−3.39 (m, 1H), 3.67 (dd, 1H, *J* = 11.6 and 2.8 Hz), 3.87 (dd, 1H, *J* = 11.6 and 10.2 Hz), 5.12−5.15 (m, 1H), 5.39 (s, 1H), 5.69 (s, 1H), 6.52 (d, 2H, *J* = 8.4 Hz, Ar), 7.24−7.49 (m, 6H, Ar), 7.77−7.85 (m, 2H, Ar), 7.96−7.98 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.66 (CH_2), 27.90 (CH_2), 28.16 (CH_2), 28.42 (CH_2), 28.54 (CH_2), 32.19 (CH_2), 50.17 (CH), 50.47 (CH), 62.77 (CH_2), 63.11 (CH_2), 81.83 (CH), 101.77 (C), 101.83 (C), 112.28 (2 × CH), 118.44 (C, J_{C-F} = 32.6 Hz), 120.08 (CH_2), 125.36 (CH), 125.47 (CH), 126.14 (CH), 126.24 (CH), 126.64 (CH), 126.84 (CH), 126.89 (CH), 128.62 (2 × CH), 131.50 (C), 133.87 (C), 137.24 (C), 143.30 (C), 149.79 (C). FAB-MS (*m*/*z*) 470 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}F_3NO_3$, 469.1865; found, 469.1860.

Trioxane 9a. Yield 87%, white solid; mp 130−131 °C. IR (KBr, cm^{-1}) 1505, 3405.; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45−2.04 (m, 8H), 2.75−2.79 and 2.81−2.87 (2 × bm, together integrating for 1H), 3.40−3.52 (m, 1H), 3.84 (dd, 1H, *J* = 11.8 and 2.4 Hz), 4.04 (dd, 1H, *J* = 11.6 and 10.7 Hz), 5.38−5.43 (m, 2H), 5.65(s, 1H), 6.58−6.72 (m, 3H), 7.13−7.25 (m, 2H), 7.50−7.55 (m, 3H), 7.80−7.84 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.41 (CH_2), 28.65 (CH_2), 28.75 (CH_2), 33.32 (CH_2), 51.39 (CH), 63.43 (CH_2), 80.64 (CH), 80.65 (CH), 102.16 (C), 114.02 (2 × CH), 117.22 (CH_2), 118.02 (CH), 124.68 (CH), 125.59 (CH), 126.59 (CH), 126.69 (CH), 127.84 (CH), 128.47 (CH), 128.55 (CH), 129.61 (2 × CH), 133.31 (C), 133.52 (C), 136.10 (C), 143.57 (C), 146.85 (C). ESI-MS (*m*/*z*) 402 $[M + H]^+$. HRMS calcd for $C_{26}H_{27}NO_3$, 401.1991; found, 401.1992; Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78%, H, 6.78%, N, 3.49%. Found: C, 77.82%, H, 7.11%, N, 3.12.

Trioxane 9b. Yield 66%, white solid; mp 92−93 °C. IR (KBr, cm^{-1}) 1634, 3434. ^1H NMR (300 MHz, $CDCl_3$) δ 1.43−2.06 (m, 8H), 2.67−2.72 and 2.86−2.90 (2 × bm, together integrating for 1H), 3.32−3.39 (bm, 1H), 3.85−3.90 (m, 1H), 3.98 and 4.07 (2 × dd, *J* = 11.6 and 10.6 Hz, together integrating for 1H),), 5.42−5.46 (m, 2H), 5.68 (s, 1H), 6.54−6.58 (m, 2H), 6.91

(t, 2H, J = 8.7 Hz, Ar), 7.50−7.57 (m, 3H, Ar), 7.84−7.87 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.85 (CH_2), 27.40 (CH_2), 28.26 (CH_2), 28.53 (CH_2), 28.78 (CH_2), 32.45 (CH_2), 33.34 (CH_2), 51.46 (CH), 51.77 (CH), 63.15 (CH_2), 63.44 (CH_2), 80.64 (CH), 80.68 (CH), 102.16 (C), 114.52 (CH), 114.62 (CH), 115.84 (CH), 116.13 (CH), 117.15 (CH_2), 117.21 (CH_2), 124.64 (CH), 125.59 (CH), 126.61 (CH), 126.72 (CH), 127.84 (CH), 128.47 (CH), 128.55 (CH), 133.30 (C), 133.51 (C), 136.06 (C), 143.50 (C), 146.66 (C), 156.04 (C, J_{C-F} = 235.1 Hz). FAB-MS (m/z) 419 $[M]^+$. HRMS calcd for $C_{26}H_{26}FNO_3$, 419.1897; found, 419.1892; Anal. Calcd for $C_{26}H_{26}FNO_3$: C, 74.44%, H, 6.25%, N, 3.34%. Found: C, 74.52%, H, 6.59%, N, 3.16.

Trioxane 9c. Yield 46%, white solid; mp 125−126 °C. IR (KBr, cm^{-1}) 1594, 3407. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36−2.05 (m, 8H), 2.70−2.76 and 2.86−2.92 (2 × bm, together integrating for 1H), 3.37−3.43 (m, 1H), 3.91 (dd, 1H, J = 11.9 and 2.9 Hz), 3.97−4.21 (m, 1H), 5.50−5.53 (m, 2H), 5.72 (s, 1H), 6.54 (d, 2H, J = 8.8 Hz, Ar), 7.17 (d, 2H, J = 8.8 Hz, Ar), 7.52−7.61 (m, 3H, Ar), 7.84−7.91 (m, 4H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.71 (CH_2), 27.22 (CH_2), 27.97 (CH_2), 28.23 (CH_2), 28.46 (CH_2), 28.55 (CH_2), 32.28 (CH_2), 33.14 (CH_2), 50.62 (CH), 50.88 (CH), 62.96 (CH_2), 63.25 (CH_2) 80.47 (CH), 101.98 (C), 102.06 (C), 114.44 (2 × CH), 117.08 (CH_2), 121.70 (C), 121.74 (C), 124.50 (CH), 125.43 (CH), 126.49 (CH), 126.59 (CH), 127.72 (CH), 128.36 (CH), 128.44 (CH), 129.24 (2 × CH), 133.16 (C), 133.38 (C), 135.90 (C), 143.32 (C), 145.88 (C). ESI-MS (m/z) 436 $[M + H]^+$. HRMS calcd for $C_{26}H_{26}ClNO_3$, 435.1601; found, 435.1605. Anal. Calcd for $C_{26}H_{26}ClNO_3$: C, 71.63%, H, 6.01%, N, 3.21. Found: C, 71.84%, H, 6.49%, N, 3.08%..

Trioxane 9d. Yield 46%, white solid; mp 90−91 °C. IR (KBr, cm^{-1}) 1591, 3406. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49−2.02 (m, 8H), 2.81−2.86 (bm, 1H), 3.39 (m, 1H), 3.85 (dd, 1H, J = 11.7 and 2.9 Hz), 4.03 (dd, 1H, J = 11.7 and 10.3 Hz,), 5.40 (dd, 1H, J = 10.3 and 2.9 Hz), 5.43 (s, 1H), 5.65 (s, 1H), 6.43 (s, 2H, Ar), 7.36 (s, 1 Hz, Ar), 7.47−7.54 (m, 3H, Ar), 7.81−7.84 (m, 4H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.32 (CH_2), 28.50 (CH_2), 28.61 (CH_2), 33.22 (CH_2), 50.89 (CH), 63.43 (CH_2), 80.64 (CH), 101.89 (C), 111.46 (2 × CH), 117.16 (CH), 117.25 (CH_2), 124.61 (CH), 125.58 (CH), 126.62 (CH), 126.73 (CH), 127.84 (CH), 128.47 (CH), 128.57 (CH), 133.30 (C), 133.49 (C), 135.79 (2 × C), 136.01 (C), 143.43 (C), 148.87 (C). FAB-MS (m/z) 470 $[M + H]^+$. HRMS calcd for $C_{26}H_{25}Cl_2NO_3$, 469.1211; found, 469.1211. Anal. Calcd for $C_{26}H_{25}Cl_2NO_3$: C, 66.39%, H, 5.36%, N, 2.98%. Found: C, 66.52%, H, 5.71%, N, 2.75.

Trioxane 9e. Yield 62%, white solid; mp 98−99 °C. IR (KBr, cm^{-1}) 1517, 3411. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39−2.03 (m, 8H), 2.23 (s, 3H), 2.62−2.66 and 2.80−2.84 (2 × bm, respectively, together integrating for 1H), 3.33−3.40 (m, 1H), 3.83 (dd, 1H, J = 11.7 and 2.6 Hz), 3.95 and 4.02 (2 × dd, J = 11.7 and 10.4 Hz, respectively, together integrating for 1H), 5.38−5.42 (m, 2H), 5.64 (s, 1H), 6.52 (d, 2H, J = 8.1 Hz, Ar), 6.97 (d, 2H, J = 8.1 Hz, Ar), 7.46−7.53 (m, 3H, Ar), 7.79−7.84 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.58 (CH_3), 26.83 (CH_2), 27.38 (CH_2), 28.29 (CH_2), 28.56 (CH_2), 28.80 (CH_2), 28.89 (CH_2), 32.45 (CH_2), 33.33 (CH_2), 50.94 (CH), 51.26 (CH), 63.11 (CH_2), 63.39 (CH_2) 80.61 (CH), 102.22 (C), 113.82 (2 × CH), 117.16 (CH_2), 124.62 (CH), 125.54 (CH), 126.56 (CH), 126.67 (CH), 126.76 (C), 127.80 (CH), 128.44 (CH), 128.51 CH), 130.04 (2 × CH), 133.26 (C), 133.48 (C), 136.04 (C), 143.48 (C), 145.09 (C). FAB-MS (m/z) 415 $[M]^+$. HRMS calcd for $C_{27}H_{29}NO_3$, 415.2147; found, 415.2149. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04%, H, 7.03%, N, 3.37%. Found: C, 78.51%, H, 6.96%, N, 2.85%.

Trioxane 9f. Yield 47%, white solid; mp 92−93 °C. IR (KBr, cm^{-1}) 1590, 3399. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39−2.03 (m, 8H), 2.62−2.66 and 2.80−2.84 (2 × bm, respectively, together integrating for 1H), 3.26−3.34 (m, 1H), 3.74 (s, 3H), 3.83 (dd, 1H, J = 11.6 and 2.5 Hz), 3.95 and 4.02 (2 × dd, J = 11.6 and, 10.4 Hz, respectively, together integrating for 1H), 5.39 (dd, 1H, J = 10.4 and 2.5 Hz), 5.42 (s, 1H), 5.64 (s, 1H), 6.97 (d, 2H, J = 8.8 Hz, Ar), 6.76 (d, 2H, J = 8.8 Hz, Ar), 7.46−7.53 (m, 3H, Ar), 7.79−7.84 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.42 (CH_2), 28.92 (CH_2), 29.01 (CH_2), 33.38 (CH_2), 52.10 (CH), 56.05 (CH_3), 63.42 (CH_2), 80.62 (CH), 102.27 (C), 115.23 (2 × CH), 115.32 (2 × CH), 117.19 (CH_2), 124.64 (CH), 125.57 (CH), 126.58 (CH), 126.69 (CH), 127.82 (CH), 128.46 (CH), 128.53 (CH), 133.28 (C), 133.50 (C), 136.06 (C), 141.56 (C), 143.50 (C), 152.43 (C). FAB-MS (m/z) 431 $[M]^+$. HRMS calcd for $C_{27}H_{29}NO_4$, 431.2097; found, 431.2123. Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15%, H, 6.77%, N, 3.25. Found: C, 75.25%, H, 6.93%, N, 3.17%.

Trioxane 9g. This was obtained as a white solid in 55% yield as a mixture of diastereomers **9gl** and **9gm**, which were separated by column chromatography.

Trioxane (9gl, Less Polar). Melting point 87−88 °C. IR (KBr, cm^{-1}) 1594, 3405. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25−1.98 (m, 8H), 2.48−2.52 (bm, 1H), 3.39−3.45 (m, 1H), 3.77 (dd, 1H, J = 11.8 and 2.9 Hz), 3.89 (dd, 1H, J = 11.8 and 10.2 Hz,), 5.34−5.38 (m, 2H), 5.60 (s, 1H), 6.70−6.75 (m, 2H, Ar), 7.06−7.08 (m, 1H, Ar), 7.18−7.24 (m, 1H, Ar), 7.28−7.49 (m, 8H, Ar), 7.76−7.80 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.80 (CH_2), 28.13 (CH_2), 28.42 (CH_2), 32.36 (CH_2), 50.58 (CH), 63.05 (CH_2), 80.61 (CH), 102.19 (C), 111.21 (CH), 117.04 (CH), 117.18 (CH_2), 124.62 (CH), 125.55 (CH), 126.55 (CH), 126.66 (CH), 127.42 (CH), 127.80 (CH), 128.02 (C), 128.43 (CH), 128.50 (CH), 128.93 (CH), 129.14 (2 × CH), 129.52 (2 × CH), 130.71 (CH), 133.25 (C), 133.46 (C), 135.99 (C), 139.70 (C), 143.49 (C), 144.15 (C). FAB-MS (m/z) 477 $[M]^+$. HRMS calcd for $C_{32}H_{31}NO_3$, 477.2304; found, 477.2320.

Trioxane (9gm, More Polar). Melting point 98−99 °C. IR (KBr, cm^{-1}) 1599, 3415. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.99 (m, 8H), 2.68−2.72 (bm, 1H), 3.37−3.47 (m, 1H), 3.80 (dd, 1H, J = 11.8 and 2.9 Hz), 3.99 (dd, 1H, J = 11.8 and 10.4 Hz,), 5.34−5.38 (m, 2H), 5.62 (s, 1H), 6.70−6.77 (m, 2H, Ar), 7.07−7.09 (m, 1 Hz, Ar), 7.18−7.24 (m, 1H, Ar), 7.30−7.51(m, 8H, Ar), 7.78−7.81 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.17 (CH_2), 28.50 (CH_2), 28.62 (CH_2), 33.06 (CH_2), 50.63 (CH), 63.22 (CH_2), 80.47 (CH), 102.08 (C), 111.19 (CH), 116.95 (CH), 116.98 (CH_2), 124.53 (CH), 125.47 (CH), 126.49 (CH), 126.60 (CH), 127.42 (CH), 127.74 (CH), 128.11 (C), 128.38 (CH), 128.44 (CH), 128.82 (CH), 129.13 (2 × CH), 129.44 (2 × CH), 130.65 (CH), 133.19 (C), 133.41 (C), 135.93 (C), 139.56 (C), 143.35 (C), 144.12 (C). FAB-MS (m/z) 477 $[M]^+$. HRMS calcd for $C_{32}H_{31}NO_3$, 477.2304; found, 477.2320.

Trioxane (9h). Yield 60%, oil. IR (neat, cm^{-1}) 1608, 3422. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47−2.03 (m, 8H), 2.63−2.69 and 2.82−2.88 (2 × bm, together integrating for 1H), 3.42 (bm, 1H), 3.84 (dd, 1H, J = 11.4 and 2.3 Hz), 4.04 (dd, 1H, J = 11.4 and 10.8 Hz), 5.41−5.43 (m, 2H), 5.65 (s, 1H), 6.69−6.77 (m, 2H, Ar), 6.88−6.92 (m, 1H, Ar), 7.19−7.27 (m, 1H, Ar), 7.46−7.54 (m, 3H, Ar), 7.80−7.84 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.95 (CH_2), 27.50 (CH_2), 28.24 (CH_2), 28.52 (CH_2), 28.76 (CH_2), 28.85 (CH_2), 32.56 (CH_2), 33.44 (CH_2), 50.61 (CH), 50.91 (CH), 63.35 (CH_2), 63.63 (CH_2), 80.81 (CH), 102.25 (C), 109.61 (CH), 113.98 (CH), 116.51 (CH), 117.44 (CH_2), 122.11 (CH), 124.81 (CH), 125.76 (CH), 126.83 (CH), 126.93 (CH), 128.04 (CH), 128.68 (CH), 128.77 (CH), 130.16 (C), 132.04 (C, J_{C-F} = 31.5 Hz), 133.48 (C), 136.19 (2 × C), 143.59(C), 147.73 (C). ESI-MS (m/z) 470 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}NF_3O_3$, 469.1865; found, 469.1830; Anal. Calcd for $C_{27}H_{26}NF_3O_3$: C, 69.07%, H, 5.58%, N, 2.98. Found: C, 69.31%, H, 5.64%, N, 2.73%.

Trioxane 9i. This was obtained as oil in 68% yield as a mixture of diastereomers **9il** and **9im**, which were separated by column chromatography.

Trioxane (9il, Less Polar). IR (neat, cm^{-1}) 1607, 3412. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47−2.05 (m, 8H), 2.81−2.86 (bm, 1H), 3.39−3.48 (m, 1H), 3.84 (dd, 1H, J = 11.7 and 2.7 Hz), 4.03 (dd, 1H, J = 11.7 and 10.2 Hz,), 5.37−5.43 (m, 2H), 5.65 (s, 1H), 6.57 (d, 2H, J = 8.4 Hz, Ar), 7.38 (d, 2H, J = 8.4 Hz, Ar), 7.46−7.53 (m, 3H, Ar), 7.80−7.83 (m, 4H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 27.36 (CH$_2$), 28.57 (CH$_2$), 28.68 (CH$_2$), 33.23 (CH$_2$), 50.64 (CH), 63.44 (CH$_2$), 80.69 (CH), 100.25 (C), 101.95 (C), 112.39 (2 × CH), 117.23 (CH$_2$), 118.72 (C, J_{C-F} = 32.3 Hz), 124.64 (CH), 125.61 (CH), 126.62 (CH), 126.72 (CH), 126.90 (CH), 126.96 (CH), 127.84 (CH), 128.46 (CH), 128.56 (CH), 133.32 (C), 133.53 (C), 136.06 (C), 143.52 (C), 149.86 (C). ESI-MS (m/z) 470 [M + H]$^+$. HRMS calcd for $C_{27}H_{26}F_3NO_3$, 469.1865; found, 469.1825. Anal. Calcd for $C_{27}H_{26}NF_3O_3$: C, 69.07%, H, 5.58%, N, 2.98. Found: C, 69.45%, H, 5.91%, N, 2.69%.

Trioxane (9im, More Polar). IR (neat, cm^{-1}) 1607, 3412. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.50−2.04 (m, 8H), 2.63−2.67 (bm, 1H), 3.44−3.51 (m, 1H), 3.85 (dd, 1H, J = 11.9 and 3.1 Hz), 3.96 (dd, 1H, J = 11.9 and 10.2 Hz,), 5.39−5.43 (m, 2H), 5.65 (s, 1H), 6.57 (d, 2H, J = 8.4 Hz, Ar), 7.38 (d, 2H, J = 8.4 Hz, Ar), 7.47−7.54 (m, 3H, Ar), 7.80−7.83 (m, 4H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.81 (CH$_2$), 28.06 (CH$_2$), 28.33 (CH$_2$), 32.37 (CH$_2$), 50.33 (CH), 63.18 (CH$_2$), 80.72 (CH), 102.04 (C), 112.41 (2 × CH), 117.18 (CH$_2$), 124.67 (CH), 125.62 (CH), 126.63 (CH), 126.74 (CH), 126.99 (2 × CH), 127.86 (CH), 128.47 (CH), 128.57 (CH), 133.33 (C), 133.54 (2 × C), 136.03 (2 × C), 143.55 (C), 149.85 (C). ESI-MS (m/z) 470 [M + H]$^+$. HRMS calcd for $C_{27}H_{26}F_3NO_3$, 469.1865; found, 469.1825. Anal. Calcd for $C_{27}H_{26}NF_3O_3$: C, 69.07%, H, 5.58%, N, 2.98. Found: C, 69.51%, H, 5.95%, N, 2.65%.

Trioxane 10a. Yield 54%, white solid; mp 135−140 °C. IR (KBr, cm^{-1}) 1597, 3401. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.21−2.02 (m, 8H), 2.61−2.66 and 2.79−2.84 (2 × bm, together integrating for 1H), 3.35−3.44 (m, 1H), 3.79−3.84 (m, 1H), 3.87 (s, 2H), 3.93 and 4.01 (2 × dd, J = 11.5 and 10.7 Hz, respectively, together integrating for 1H), 5.31−5.33 (m, 2H), 5.55 (s, 1H), 6.58 (d, 2H, J = 7.8 Hz, Ar), 6.77 (t, 1H, J = 7.3 Hz, Ar), 7.15 (t, 2H, J = 7.5 Hz, Ar), 7.29−7.40 (m, 3H, Ar), 7.51−7.55 (m, 2H, Ar), 7.70−7.76 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.80 (CH$_2$), 27.35 (CH$_2$), 28.25 (CH$_2$), 28.51 (CH$_2$), 28.75 (CH$_2$), 28.86 (CH$_2$), 32.44 (CH$_2$), 33.33 (CH$_2$), 37.11 (CH$_2$), 50.58 (CH), 50.90 (CH), 63.09 (CH$_2$), 63.37 (CH$_2$), 80.70 (CH), 102.12 (C), 113.47 (2 × CH), 116.28 (CH$_2$), 117.46 (CH), 120.10 (CH), 120.24 (CH), 123.21 (CH), 125.28 (CH), 125.41 (CH), 127.07 (CH), 127.19 (CH), 129.54 (2 × CH), 137.31 (C), 141.31 (C), 142.06 (C), 143.67 (C), 143.82 (2 × C), 147.38 (C). FAB-MS (m/z) 439 [M]$^+$. HRMS calcd for $C_{29}H_{29}NO_3$, 439.2147; found, 439.2137. Anal. Calcd for $C_{29}H_{29}NO_3$: C, 79.24%, H, 6.65%; N, 3.19%. Found: C, 79.39%, H, 6.33%, N, 3.11%.

Trioxane 10b. Yield 66%, white solid; mp 125−126 °C. IR (KBr, cm^{-1}) 1598, 3409. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.38−2.00 (m, 8H), 2.60−2.65 and 2.79−2.83 (2 × bm, together integrating for 1H), 3.25−3.30 (m, 1H), 3.81 (dd, 1H, J = 11.6 and 2.6 Hz), 3.86 (s, 2H), 3.93 and 4.01 (2 × dd, J = 11.6 and 10.7 Hz, respectively, together integrating for 1H), 5.30−5.33 (m, 2H), 5.55 (s, 1H), 6.48−6.53 (m, 2H, Ar), 6.86 (t, 2H, J = 8.6 Hz, Ar), 7.22−7.40 (m, 3H, Ar), 7.51−7.55 (m, 2H, Ar), 7.70−7.76 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 27.77 (CH$_2$), 27.33 (CH$_2$), 28.21 (CH$_2$), 28.48 (CH$_2$), 28.73 (CH$_2$), 28.83 (CH$_2$), 32.43 (CH$_2$), 33.35 (CH$_2$), 37.11 (CH$_2$), 51.91 (CH), 51.67 (CH), 63.10 (CH$_2$), 63.39 (CH$_2$), 80.66 (CH), 80.69 (CH), 102.09 (C), 102.17 (C), 114.40 (CH), 114.50 (CH), 115.80 (CH), 116.09 (CH), 116.31 (CH$_2$), 120.12 (CH), 120.26 (CH), 123.20 (CH), 125.30 (CH), 125.39 (CH), 127.08 (CH), 127.21 (CH), 137.25 (C), 141.29 (C), 142.07 (C), 143.66 (3 × C), 143.83 (C), 155.91 (C, J_{C-F} = 235.1 Hz). FAB-MS (m/z) 457 [M]$^+$. HRMS Calcd for $C_{29}H_{28}FNO_3$, 457.2053; found, 457.2047. Anal. Calcd for $C_{29}H_{28}FNO_3$: C, 76.13%, H, 6.17%, N, 3.06%. Found: C, 76.77%, H, 6.17%, N, 2.93%.

Trioxane 10c. Yield 58%, white solid; mp 160−163 °C. IR (KBr, cm^{-1}) 1598, 3403. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.50−2.02 (m, 8H), 2.62−2.65 and 2.80−2.85 (2 × bm, together integrating for 1H), 3.31−3.40 (m, 1H), 3.82 (dd, 1H, J = 11.6 and 2.8 Hz), 3.89 (s, 2H), 3.94 and 4.02 (2 × dd, J = 11.6 and 10.5 Hz, respectively, together integrating for 1H), 5.31−5.34 (m, 2H), 5.56 (s, 1H), 6.51 (d, 2H, J = 8.8 Hz, Ar), 7.09 (d, 2H, J = 8.8 Hz, Ar), 7.28−7.42 (m, 3H, Ar), 7.53−7.56 (m, 2H, Ar), 7.73−7.79 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.77 (CH$_2$), 28.12 (CH$_2$), 28.38 (CH$_2$), 32.39 (CH$_2$), 37.14 (CH$_2$), 50.77 (CH), 63.11 (CH$_2$), 63.39 (CH$_2$), 80.74 (CH), 102.10 (C), 114.53 (2 × CH), 116.25 (CH$_2$), 120.12 (CH), 120.26 (CH), 121.99 (CH), 123.24 (CH), 125.30 (CH), 125.44 (CH), 127.09 (CH), 127.22 (CH), 129.36 (2 × CH), 137.26 (C), 141.32 (C), 142.10 (C), 143.68 (C), 143.78 (C), 143.85 (C), 145.90 (C). FAB-MS (m/z) 474 [M + H]$^+$. HRMS Calcd for $C_{29}H_{28}ClNO_3$, 473.1758; found, 473.1759. Anal. Calcd for $C_{29}H_{28}ClNO_3$: C, 73.48%, H, 5.95%, N, 2.96%. Found: C, 73.97%, H, 5.99%, N, 2.93%.

Trioxane 10d. Yield 65%, white solid; mp 183−184 °C. IR (KBr, cm^{-1}) 1592, 3406. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.46−2.05 (m, 8H), 2.65−2.70 and 2.84−2.89 (2 × bm, together integrating for 1H), 3.36−3.38 (m, 1H), 3.86 (dd, 1H, J = 11.9 and 2.7 Hz), 3.93 (s, 2H), 3.97 and 4.05 (2 × dd, J = 11.9 and 10.5 Hz, respectively, together integrating for 1H), 5.35−5.37 (m, 2H), 5.59−5.60 (2 × s, together integrating for 1H), 6.45 (d, 2H, J = 1.6 Hz, Ar), 6.66−6.67 (m, 1H, Ar), 7.32−7.45 (m, 3H, Ar), 7.56−7.60 (m, 2H, Ar), 7.76−7.82 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.73 (CH$_2$), 27.29 (CH$_2$), 27.99 (CH$_2$), 28.28 (CH$_2$), 28.51 (CH$_2$), 28.63 (CH$_2$), 32.34 (CH$_2$), 33.23 (CH$_2$), 37.14 (CH$_2$), 50.48 (CH), 50.79 (CH), 63.12 (CH$_2$), 63.40 (CH$_2$), 80.75 (CH), 101.85 (C), 101.91 (C), 111.33 (2 × CH), 116.37 (CH$_2$), 117.00 (CH), 120.14 (CH), 120.28 (CH), 123.24 (CH), 125.31 (CH), 125.43 (CH), 127.10 (CH), 127.24 (CH), 135.76 (2 × C), 137.26 (C), 141.31 (C), 142.12 (C), 143.68 (2 × C), 143.86 (C), 148.96 (C). FAB-MS (m/z) 507 [M]$^+$. HRMS calcd for $C_{29}H_{27}Cl_2NO_3$, 507.1368; found, 507.1388. Anal. Calcd for $C_{29}H_{27}Cl_2NO_3$: C, 68.51%, H, 5.35%, N, 2.75%. Found: C, 68.97%, H, 5.43%, N, 2.79%.

Trioxane 10e. Yield 72%, white solid; mp 95−96 °C. IR (KBr, cm^{-1}) 1598, 3427. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.39−2.02 (m, 8H), 2.23 (s, 3H), 2.61−2.65 and 2.79−2.83 (2 × bm, together integrating for 1H), 3.34−3.39 (m, 1H), 3.79−3.84 (m, 1H), 3.88 (s, 2H), 3.94 and 4.01 (2 × dd, J = 11.5 and 10.5 Hz, respectively, together integrating for 1H), 5.31−5.34 (m, 2H), 5.56 (s, 1H), 6.52 (d, 2H, J = 8.2 Hz, Ar), 6.97 (d, 2H, J = 8.2 Hz, Ar), 7.28−7.41(m, 3H, Ar), 7.51−7.56 (m, 2H, Ar), 7.72−7.78 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.58 (CH$_3$), 26.82 (CH$_2$), 27.38 (CH$_2$), 28.30 (CH$_2$), 28.57 (CH$_2$), 28.82 (CH$_2$), 28.92 (CH$_2$) 32.46 (CH$_2$), 33.37 (CH$_2$), 37.14 (CH$_2$), 50.96 (CH), 51.30 (CH), 63.11 (CH$_2$), 63.39 (CH$_2$), 80.72 (CH), 102.19 (C), 113.83 (2×CH), 116.20 (CH$_2$), 116.31 (CH$_2$), 120.11 (CH), 120.26 (CH), 123.24 (CH), 125.29 (CH), 125.44 (CH), 126.79 (C), 127.08 (CH), 127.20 (CH), 130.04 (2×CH), 137.35 (C), 141.34 (C), 142.08 (C), 143.69 (C), 143.84 (2 × C), 145.08 (C). FAB-MS (m/z) 453 [M]$^+$. HRMS calcd for $C_{30}H_{31}NO_3$, 453.2304; found, 453.2265. Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44%, H, 6.89%, N, 3.09%. Found: C, 79.94%, H, 6.93%, N, 3.13%.

Trioxane 10f. Yield 59%, white solid; mp 150−151 °C. IR (KBr, cm^{-1}) 1595, 3429. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34−2.01 (m, 8H), 2.61−2.66 and 2.79−2.84 (2 × bm, together integrating for 1H), 3.26−3.36 (m, 1H), 3.73 (s, 3H), 3.79−3.84 (m, 1H), 3.87 (s, 2H), 3.93 and 4.01 (2 × dd, J = 11.7 and 10.5 Hz, respectively, together integrating for 1H), 5.31−5.33 (m, 2H), 5.56 (s, 1H), 6.56 (d, 2H, J = 8.9 Hz, Ar), 6.76 (d, 2H, J = 8.9 Hz, Ar), 7.27−7.41 (m, 3H, Ar), 7.51−7.56 (m, 2H, Ar), 7.71−7.77 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$) δ 26.79 (CH$_2$), 27.34 (CH$_2$), 28.33 (CH$_2$), 28.60 (CH$_2$), 28.86 (CH$_2$), 28.95 (CH$_2$), 32.45 (CH$_2$) 33.37 (CH$_2$), 37.09 (CH$_2$), 51.70 (CH), 52.03 (CH), 55.98 (CH$_3$), 63.06 (CH$_2$), 63.36 (CH$_2$), 80.65 (CH), 102.18 (C), 102.27 (C), 115.15 (2 × CH), 115.23 (2 × CH), 116.19 (CH$_2$), 116.27 (CH$_2$), 120.09 (CH), 120.23 (CH), 123.19 (CH), 125.27 (CH), 125.38 (CH), 127.05 (CH), 127.17 (CH), 137.27 (C), 141.29 (C), 141.49 (C), 142.04 (C), 143.65 (2 × C), 143.80 (C), 152.34 (C). FAB-MS (*m*/*z*) 469 $[M]^+$. HRMS Calcd for $C_{30}H_{31}NO_4$, 469.2253; found, 469.2247. Anal. Calcd for $C_{30}H_{31}NO_4$: C, 76.73%, H, 6.65%, N, 2.98%. Found: C, 76.51%, H, 6.81%, N, 3.42%.

Trioxane 10g. This was obtained as a white solid in 64% yield as a mixture of diastereomers **10gl** and **10gm**, which were separated by column chromatography.

Trioxane (10gl, Less Polar). Melting point 80−81 °C. IR (KBr, cm^{-1}) 1582, 3406. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31−1.99 (m, 8H), 2.48−2.52 (bm, 1H), 3.39−3.46 (m, 1H), 3.77 (dd, 1H, *J* = 11.8 and 2.9 Hz), 3.85−3.93 (m, 3H), 5.27−5.30 (m, 2H), 5.53 (s, 1H), 6.70−6.76 (m, 2H, Ar), 7.06−7.08 (m, 1H, Ar), 7.18−7.53 (m, 11H, Ar), 7.69−7.75 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.75 (CH_2), 28.09 (CH_2), 28.39 (CH_2), 32.35 (CH_2), 37.09 (CH_2), 50.57 (CH), 63.02 (CH_2), 80.67 (CH), 102.13 (C), 111.21 (CH), 116.27 (CH_2), 117.05 (CH), 120.08 (CH), 120.23 (CH), 123.20 (CH), 125.27 (CH), 125.39 (CH), 127.05 (CH), 127.17 (CH), 127.41 (CH), 127.99 (C), 128.91 (CH), 129.13 (2 × CH), 129.50 (2 × CH), 130.70 (CH), 137.24 (C), 139.65 (C), 141.29 (C), 142.03 (C), 143.64 (C), 143.73 (C), 143.79 (C), 144.07 (C). FAB-MS (*m*/*z*) 515 $[M]^+$. HRMS calcd for $C_{35}H_{33}NO_3$, 515.2460; found, 515.2418. Anal. Calcd for $C_{35}H_{33}NO_3$: C, 81.52%, H, 6.45%, N, 2.72%. Found: C, 81.71%, H, 6.82%, N, 2.51.

Trioxane (10gm, More Polar). Melting point 128−129 °C. IR (KBr, cm^{-1}) 1582, 3406. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30−1.98 (m, 8H), 2.66−2.72 (bm, 1H), 3.38−3.45 (m, 1H), 3.79 (dd, 1H, *J* = 11.7 and 2.7 Hz), 3.86 (s, 2H), 3.98 (dd, 1H, *J* = 11.7 and 10.7 Hz), 5.27−5.30 (m, 2H), 5.53 (s, 1H), 6.71−6.76 (m, 2H, Ar), 7.07−7.09 (m, 1H, Ar), 7.19−7.54 (m, 11H, Ar), 7.69−7.76 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.22 (CH_2), 28.55 (CH_2), 28.68 (CH_2), 33.15 (CH_2), 37.12 (CH_2), 50.76 (CH), 63.30 (CH_2), 80.67 (CH), 102.11 (C), 111.29 (CH), 116.23 (CH_2), 117.06 (CH), 120.10 (CH), 120.25 (CH), 123.21 (CH), 125.28 (CH), 125.42 (CH), 127.07 (CH), 127.19 (CH), 127.49 (CH), 128.22 (C), 128.86 (CH), 129.19 (2 × CH), 129.50 (2 × CH), 130.70 (CH), 137.30 (C), 139.59 (C), 141.32 (C), 142.07 (C), 143.67 (C), 143.72 (C), 143.82 (C), 144.13 (C). FAB-MS (*m*/*z*) 515 $[M]^+$. HRMS calcd for $C_{35}H_{33}NO_3$, 515.2460; found, 515.2418. Anal. Calcd for $C_{35}H_{33}NO_3$: C, 81.52%, H, 6.45%, N, 2.72%. Found: C, 81.68%, H, 6.46%, N,2.32%.

Trioxane 10h. Yield 65%, oil. IR (neat, cm^{-1}) 1599, 3391. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40−1.95 (m, 8H), 2.60−2.65 and 2.79−2.83 (2 × bm, together integrating for 1H), 3.37−3.40 (m, 1H), 3.72−3.79 (m, 1H), 3.84 (s, 2H), 3.89−4.04 (m, 1H), 5.32 (bm, 2H), 5.53 (s, 1H), 6.66 (d, 1H, *J* = 7.9 Hz, Ar), 6.76 (s, 1H, Ar), 6.88 (d, 1H, *J* = 7.5 Hz, Ar), 7.17−7.25 (m, 1H, Ar), 7.30−7.38 (m, 3H, Ar), 7.49−7.54 (m, 2H, Ar), 7.68−7.78 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.73 (CH_2), 27.26 (CH_2), 28.03 (CH_2), 28.31 (CH_2), 28.55 (CH_2), 28.64 (CH_2), 32.33 (CH_2), 33.21 (CH_2), 37.09 (CH_2), 50.42 (CH), 50.71 (CH), 63.09 (CH_2), 63.36 (CH_2), 80.73 (CH), 102.01 (C), 109.46 (CH), 113.72 (CH), 116.22 (CH), 116.27 (CH_2), 120.09 (CH), 120.24 (CH), 123.21 (CH), 125.28 (CH), 125.40 (CH), 127.07 (CH), 127.20 (CH), 128.54 (CH), 129.91 (CH), 131.83 (C, J_{C-F} = 31.9 Hz), 137.25 (C), 137.28 (C), 141.30 (C), 142.08 (C), 143.67 (C), 143.84 (2 × C), 147.52(C). FAB-MS (*m*/*z*) 507 $[M]^+$. HRMS calcd for $C_{30}H_{28}F_3NO_3$, 507.2021; found, 507.2030. Anal. Calcd for $C_{30}H_{28}F_3NO_3$: C, 70.99%, H, 5.56%, N, 2.76%. Found: C, 70.81%, H, 5.32%, N, 2.42%.

Trioxane 10i. This was obtained as oil in 58% yield as a mixture of diastereomers **10il** and **10im**, which were separated by column chromatography.

Trioxane (10il, Less Polar). IR (neat, cm^{-1}) 1617, 3420. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46−2.04 (m, 8H), 2.81−2.86 (bm, 1H), 3.39−3.46 (m, 1H), 3.83 (dd, 1H, *J* = 11.8 and 2.8 Hz), 3.89 (s, 2H), 4.02 (dd, 1H, *J* = 11.8 and 10.5 Hz,), 5.31−5.34 (m, 2H), 5.57 (s, 1H), 6.57 (d, 2H, *J* = 8.4 Hz, Ar), 7.24−7.42 (m, 5H, Ar), 7.53−7.57 (m, 2H, Ar), 7.72−7.78 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.32 (CH_2), 28.55 (CH_2), 28.66 (CH_2), 33.26 (CH_2), 37.16 (CH_2), 50.62 (CH), 63.42 (CH_2), 80.76 (CH), 101.91 (C), 112.36 (2 × CH), 116.37 (CH_2), 118.65 (C, J_{C-F} = 32.1 Hz), 120.14 (CH), 120.28 (CH), 123.25 (CH), 125.32 (CH), 125.45 (CH), 126.91 (CH), 126.95 (CH), 127.11 (CH), 127.25 (CH), 137.31 (C), 141.34 (C), 142.14 (C), 143.75 (2 × C), 143.88 (2 × C), 149.84 (C). FAB-MS (*m*/*z*) 508 $[M + H]^+$. HRMS calcd for $C_{30}H_{28}F_3NO_3$, 507.2021; found, 507.2003; Anal. Calcd for $C_{30}H_{28}F_3NO_3$: C, 70.99%, H, 5.56%, N, 2.76%. Found: C, 71.47%, H, 5.75%, N, 2.44%.

Trioxane (10im, More Polar). IR (neat, cm^{-1}) 1617, 3420. ^1H NMR (300 MHz, $CDCl_3$) δ 1.57−2.03 (m, 8H), 2.62−2.67 (bm, 1H), 3.43−3.49 (m, 1H), 3.83 (dd, 1H, *J* = 11.8 and 2.9 Hz), 3.89 (s, 2H), 3.94 (dd, 1H, *J* = 11.8 and 10.4 Hz), 5.31−5.36 (m, 2H), 5.56 (s, 1H), 6.57 (d, 2H, *J* = 8.5 Hz, Ar), 7.28−7.41 (m, 5H, Ar), 7.53−7.57 (m, 2H, Ar), 7.72−7.78 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.76 (CH_2), 28.03 (CH_2), 28.29 (CH_2), 32.37 (CH_2), 37.16 (CH_2), 50.29 (CH), 63.15 (CH_2), 80.78 (CH), 101.99 (C), 112.37 (2 × CH), 116.29 (CH_2), 119.69 (C, J_{C-F} = 31.8 Hz), 120.15 (CH), 120.29 (CH), 123.27 (CH), 125.33 (CH), 125.46 (CH), 126.93 (CH), 126.97 (CH), 127.12 (CH), 127.26 (CH), 137.27 (C), 141.34 (C), 142.15 (C), 143.70 (2 × C), 143.78 (C), 143.88 (C), 149.82 (C). FAB-MS (*m*/*z*) 508 $[M + H]^+$. HRMS calcd for $C_{30}H_{28}F_3NO_3$, 507.2021; found, 507.2003. Anal. Calcd for $C_{30}H_{28}F_3NO_3$: C, 70.99%, H, 5.56%, N, 2.76%. Found: C, 71.51%, H, 5.81%, N, 2.39%.

Trioxane 11a. Yield 67%, white solid; mp 81−82 °C. IR (KBr, cm^{-1}) 1639, 3433. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40−2.04 (m, 8H), 2.63−2.68 and 2.82−2.86 (2 × bm, together integrating for 1H), 3.36−3.42 (m, 1H), 3.82−3.87 (m, 1H), 3.98 and 4.05 (2 × dd, *J* = 11.8 and 10.6 Hz, respectively, together integrating for 1H), 5.44−5.47 (m, 2H), 5.68 (s, 1H), 6.58 (d, 2H, *J* = 8.1 Hz, Ar), 6.68 (t, 1H, *J* = 7.2 Hz, Ar), 7.16 (t, 2H, *J* = 8.1 Hz, Ar), 7.56−7.74 (m, 5H, Ar), 7.82−7.88 (m, 2H, Ar), 8.67−8.69 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.86 (CH_2), 27.45 (CH_2), 28.26 (CH_2), 28.53 (CH_2), 28.78 (CH_2), 28.88 (CH_2), 32.43 (CH_2), 33.32 (CH_2), 50.60 (CH), 50.94 (CH), 63.07 (CH_2), 63.33 (CH_2), 80.04 (CH), 102.19 (C), 102.27 (C), 113.50 (2 × CH), 117.51 (CH), 117.77 (CH_2), 120.78 (CH), 122.83 (CH), 125.25 (CH), 126.60 (CH), 126.97 (CH), 127.07 (CH), 127.68 (CH), 128.92 (CH), 129.07 (CH), 129.56 (2 × CH), 130.42 (2 × C), 132.00 (C), 132.49 (C), 136.94 (C), 144.04 (C), 147.39 (C). ESI-MS (*m*/*z*) 452 $[M + H]^+$. HRMS calcd for $C_{30}H_{29}NO_3$, 451.2147; found, 451.2102. Anal. Calcd for $C_{30}H_{29}NO_3$: C, 79.80%, H, 6.47%, N, 3.10%. Found: C, 79.92%, H, 6.68%, N, 2.98.

Trioxane 11b. Yield 82%, white solid; mp 96−97 °C. IR (KBr, cm^{-1}) 1596, 3403. ^1H NMR (300 MHz, $CDCl_3$) δ 1.41−1.96 (m, 8H), 2.80−2.85 (bm, 1H), 3.25−3.31 (m, 1H), 3.82 (dd, 1H, *J* = 11.5 and 2.7 Hz), 4.03 (dd, 1H, *J* = 11.5 and 10.2 Hz), 5.41−5.46 (m, 2H), 5.66 (s, 1H), 6.47−6.51 (m, 2H, Ar), 6.82−6.88 (m, 2H, Ar), 7.54−7.72 (m, 5H, Ar), 7.80−7.86 (m, 2H, Ar), 8.66 (bm, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.43 (CH_2), 28.75 (CH_2), 28.86 (CH_2), 33.32 (CH_2), 51.69 (CH), 63.33 (CH_2), 81.04 (CH), 102.16 (C), 114.44 (CH), 114.54 (CH), 115.80 (CH), 116.09 (CH), 117.79 (CH_2), 120.77 (CH), 122.82 (CH), 125.25 (CH), 126.61 (CH), 126.97 (CH), 127.08 (CH), 127.69 (CH), 128.94 (CH), 129.08 (CH), 130.42 (2 × C), 132.00 (C), 132.48 (C), 136.92 (C), 143.71 (C), 144.00 (C), 155.94 (C, J_{C-F} = 235.1 Hz). ESI-MS (*m*/*z*) 470 $[M + H]^+$. HRMS calcd for $C_{30}H_{28}FNO_3$, 469.2053; found, 469.2028. Anal. Calcd for $C_{30}H_{28}FNO_3$: C, 76.74%, H, 6.01%, N, 2.98%. Found: C, 76.89%, H, 6.45%, N, 2.75%.

Trioxane 11c. Yield 63%, white solid; mp 60−61 °C. IR (KBr, cm^{-1}) 1597, 3402. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42−2.01 (m, 8H), 2.65−2.70 and 2.85−2.89 (2 × bm, together integrating for 1H), 3.32−3.42 (m, 1H), 3.88 (dd, 1H, *J* = 11.9 and 2.9 Hz), 4.01 and 4.08 (2 × dd, *J* = 11.9 and 10.4 Hz, respectively, together integrating for 1H), 5.47−5.52 (m, 2H), 5.72 (s, 1H), 6.52 (d, 2H, *J* = 8.6 Hz, Ar), 7.13 (d, 2H, *J* = 8.6 Hz, Ar), 7.61−7.78 (m, 5H, Ar), 7.86−7.92 (m, 2H, Ar), 8.71−8.72 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.39 (CH_2), 28.61 (CH_2), 28.70 (CH_2), 33.25 (CH_2), 51.06 (CH), 63.31 (CH_2), 81.02 (CH), 102.06 (C), 114.52 (2 × CH), 117.78 (CH_2), 120.76 (CH), 121.90 (C), 122.80 (CH), 125.23 (CH), 126.59 (CH), 126.96 (CH), 127.07 (CH), 127.68 (CH), 128.92 (CH), 129.07 (CH), 129.34 (2 × CH), 130.42 (2 × C), 131.99 (C), 132.47 (C), 136.89 (C), 143.98 (C), 145.93 (C). ESI-MS (*m*/*z*) 486 [M + H]$^+$. HRMS calcd for $C_{30}H_{28}ClNO_3$:, 485.1758; found, 485.1768. Anal. Calcd for $C_{30}H_{28}ClNO_3$: C, 74.14%, H, 5.81%, N, 2.88%. Found: C, 74.35%, H, 6.11%, N, 2.62%.

Trioxane 11d. Yield 78%, white solid; mp 70−71 °C. IR (KBr, cm^{-1}) 1590, 3406. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39−1.98 (m, 8H), 2.65−2.68 and 2.84−2.88 (2 × bm, together integrating for 1H), 3.33 (bm, 1H), 3.84−3.89 (m, 1H), 3.98 and 4.06 (2 × dd, *J* = 11.7 and 10.3 Hz, respectively, together integrating for 1H), 5.46−5.50 (m, 2H), 5.71 (s, 1H), 6.43 (s, 2H, Ar), 6.65 (s, 1H, Ar), 7.59−7.77 (m, 5H, Ar), 7.85−7.91 (m, 2H, Ar), 8.69−8.72 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.78 (CH_2), 27.37 (CH_2), 27.99 (CH_2), 28.29 (CH_2), 28.51 (CH_2), 28.62 (CH_2), 32.31 (CH_2), 33.20 (CH_2), 50.48 (CH), 50.79 (CH), 63.08 (CH_2), 63.34 (CH_2), 81.03 (CH), 101.90 (C), 111.34 (2 × CH), 117.01 (CH), 117.81 (CH_2), 120.79 (CH), 122.82 (CH), 125.24 (CH), 126.62 (CH), 126.99 (CH), 127.11 (CH), 127.72 (CH), 128.96 (CH), 129.10 (CH), 130.41 (2 × C), 132.02 (C), 132.50 (C), 135.77 (2 × C), 136.89 (C),143.97 (C), 148.98 (C). ESI-MS (*m*/*z*) 520 [M + H]$^+$. Anal. Calcd for $C_{30}H_{27}Cl_2NO_3$: C, 69.23%, H, 5.23%, N, 2.69%. Found: C, 69.41%, H, 5.61%, N, 2.52%.

Trioxane 11e. Yield 74%, white solid; mp 63−64 °C. IR (KBr, cm^{-1}) 1594, 3421. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24−2.02 (m, 8H), 2.22 (s, 3H), 2.62−2.67 and 2.81−2.85 (2 × bm, together integrating for 1H), 3.33−3.40 (m, 1H), 3.81−3.86 (m, 1H), 3.96 and 4.04 (2 × dd, *J* = 11.7 and 10.3 Hz, respectively, together integrating for 1H), 5.42−5.47 (m, 2H), 5.67 (s, 1H), 6.51 (d, 2H, *J* = 7.9 Hz, Ar), 6.96 (d, 2H, *J* = 7.9 Hz, Ar), 7.56−7.73 (m, 5H, Ar), 7.81−7.87 (m, 2H, Ar), 8.66−8.68 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.59 (CH_3), 26.82 (CH_2), 27.41 (CH_2), 28.24 (CH_2), 28.52 (CH_2), 28.77 (CH_2), 28.88 (CH_2), 32.42 (CH_2), 33.33 (CH_2), 50.89 (CH), 51.25 (CH), 63.04 (CH_2), 63.31 (CH_2), 80.97 (CH), 102.22 (C), 102.31 (C), 113.81 (2 × CH), 117.58 (CH_2), 117.75 (CH_2), 120.73 (CH), 122.81 (CH), 125.21 (CH), 126.58 (CH), 126.76 (CH), 126.95 (CH), 127.05 (CH), 127.66 (CH), 128.90 (CH), 129.06 (CH), 130.02 (2 × CH), 130.39 (2 × C), 131.96 (C), 132.43 (C), 136.87 (C), 143.94 (C), 145.03 (C). ESI-MS (*m*/*z*) 466 [M + H]$^+$. HRMS calcd for $C_{31}H_{31}NO_3$, 465.2304; found, 465.2282; Anal. Calcd for $C_{31}H_{31}NO_3$: C, 79.97%, H, 6.71%, N, 3.01%. Found: C, 79.89%, H, 6.98%, N, 2.97%.

Trioxane 11f. Yield 65%, white solid; mp 110−111 °C. IR (KBr, cm^{-1}) 1593, 3412. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42−2.02 (m, 8H), 2.80−2.85 (bm, 1H), 3.26−3.34 (m, 1H), 3.72(s, 3H), 3.83 (dd, 1H, *J* = 11.8 and 2.8 Hz), 4.04 (dd, 1H, *J* = 11.8 and 10.5 Hz), 5.42−5.47 (m, 2H), 5.67 (s, 1H), 6.56 (d, 2H, *J* = 8.8 Hz, Ar), 6.76 (d, 2H, *J* = 8.8 Hz, Ar), 7.56−7.74 (m, 5H, Ar), 7.82−7.88 (m, 2H, Ar), 8.66−8.68 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.46 (CH_2), 28.90 (CH_2), 29.01 (CH_2), 33.34 (CH_2), 52.08 (CH), 56.02 (CH_3), 63.31 (CH_2), 81.04 (CH), 102.25 (C), 115.23 (2 × CH), 115.29 (2 × CH), 117.74 (CH_2), 120.78 (CH), 122.82 (CH), 125.25 (CH), 126.59 (CH), 126.95 (CH), 127.05 (CH), 127.65 (CH), 128.91 (CH), 129.05 (CH), 130.43 (2 × C), 131.99 (C), 132.48 (C), 136.95 (C), 141.58 (C), 144.06 (C), 152.42 (C). ESI-MS (*m*/*z*) 482 [M + H]$^+$. HRMS calcd for $C_{31}H_{31}NO_4$, 481.2253; found, 481.2247. Anal. Calcd for $C_{31}H_{31}NO_4$: C, 77.31%, H, 6.49%, N, 2.91%. Found: C, 77.53%, H, 6.89%, N, 3.21%.

Trioxane 11g. This was obtained as a white solid in 54% yield as a mixture of diastereomers **11gl** and **11gm**, which were separated by column chromatography.

Trioxane (11gl, Less Polar). Melting point 55−56 °C. IR (KBr, cm^{-1}) 1582, 3406. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−1.99 (m, 8H), 2.49−2.53 (bm, 1H), 3.41−3.46 (m, 1H), 3.80 (dd, 1H, *J* = 11.9 and 2.9 Hz), 3.93 (dd, 1H, *J* = 11.9 and 10.2 Hz), 5.40−5.45 (m, 2H), 5.66 (s, 1H), 6.70−6.76 (m, 2H, Ar), 7.06−7.08 (m, 1H, Ar), 7.18−7.24 (m, 1H, Ar), 7.30−7.43 (m, 5H, Ar),7.56−7.73 (m, 5H, Ar), 7.81−7.88 (m, 2H, Ar), 8.65−8.68 (m, 2H, Ar).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.85 (CH_2), 28.15 (CH_2), 28.46 (CH_2), 32.37 (CH_2), 50.58 (CH), 63.03 (CH_2), 81.02 (CH), 102.24 (C), 111.21 (CH), 117.05 (CH), 117.73 (CH_2), 120.80 (CH), 122.84 (CH), 125.27 (CH), 126.62 (CH), 126.98 (CH), 127.08 (CH), 127.44 (CH), 127.69 (CH), 128.05 (C), 128.94 (2 × CH), 129.07 (CH), 129.16 (2 × CH), 129.54 (2 × CH), 130.44 (CH), 130.73 (2 × C), 132.01 (C), 132.50 (C), 136.94 (C), 139.72 (C), 144.08 (C), 144.18 (C). ESI-MS (*m*/*z*) 528 [M + H]$^+$. HRMS calcd for $C_{36}H_{33}NO_3$, 527.2460; found, 527.2468. Anal. Calcd for $C_{36}H_{33}NO_3$: C, 81.95%, H, 6.30%, N, 2.65%. Found: C, 81.51%, H, 6.17%, N, 2.82%.

Trioxane (11gm, More Polar). Melting point 70−71 °C. IR (KBr, cm^{-1}) 1582, 3406. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33−1.96 (m, 8H), 2.70−2.75 (bm, 1H), 3.38−3.46 (m, 1H), 3.82 (dd, 1H, *J* = 11.8 and 2.9 Hz), 4.02 (dd, 1H, *J* = 11.8 and 10.5 Hz), 5.40−5.44 (m, 2H), 5.66 (s, 1H), 6.70−6.76 (m, 2H, Ar), 7.07−7.10 (m, 1H, Ar), 7.18−7.24 (m, 1H, Ar), 7.33−7.46 (m, 5H, Ar), 7.56−7.71 (m, 5H, Ar), 7.81−7.88 (m, 2H, Ar), 8.65−8.68 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.31 (CH_2), 28.61 (CH_2), 28.73 (CH_2), 32.16 (CH_2), 50.78 (CH), 63.29 (CH_2), 80.96 (CH), 102.18 (C), 111.25 (CH), 117.03 (CH), 117.64 (CH_2), 120.77 (CH), 122.84 (CH), 125.24 (CH), 126.61 (CH), 126.97 (CH), 127.08 (CH), 127.50 (CH), 127.68 (CH), 128.20 (C), 128.88 (CH), 128.93 (CH), 129.08 (CH), 129.20 (2 × CH), 129.53 (2 × CH), 130.42 (2 × C), 130.72 (CH), 132.01 (C), 132.49 (C), 136.93 (C), 139.63 (C), 144.01 (C), 144.22 (C). ESI-MS (*m*/*z*) 528 [M + H]$^+$. Anal. Calcd for $C_{36}H_{33}NO_3$: C, 81.95%, H, 6.30%, N, 2.65%. Found: C, 81.59%, H, 6.45%, N, 2.42%.

Trioxane 11h. Yield 72%, white solid; mp 55−57 °C. IR (KBr, cm^{-1}) 1570, 3412. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−2.01 (m, 8H), 2.62−2.67 and 2.82−2.87 (2 × bm, together integrating for 1H), 3.38−3.43 (m, 1H), 3.83 (dd, 1H, *J* = 11.7 and 2.8 Hz), 3.96 and 4.04 (2 × dd, *J* = 11.7 and 10.5 Hz, respectively, together integrating for 1H), 5.43−5.46 (m, 2H), 5.67 (s, 1H), 6.67 (d, 1H, *J* = 8.0 Hz, Ar), 6.75 (s, 1H, Ar), 6.88 (d, 1H, *J* = 7.6 Hz, Ar), 7.18−7.23 (m, 1H, Ar), 7.58−7.70 (m, 5H, Ar), 7.82−7.88 (m, 2H, Ar), 8.66−8.68 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.78 (CH_2), 27.37 (CH_2), 28.05 (CH_2), 28.34 (CH_2), 28.60 (CH_2), 28.70 (CH_2), 32.35 (CH_2), 33.25 (CH_2), 50.42 (CH), 50.76 (CH), 63.10 (CH_2), 63.36 (CH_2), 81.04 (CH), 102.03 (C), 109.38 (CH), 113.79 (CH), 116.30 (CH), 117.84 (CH_2), 120.79 (CH), 122.83 (CH), 125.25 (CH), 126.62 (CH), 127.00 (CH), 127.11 (CH), 127.72 (CH), 128.96 (CH), 129.11 (CH), 129.95 (C) 130.40 (C), 131.66 (C), 131.87 (C, J_{C-F} = 31.8 Hz), 132.02 (C), 132.49 (C), 136.90 (C), 143.96 (C), 147.52 (C). ESI-MS (*m*/*z*) 520 [M + H]$^+$. HRMS calcd for $C_{31}H_{28}F_3NO_3$, 519.2021; found, 519.2027. Anal. Calcd for $C_{31}H_{28}F_3NO_3$: C, 71.66%, H, 5.43%; N, 2.70%. Found: C, 71.22%, H, 5.82%; N, 2.66%.

Trioxane 11i. This was obtained as oil in 56% yield as a mixture of diastereomers **11il** and **11im**, which were separated by column chromatography.

Trioxane (11il, Less Polar). IR (neat, cm^{-1}) 1589, 3413. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−2.02 (m, 8H), 2.87−2.91 (bm, 1H), 3.42−3.43 (m, 1H), 3.89 (dd, 1H, *J* = 11.8 and 2.8 Hz), 4.09 (dd, 1H, *J* = 11.8 and 10.3 Hz,), 5.48−5.52 (m, 2H), 5.73 (s, 1H), 6.58 (d, 2H, *J* = 8.5 Hz, Ar), 7.41 (d, 2H, *J* = 8.5 Hz, Ar), 7.61−7.78 (m, 5H, Ar). 7.86−7.93 (m, 2H, Ar), 8.70−8.72 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.36 (CH_2), 28.51 (CH_2), 28.61 (CH_2), 33.21 (CH_2), 50.56 (CH), 63.33 (CH_2), 81.05 (CH), 101.96 (C), 112.34 (2×CH), 117.82 (CH_2), 118.77 (C, J_{C-F} = 32.4 Hz), 120.78 (CH), 122.81 (CH), 123.45 (C), 125.24 (CH), 126.61 (CH), 126.88 (CH), 126.93 (CH), 126.98 (CH), 127.10 (CH), 127.72 (CH), 128.96 (CH), 129.10

(CH), 130.41 (C), 130.45 (C), 132.02 (C), 132.50 (C), 136.90 (C), 143.96 (C), 149.84 (C). ESI-MS (*m*/*z*) 520 [M + H]$^+$. HRMS calcd for $C_{31}H_{28}F_3NO_3$, 519.2021; found, 519.2016; Anal. Calcd for $C_{31}H_{28}F_3NO_3$: C, 71.66%, H, 5.43%, N, 2.70%. Found: C, 71.93%, H, 4.96%, N, 2.60%.

Trioxane (11im, More Polar). IR (neat, cm^{-1}) 1685, 3415. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28−2.06 (m, 8H), 2.68−2.72 (bm, 1H), 3.44−3.47 (m, 1H), 3.87−3.92 (m, 1H), 4.01 (dd, 1H, J = 11.8 and 10.4 Hz,), 5.48−5.52 (m, 2H), 5.72 (s, 1H), 6.58 (d, 2H, J = 8.4 Hz, Ar), 7.41 (d, 2H, J = 8.4 Hz, Ar), 7.61−7.78 (m, 5H, Ar). 7.86−7.92 (m, 2H, Ar), 8.66−8.74 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.77 (CH_2), 27.97 (CH_2), 28.24 (CH_2), 32.31 (CH_2), 50.23 (CH), 63.05 (CH_2), 80.99 (CH), 102.00 (C), 112.32 (2 × CH), 117.64 (CH_2), 118.81 (C, J_{C-F} = 32.3 Hz), 120.75 (CH), 122.80 (CH), 123.33 (C), 125.23 (CH), 126.59 (CH), 126.87 (CH), 126.97 (2 × CH), 127.08 (CH), 127.70 (CH), 128.93 (CH), 129.08 (CH), 130.39 (C), 130.44 (C), 132.00 (C), 132.48 (C), 136.86 (C), 143.99 (C), 149.78 (C). ESI-MS (*m*/*z*) 520 [M + H]$^+$. Anal. Calcd for $C_{31}H_{28}F_3NO_3$: C, 71.66%, H, 5.43%, N, 2.70%. Found: C, 71.78%, H, 5.68%, N, 2.43%.

Trioxane 12a. Yield 14% yield, oil. IR (neat, cm^{-1}) 1587, 3425. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48−1.82 (m, 7H), 2.33−2.58 (m, 2H), 3.62−3.81 (m, 2H) 3.86−3.96 (m, 1H), 5.11 (dd, 1H, J = 10.3 and 2.2 Hz), 5.38 (s, 1H), 5.68 (s, 1H), 7.23 (d, 1H, J = 7.3 Hz, Ar), 7.38 (t, 1H, J = 7.5 Hz, Ar), 7.43−7.51 (m, 2H, Ar), 7.76−7.83 (m, 2H, Ar), 7.96 (d, 1H, J = 7.6 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.02 (CH_2), 25.51 (CH_2), 29.96 (CH_2), 30.13 (CH_2), 30.38 (CH_2), 30.50 (CH_2), 30.78 (CH_2), 31.49 (CH_2), 62.63 (CH_2), 63.00 (CH_2), 67.79 (CH), 68.30 (CH), 81.67 (CH), 102.02 (C), 119.83 (CH_2), 125.24 (CH), 125.35 (CH), 125.99 (CH), 126.10 (CH), 126.52 (CH), 128.45 (CH), 128.49 (CH), 131.35 (C), 133.72 (C), 137.19 (C), 143.27 (C). ESI-MS (*m*/*z*) 326 [M]$^+$. HRMS calcd for $C_{20}H_{22}O_4$, 326.1518; found, 326.1519.

Trioxane 12b. Yield 12%, white solid; mp 105−106 °C. IR (KBr, cm^{-1}) 1595, 3425. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37−2.17 (m, 8H), 2.37−2.42 (m, 1H), 3.80−3.96 (m, 2H), 4.01 (dd, 1H, J = 11.7 and 10.4 Hz), 5.38−5.42 (m, 2H), 5.65 (s, 1H), 7.46−7.55 (m, 3H, Ar), 7.80−7.84 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.35 (CH_2), 30.43 (CH_2), 30.60 (CH_2), 31.20 (CH_2), 63.28 (CH_2), 67.78 (CH), 68.29 (CH), 80.77 (CH), 102.46 (C), 117.28 (CH_2), 124.80 (CH), 125.72 (CH), 126.76 (CH), 126.87 (CH), 128.01 (CH), 128.65 (CH), 128.71 (CH), 133.43 (C), 133.65 (C), 136.20 (C), 143.65 (C). ESI-MS (*m*/*z*) 327 [M + H]$^+$. HRMS calcd for $C_{20}H_{22}O_4$, 326.1518; found, 326.1520.

Trioxane 12c. Yield 10%, white solid; mp 150−151 °C. IR (KBr, cm^{-1}) 1596, 3411. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53−2.10 (m, 8H), 2.35−2.43 and 2.58−2.62 (2 × m, together integrating for 1H), 3.78−3.85 (m, 2H), 3.87 (s, 2H), 3.95 and 3.97 (2 × dd, J = 11.7 and 2.8 Hz, together integrating for 1H), 5.28−5.32 (m, 2H), 5.54 (s, 1H), 7.23−7.40 (m, 3H, Ar), 7.51−7.55 (m, 2H, Ar), 7.70−7.76 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.16 (CH_2), 30.25 (CH_2), 30.42 (CH_2), 31.02 (CH_2), 37.13 (CH_2), 63.07 (CH_2), 68.11 (CH), 80.72 (CH), 102.22 (C), 116.20 (CH_2), 120.11 (CH), 120.26 (CH), 123.23 (CH), 125.29 (CH), 125.43 (CH), 127.08 (CH), 127.19 (CH), 137.34 (C), 141.34 (C), 142.07 (C), 143.69 (C), 143.83 (2 × C). ESI-MS (*m*/*z*) 364 [M]$^+$. HRMS calcd for $C_{23}H_{24}O_4$, 364.1675; found, 364.1665. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80%, H, 6.64%. Found: C, 75.31%, H, 6.24%.

Trioxane 12d. Yield 13%, oil. IR (neat, cm^{-1}) 1656, 3428. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63−2.00 (m, 8H), 2.42−2.47 and 2.66−2.67 (2 × m, together integrating for 1H), 3.82−3.89 (m, 2H), 3.99−4.06 (m, 1H), 5.45−5.50 (m, 2H), 5.69 (s, 1H), 7.59−7.76 (m, 5H, Ar), 7.84−7.90 (m, 2H, Ar), 8.70−8.72 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.14 (CH_2), 25.64 (CH_2), 30.11 (CH_2), 30.28 (CH_2), 30.54 (CH_2), 30.63 (CH_2), 30.93 (CH_2), 31.62 (CH_2), 62.91 (CH_2), 63.25 (CH_2), 67.93 (CH), 68.46 (CH), 80.89 (CH), 102.12 (C), 117.58 (CH_2), 117.70 (CH_2), 120.64 (CH), 122.75 (CH), 125.15 (CH), 126.52 (CH), 126.89 (CH), 126.98 (CH), 127.57 (CH), 128.83 (CH), 128.99 (CH), 130.31 (2 × C), 131.87 (C), 132.36 (C), 136.81 (C), 143.87 (C). ESI-MS (*m*/*z*) 394 [M + NH_4]$^+$. HRMS calcd for $C_{24}H_{24}O_4$, 376.1675; found, 376.1676.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR Spectra of trioxanes **7a−d**, **8a−i**, **9a−i**, **10a−i**, and **11a−i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) 100% protection means none of the treated mice developed patent infection during the 28 days observation period and hence were recorded as cured. Similarly, 20% protection means only one out of five mice was cured. (b) 100% suppression of parasitemia means no parasites were detected in 50 oil immersion microscopic fields (parasites if at all present are below the detection limit). The parasites present below the detection limit can multiply and eventually can be detected during observation on subsequent days. In such cases, though, the drug is providing near 100% suppression of the parasitaemia on day 4 but will not provide full protection to the treated mice in the 28 day survival assay. Multidrug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine, and halofantrine.

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