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Synthesis of novel 1,2,4-trioxanes and antimalarial evaluation against multidrug-resistant *Plasmodium yoelii nigeriensis*

Monika Shukla [b], Mohammad Hassam [a,*], Dinesh Kumar Yadav [c], Siddharth Sharma [c], Chandan Singh [a], Sunil K. Puri [d], Rahul Shrivastava [e], Ved Prakash Verma [a,b,*]

[a] Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, India
[b] Department of Chemistry, Banasthali University, Banasthali Newai 304022, Rajasthan, India
[c] Department of Chemistry, Mohanlal Sukhadia University, Udaipur 313001, India
[d] Parasitology Division, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, India
[e] Department of Chemistry, Manipal University Jaipur, VPO-DehmiKalan, off Jaipur-Ajmer Express Way, Jaipur, Rajasthan, India

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ABSTRACT

Malaria epidemics represent one of the life-threatening diseases to low-income lying countries which subsequently affect the economic and social condition of mankind. In continuation in the development of a novel series of 1,2,4-trioxanes **13a1-c1**, **13a2-c2**, and **13a3-c3** have been prepared and further converted into their hemisuccinate derivatives **14a1-c1**, **14a2-c2**, and **14a3-c3** respectively. All these new compounds were evaluated for their antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in mice by both oral and intramuscular (im) routes. Hydroxy-functionalized trioxane **13a1** showed 80% protection and its hemisuccinate derivative **14a1** showed 100% protection at a dose of 48 mg/kg × 4 days by both routes, which is twice active than artemisinin by oral route.

Malaria is one of the major diseases that cause higher mortality among the low-income tropical and sub-tropical areas of the world. Despite comprehensive global efforts for the eradication of malaria, about 40% of the world population still is at risk of the disease. Of these 2.5 billion people at risk, more than 500 million become ill and more than a million, mostly children, die of malaria every year.[1] The rapid emergence of multidrug-resistant *P. falciparum* has been further complicated the problem against commonly used antimalarial drugs.[2–4] Artemisinin **1**, and its semi-synthetic analogs are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *P. falciparum*.[5–9] The lesser abundance from natural resources has made the artemisinin circumscribed used for the synthesis of semi-synthetic analogs.[10] The discovery of peroxide group present in the form of 1,2,4-trioxane in artemisinin as an active pharmacophore for its antimalarial activity, has encouraged the scientist to develop simple, economical, and effective substitute having 1,2,4-trioxane units.[11] Since then, numerous simple molecules containing 1,2,4-trioxanes have been synthesized and evaluated antimalarial activity by the different group including us.[12–19]

In continuation with these efforts herein, we report the synthesis and antimalarial activity of hydroxy-functionalized trioxanes and their hemisuccinates derivatives, hemisuccinate **14a1** has shown a better antimalarial profile than artemisinin by both oral and im routes. A graphical representation of the evolution of our work on trioxanes resulting in the current series of molecules is shown in Fig 1.[20–22]

Hydroxy-functionalized trioxanes **13a1**–**c1**, **13a2**–**c2**, and **13a3**–**c3**, and their corresponding hemisuccinate derivatives **14a1**–**c1**, **14a2**–**c2**, and **14a3**–**c3** were prepared by the procedure shown in Scheme 1. Thus, the reaction of *p*-fluoroacetophenone **6** with 2,7-dihydroxynaphthalene **7a** in refluxing in DMSO furnished ketone **8a** in 41% yield. A similar reaction of *p*-fluoroacetophenone **6** with 1,5-dihydroxynaphthalene **7b** and quinol **7c**, furnished ketones **8b** and **8c** in 32% and 31% yields, respectively. Compounds **8a–c** on reaction with ethyl chloroacetate furnished ketoesters **9a–c** in 86–93% yields. Wittig reaction of compounds **9a–c** with triethyl phosphonoacetate/NaH furnished α,β-unsaturated esters **10a–c** in 75–92% yields. Reduction of α,β-unsaturated esters **10a–c** with $LiAlH_4$ furnished allylic alcohols **11a–c** in 75–86% yields. Dye-sensitized photooxygenation[23] of allylic alcohols **11a–c** furnished β-hydroxyhydroperoxides **12a–c**, which were reacted in situ with cyclopentanone, cyclohexanone and, 2-

* Corresponding authors at: Department of Chemistry, Banasthali University, Banasthali Newai 304022, Rajasthan, India (V.P. Verma).
E-mail addresses: hassam2@gmail.com (M. Hassam), vedprakash@banasthali.in (V. Prakash Verma).

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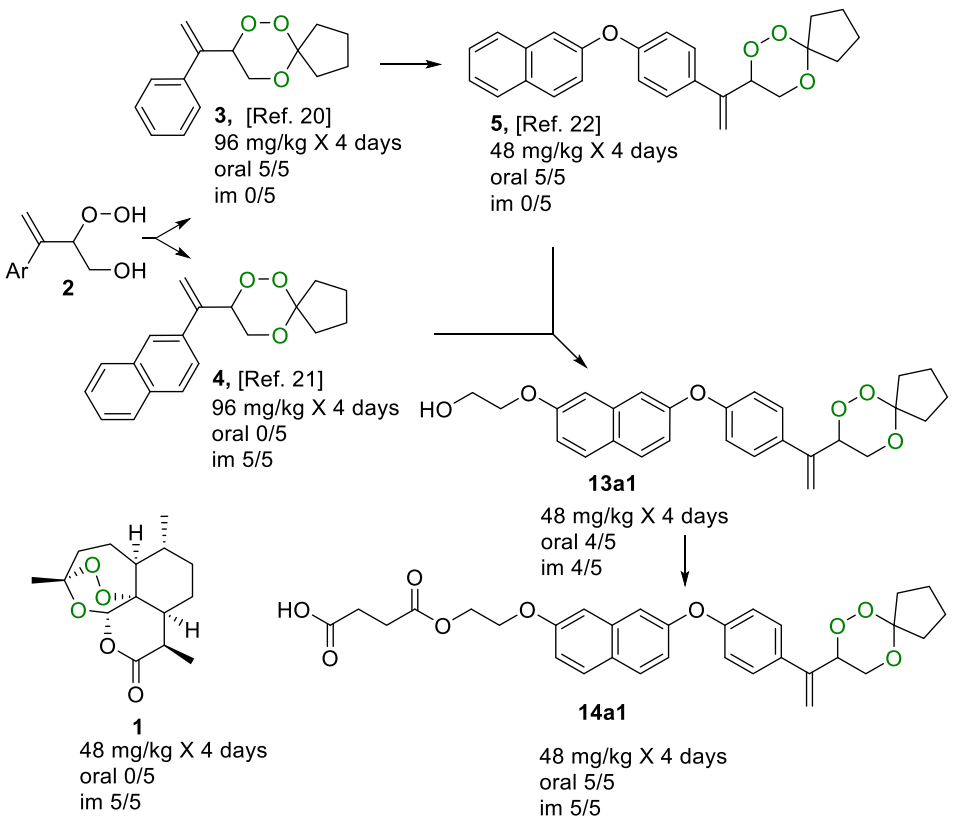
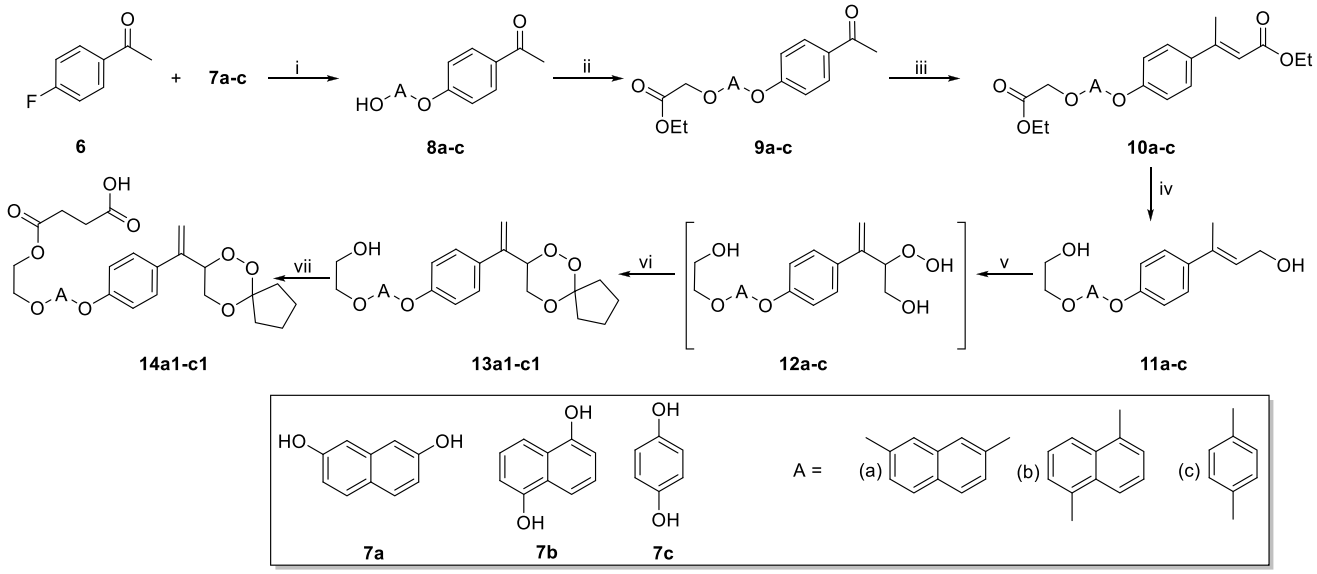


Fig. 1. Graphical depiction of the evolution of our work on trioxanes leading to the current series of hydroxy-functionalized 1,2,4-trioxanes and hemisuccinate.

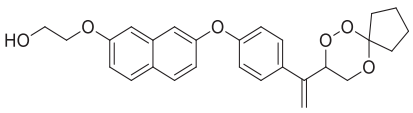
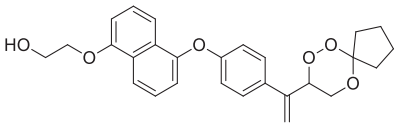
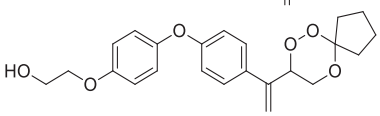
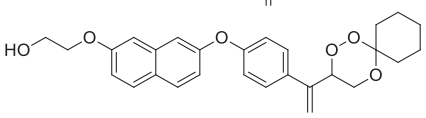
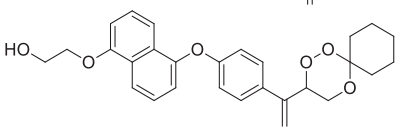
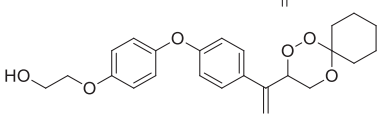
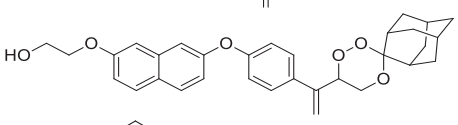
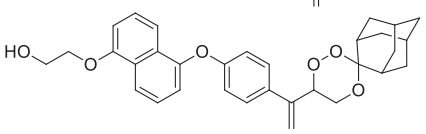
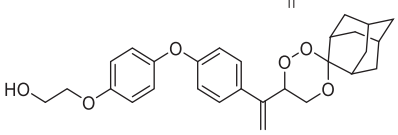
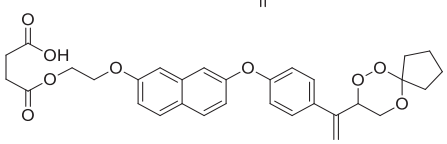
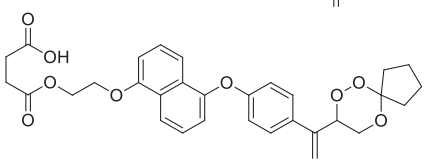
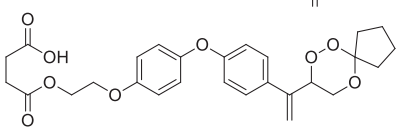
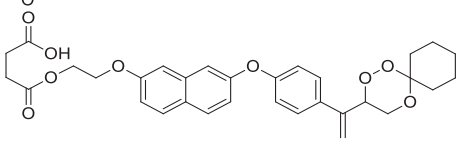


Scheme 1. The synthesis of compounds **13a1-c1, 13a2-c2, 13a3-c3** and **14a1–c1, 14a2–c2, 14a3–c3;** Reaction conditions: (i) Anhyd. K_2CO_3/DMSO, reflux, 4 h; (ii) Anhyd. K_2CO_3/$ClCH_2COEt$, Acetone, reflux, 8 h; (iii) $(OEt)_2P(O)CH_2CO_2Et$/NaH, THF, rt., 16–21 h; (iv) LAH/THF, 0 °C, 1 h; (v) $^1O_2$/CH_3CN, THF, −10 to 0 °C, 6–8 h; (vi) Cyclopentanone, cyclohexanone and 2-adamantanone/CH_3CN, conc. HCl, rt, 1 h. (vii) Succinic anhydride, Et_3N, DMAP, CH_2Cl_2, rt., 3 h.

adamantanone to furnish trioxanes **13a1–c1**, **13a2–c2** and **13a3–c3** in 48–69% yields (Scheme 1). These hydroxy-functionalized trioxanes were converted into hemisuccinate derivatives **14a1–c1**, **14a2–c2** and **14a3–c3** by treating with triethylamine and succinic anhydride at room temperature.[24]

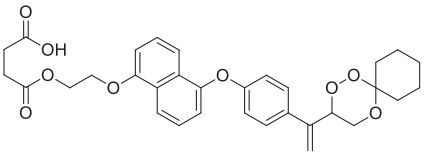
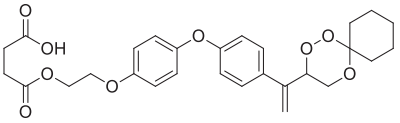
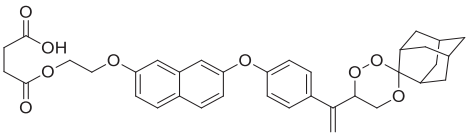
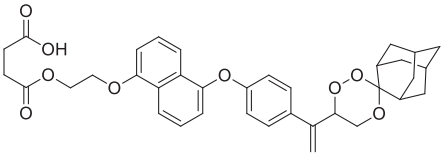
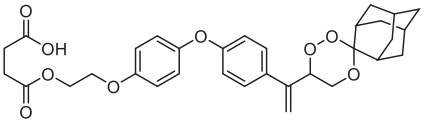
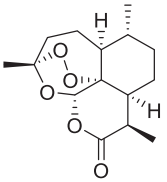
Trioxanes **13a1**, **13b1**, **13a2**, **13b2**, **13a3**, **3b3** and hemisuccinates **14a1**, **14b1**, **14a2**, **14b2**, **14a3, 14b3** (Table 1), were screened for antimalarial activity against multidrug-resistant *P. yoelii* in Swiss mice initially at a dose of 48 mg/kg × 4 days by both oral and intramuscular (im) antimalarial activity.[25–27] Trioxanes **13c1**, **13c2**, **13c3**, hemisuccinates **14c1**, **14c2** and **14c3** were screened at 96 mg/kg. Trioxane **13a1**, the most active compound of the series, showed 100% clearance of parasitaemia by both oral and im routes at 48 mg/kg × 4 days and 80% of the treated mice survived beyond day 28. Trioxane **13b3**, the next best compound of the series, showed 100% clearance of parasitaemia by oral route at 48 mg/kg × 4 days and 40% of the treated mice

Table 1
Blood schizontocidal activity of hydroxy-functionalized trioxanes **13a1-c1**, **13a2-c2**, **13a3-c3** and hemisuccinates **14a1-c1**, **14a2-c2**, and **14a3-c3**, against multidrug-resistant *P. yoelii* in Swiss mice via oral and im routes.

Compd.	Structure	Log *P*	Dose Mg/kg × 4 days	Route	% supp. on day-4[a,b]	Cured/Treated mice
13a1		5.49	48	oral	100	4/5
			48	im	100	4/5
13b1		5.49	48	oral	44.12	0/5
			48	im	46.18	0/5
13c1		4.49	96	oral	38.40	0/5
			96	im	85.23	0/5
13a2		5.91	48	oral	83.49	0/5
			48	im	71.60	0/5
13b2		5.91	48	oral	38.24	0/5
			48	im	46.18	0/5
13c2		4.91	96	oral	45.36	0/5
			96	im	72.42	0/5
13a3		6.54	48	oral	83.17	0/5
			48	im	51.39	0/5
13b3		6.54	48	oral	100	2/5
			48	im	46.18	0/5
13c3		5.55	96	oral	100	5/5
			48	oral	85.47	0/5
			96	im	100	0/5
14a1		5.39	48	oral	100	5/5
			24	oral	100	0/5
			48	im	100	5/5
			24	im	100	4/5
14b1		5.39	48	oral	39.41	0/5
			48	im	28.32	0/5
14c1		4.39	96	oral	44.34	0/5
			96	im	77.76	0/5
14a2		5.81	48	oral	100	1/5
			48	im	100	3/5
14b2		5.81	48	oral	49.77	0/5
			48	im	26.57	0/5

(*continued on next page*)

Table 1 (*continued*)

Compd.	Structure	Log *P*	Dose Mg/kg × 4 days	Route	% supp. on day-4[a,b]	Cured/Treated mice
						
14c2		4.81	96	oral	10.03	0/5
			96	im	28.41	0/5
14a3		6.44	48	oral	77.38	0/5
			48	im	58.82	0/5
14b3		6.44	48	oral	27.49	0/5
			48	im	42.23	0/5
14c3		5.44	96	oral	35.65	0/5
			96	im	100	2/5
1		3.17	96	oral	100	0/5
			48	im	100	5/5
			24	im	100	4/5

[a] Percent suppression = [(C−T)/C] × 100, where C = parasitaemia in control group and T = parasitaemia in treated group.
[b] log *P* values have been calculated from ChemDraw Professional 15.1.

survived beyond day 28; there was no survival when the compound was given intramuscularly. Trioxane **13c3**, showed 100% clearance of parasitaemia by oral route at 96 mg/kg × 4 days and 100% of the treated mice survived beyond day 28. Even at dose 48 mg/kg × 4 days it gave 86% suppression of parasitaemia by oral route, none of the treated mice survived beyond day 28; when it administered through im route at 96 mg/kg × 4 days it gave 100% suppression of parasitaemia but none of the treated mice survived beyond day 28. Trioxanes **13a2**, **13a3**, **13b1**, **13b2**, **13c1** and **13c2** showed only moderate suppression of parasitaemia and none of the treated mice survived.

Hemisuccinate **14a1**, the most active compound of the series, showed 100% clearance of parasitaemia by both oral and im routes at 48 mg/kg × 4 days and all the treated mice survived beyond day 28. Even at 24 mg/kg × 4 days it showed 100% clearance of parasitaemia and 80% of the treated mice survived beyond day 28; when the compound was given intramuscularly; there was no survival, when the compound was given orally. Hemisuccinate **14a2**, the next best compound of the series, showed 100% clearance of parasitaemia by both oral and im routes at 48 mg/kg × 4 days and 60% of the treated mice survived beyond day 28; when the compound was given by im route, but only 10% of the treated mice survived when compound was given orally. Hemisuccinate **14c3**, showed 100% clearance of parasitaemia by im route at 96 mg/kg × 4 days and 40% of the treated mice survived beyond day 28. Hemisuccinates **14a3** showed 58–77% suppression of parasitaemia by both oral and im routes at 48 mg/kg × 4 days and none of the treated mice survived till day 28. Other hemisuccinates **14b1**, **14b2**, **14b3**, **14c1** and **14c2** showed poor antimalarial activity.

The present work reports a series of hydroxy-functionalized trioxanes **13a1–c1**, **13a2–c2**, **13a3–c3**, and their corresponding hemi succinate derivatives **14a1–c1**, **14a2–c2**, and **14a3–c3**, respectively. Hydroxy-functionalized trioxane **13a1** provided 80% protection and its hemisuccinate derivative **14a1** showed 100% protection at a dose of 48 mg/kg × 4 days by both routes, which is twice active than artemisinin by oral route. Hopefully, the outcome of our finding the antimalarial activity of current trioxanes series by both routes helps the scientist in finding the better drug candidate in fighting against malaria.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interest

The authors confirm that this article content has no conflict of interest.

Appendix A. Supplementary data

Supplementary data (^{1}H and ^{13}C NMR Spectra of **8a–c, 9a–c**, **10a–c,**

11a-c, 13a1–a3, 13b1–b3, 13c1–c3, 14a1–a3, 14b1–b3, and **14c1–c3**) to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.128305.

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24 General procedure for the preparation of ketones 8a-c: preparation of ketone **8a**. A mixture of *p*-fluoroacetophenone **6** (17.0 g, 123 mmol), 2,7-dihydroxynaphthalene **7a** (39.42 g, 246 mmol, 2.0 equiv) and anhyd. K_2CO_3 (67.89 g, 492 mmol, 4.0 equiv) in DMSO (50 mL) was refluxed for 4 h, with continuous stirring. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ether (3 × 200 mL). The organic layer was dried over anhyd. Na_2SO_4 and concentrated to furnish a crude product, which was purified by column chromatography over silica gel (60–120 mesh) using EtOAc/Hexane (2:98) as eluent furnished ketone **8a** (14.04 g, 41% yield) as a white solid, mp 140–142 °C. Compounds **8b–c** were prepared by the above procedure by condensing *p*-fluoroacetophenone with 1,5-dihydroxynaphthalene 7b and quinol 7c, respectively. *1-[4-(7-Hydroxy-naphthalen-2-yloxy)-phenyl]-ethanone* (**8a**). Yield 41%, white solid, mp 140–142 °C; IR (KBr, cm^{-1}) 1655, 3429; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 5.52 (s, phenolic OH), 7.10–7.03 (m, 5H, Ar), 7.28–7.26 (m, 1H, Ar), 7.76 (d, 1H, Ar, J = 8.5 Hz), 7.79 (d, 2H, Ar, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.73 (CH3), 109.22 (CH), 114.98 (CH), 117.46 (CH), 118.06 (CH), 126.38 (C), 130.01 (CH), 130.31 (CH), 130.89 (CH), 132.11 (C), 135.87 (C), 154.09 (C), 154.56 (C), 162.18 (C), 197.37 (C); FAB-MS (m/z) 279 $[M+H]^+$. *1-[4-(5-Hydroxy-naphthalen-1-yloxy)-phenyl]-ethanone* (**8b**). Yield 32%, white solid, mp 175–177 °C; IR (KBr, cm^{-1}) 1655, 3209; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 5.89 (s, phenolic OH), 6.89 (d, 1H, Ar, J = 7.3 Hz), 7.01 (d, 2H, Ar, J = 8.8 Hz), 7.17 (d, 1H, Ar, J = 6.8 Hz), 7.31 (t, 1H, Ar, J = 7.5 Hz), 7.47 (t, 1H, Ar, J = 7.5 Hz), 7.58 (d, 1H, Ar, J = 8.5 Hz), 7.95 (d, 2H, Ar, J = 8.8 Hz), 8.11 (d, 1H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.52 (CH3), 109.48 (CH), 114.41 (CH), 116.74 (CH), 116.80 (CH), 119.03 (CH), 125.11 (CH), 126.17 (C), 126.52 (CH), 128.48 (C), 130.76 (CH), 131.66 (C), 150.88 (C), 151.82 (C), 162.83 (C), 197.12 (C); ESI (m/z) 279 $[M+H]^+$. *1-[4-(4-Hydroxy-phenoxy)-phenyl]-ethanone* (**8c**). Yield 31%, white solid, mp 150–153 °C; IR (KBr, cm^{-1}) 1656, 3316; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 5.21 (s, phenolic OH), 6.87 (d, 2H, Ar J = 9.0 Hz), 6.94 (d, 2H, Ar, J = 8.9 Hz), 6.97 (d, 2H, Ar, J = 9.0 Hz), 7.92 (d, 2H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.68 (CH3), 116.53 (CH), 116.79 (CH), 122.12 (CH), 130.84 (CH), 131.51 148.66 (C), 152.96 (C), 163.18 (C), 197.30 (C); ESI (m/z) 229 $[M+H]^+$. *General procedure for the preparation of esters 9a–c: preparation of ester* **9a**. A mixture of 8a (8 g, 28.77 mmol), ethyl chloroacetate (5.26 mL, 43.16 mmol, 1.5 equiv) and anhyd. K_2CO_3 (11.91 g, 86.33 mmol, 3.0 equiv) in acetone (50 mL) was refluxed for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, filter and combined organic layer was dried over anhydrous Na_2SO_4 and concentrated and the crude product was purified by column chromatography over silica gel (60–120 mesh) using EtOAc/Hexane (2:98) as eluent furnished compound **9a** (9.0 g, 86% yield) as a white solid, mp 115-120 °C. Compounds **9b** and **9c** were prepared by the above procedure. *[7-(4-Acetyl-phenoxy)-naphthalen-2-yloxy]-acetic acid ethyl ester* (**9a**). Yield 86%, white solid, mp 115–120 °C; IR (KBr, cm^{-1}) 1680, 1752; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 2.58 (s, CH3), 4.28 (q, 2H, J = 7.2 Hz), 4.71 (s, 2H), 6.97 (d, 1H, Ar, J = 2.4 Hz), 7.05 (d, 2H, Ar, J = 8.9 Hz), 7.11 (dd, 1H, Ar, J = 8.8 and 2.4 Hz), 7.20 (dd, 1H, Ar, J = 8.9 and 2.5 Hz), 7.31 (d, 1H, Ar, J = 2.3 Hz), 7.77 (d, 1H, Ar, J = 9 Hz), 7.80 (d, 1H, Ar, J = 8.9 Hz), 7.95 (d, 2H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.36 (CH3), 26.70 (CH3), 61.71 (CH2), 65.51 (CH2), 106.72 (CH), 115.48 (CH), 117.81 (CH), 118.23 (CH), 118.48 (CH), 126.81 (C), 129.86 (CH), 130.17 (CH), 130.82 (CH), 132.22 (CH), 135.52 (C), 154.18 (C), 156.71 (C), 162.02 (C), 168.88 (C), 197.04 (C); FAB-MS (m/z) 365 $[M+H]^+$. *[5-(4-Acetyl-phenoxy)-naphthalen-1-yloxy]-acetic acid ethyl ester* (**9b**). Yield 93%, white solid, mp 95–98 °C; IR (KBr, cm^{-1}) 1672, 1744; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 2.53 (s, CH3), 4.29 (q, 2H, J = 7.2 Hz), 4.81 (s, 2H), 6.73 (d, 1H, Ar, J = 7.4 Hz), 6.96 (d, 2H, Ar, J = 8.9 Hz), 7.14 (dd, 1H, Ar, J = 7.5 and 1 Hz), 7.32 (t, 1H, Ar, J = 7.7 Hz), 7.45 (dd, 1H, Ar, J = 8.5 and 7.5 Hz), 7.59 (d, 1H, Ar, J = 8.4 Hz), 7.90 (d, 2H, Ar, J = 8.9 Hz), 8.23 (d, 1H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.40 (CH3), 26.64 (CH3), 61.68 (CH2), 66.01 (CH2), 106.1 (CH), 115.42 (CH), 116.94 (CH), 117.19 (CH), 119.64 (CH), 125.65 (CH), 126.37 (CH), 127.56 (C), 128.54 (C), 130.88 (CH), 132.0 (C), 150.99 (C), 154.1 (C), 162.94 (C), 168.87 (C), 196.93 (C); FAB-MS (m/z) 365 $[M+H]^+$.ESI (m/z) 365 $[M+H]^+$. *[4-(4-Acetyl-phenoxy)-phenoxy]-acetic acid ethyl ester* (**9c**). Yield 86%, oil; IR (Neat, cm^{-1}) 1677, 1757; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 2.56 (s, 3H), 4.29 (q, 2H, J = 7.2 Hz), 4.63 (s, 2H), 6.93–6.95 (m, 4H, Ar), 7.02 (d, 2H, Ar, J = 9.1 Hz), 7.92 (d, 2H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.37 (CH3), 26.65 (CH3), 61.66 (CH2), 66.04 (CH2), 116.24 (CH), 116.70 (CH), 121.86 (CH), 130.78 (CH), 131.70 (C), 149.50 (C), 155.04 (C), 162.81 (C), 169.02 (C), 196.99 (C); ESI (m/z) 471 $[M+Na]^+$; HRMS calcd for $C_{27}H_{28}O_6$ 448.1885; found, 488.1884.ESI (m/z) 315 $[M+H]^+$. *General procedure for the preparation of α,β-unsaturated esters* **10a-c**: preparation of compound 10a. To a stirred slurry of NaH (60% dispersion in mineral oil, 6.15 g, 250 mmol, 4.0 equiv), in dried THF (20 mL) kept at 0 °C under N_2 atmosphere, a solution of triethyl phosphonoacetate (38.46 g, 153 mmol, 4.0 equiv) in dried THF (50 mL) was added, and the reaction mixture was allowed to stir at rt for 1 h. The ketone **9a** (14 g, 38.46 mmol) dissolved in dried THF (100 mL) was added dropwise and the reaction mixture was further stirred at room temperature for 20 h. The reaction mixture was quenched with water (100 mL), extracted with ether (3 × 200 mL). The organic layer was dried over anhyd. Na_2SO_4, concentrated and purified by column chromatography over silica gel (60-120 mesh) using EtOAc/Hexane (1:99) as eluent furnished diester **10a** (14.69 g, 84% yield) as an oil. Compounds **10b** and **10c** were prepared by the above procedure *3-[4-(7-Ethoxycarbonylmethoxy-naphthalen-2-yloxy)-phenyl]-but-2-enoic acid ethyl ester* (**10a**). Yield 84%, oil; IR (Neat, cm^{-1}) 1709, 1759; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 1.29 (t, 3H, J = 7.2 Hz), 2.56 (d, 3H, J = 1.2 Hz), 4.19 (q, 2H, J = 7.2 Hz), 4.26 (q, 2H, J = 7.2 Hz), 4.68 (s, 2H), 6.12 (d, 1H, J = 1.2 Hz), 6.92 (d, 1H, Ar, J = 2.5 Hz), 7.01 (d, 2H, Ar, J = 8.8 Hz), 7.10 (dd, 1H, Ar, J = 8.8 and 2.4 Hz), 7.15 (dd, 1H, Ar, J = 9 and 2.5 Hz), 7.21 (d, 1H, Ar, J = 2.3 Hz), 7.46 (d, 2H, Ar, J = 8.9 Hz), 7.73 (t, 2H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.36 (CH3), 14.54 (CH3), 17.98 (CH3), 60.03 (CH2), 61.67 (CH2), 65.53 (CH2), 106.65 (CH), 114.14 (CH), 116.56 (CH), 117.82 (CH), 118.20 (CH), 118.82 (CH), 126.42 (C), 128.09 (CH), 129.80 (CH), 129.96 (C), 135.55 (CH), 137.19 (C), 154.77 (C), 155.35 (C), 156.65 (C), 158.30 (C), 167.12 (C), 168.92 (C); ESI (m/z) 435 $[M+H]^+$, 457 $[M+Na]^+$. *3-[4-(5-Ethoxycarbonylmethoxy-naphthalen-1-yloxy)-phenyl]-but-2-enoic acid ethyl ester* (**10b**). Yield 92%, oil; IR (Neat, cm^{-1}) 1709, 1760; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.32 (m, 6H), 2.54 (d, 3H, J = 1.2 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.29 (q, 2H, J = 7.2 Hz), 4.81 (s, 2H), 6.09 (d, 1H, J = 1 Hz), 6.74 (d, 1H, Ar, J = 7.5 Hz), 6.96 (d, 2H, Ar, J = 8.8 Hz), 7.06 (dd, 1H, Ar, J = 7.4 and 1 Hz), 7.33 (t, 1H, Ar, J = 7.8 Hz), 7.39-7.44 (m, 3H, Ar), 7.71 (d, 1H, Ar, J = 8.5 Hz), 8.17 (d, 1H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.40 (CH3), 14.55 (CH3), 17.97 (CH3), 60.01 (CH2), 61.66 (CH2), 65.96 (CH2), 105.99 (CH), 115.56 (CH), 115.89 (CH), 116.35 (CH), 117.83 (CH), 118.70 (CH), 125.64 (CH), 126.08 (CH), 127.40 (C), 128.08 (CH), 128.43 (C), 136.69 (C), 152.0 (C), 153.96 (C), 154.83 (C), 159.34 (C), 167.16 (C), 168.93 (C); ESI (m/z) 435 $[M+H]^+$. *3-[4-(4-Ethoxycarbonylmethoxy-phenoxy)-phenyl]-but-2-enoic acid ethyl ester* (**10c**). Yield 75%, oil; IR (Neat, cm^{-1}) 1755; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 2 × 2H, J = 7.1 Hz), 2.58 (d, 3H, J = 1.2 Hz), 4.22 (q, 2H, J = 7.1 Hz), 4.30 (q, 2H, J = 7.1 Hz), 4.64 (s, 2H), 6.12-6.13 (m, 1H), 6.92-6.95 (m, 4H, Ar), 7.01 (d, 2H, Ar, J = 9.1 Hz), 7.45 (d,

2H, Ar, J = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.39 (CH3), 14.56 (CH3), 17.96 (CH3), 60.02 (CH2), 61.65 (CH2), 66.13 (CH2), 116.15 (CH), 116.25 (CH), 117.49 (CH), 121.27 (CH), 127.98 (CH), 136.41 (C), 150.58 (C), 154.57 (C), 154.85 (C), 159.37 (C), 167.17 (C), 169.12 (C); EI+ (m/z) 384. *General procedure for the preparation of allylic alcohols **11a-c**: preparation of allylic alcohol* (**11a**). To a magnetically stirred, ice-cooled mixture of $LiAlH_4$ (3.49 g, 92 mmol, 4.0 equiv) in dried THF (100 mL) diester 10a (10 g, 23.04 mmol) was added under nitrogen atmosphere and the reaction mixture was allowed to stir for 1 h at 0 °C. The reaction mixture was quenched with 5% aqueous NaOH (5 mL) and water (10 mL) and. The organic layer was decanted, dried over anhyd. Na_2SO_4, concentrated to furnish a crude product which was crystallized in ethyl acetate furnished allylic alcohol 11a (6.04 g, 75% yield) as a white solid, mp 120–122 °C. Allylic alcohols **11b** and **11c** *were prepared by the above procedure. 3-{4-[7-(2-Hydroxy-ethoxy)-naphthalen-2-yloxy]-phenyl}-but-2-en-1-ol* (**11a**) Yield 75%, white solid, mp 120–122 °C; IR (KBr, cm^{-1}) 1680, 3283; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (d, 3H, J = 1 Hz), 3.76 (q, 2H, J = 5.3 Hz), 4.06 (t, 2H, J = 4.8 Hz), 4.16 (t, 2H, J = 4.8 Hz), 4.73 (t, 1H, J = 5.4 Hz), 4.91 (t, 1H, J = 5.5 Hz), 5.88-5.91 (m, 1H), 7.05 (d, 2H, Ar, J = 8.8 Hz), 7.07–7.12 (m, 2H, Ar), 7.27 (dd, 2H, Ar, J = 7.5 and 2.4 Hz), 7.48 (d, 2H, Ar, J = 8.8 Hz), 7.81 (d, 1H, Ar, J = 8.9 Hz), 7.87 (d, 1H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.07 (CH3), 58.70 (CH2), 59.97 (CH2), 70.02 (CH2), 106.65 (CH), 113.14 (CH), 117.41 (CH), 118.06 (CH), 119.28 (CH), 125.56 (CH), 127.46 (CH), 128.65 (CH), 129.62 (CH), 130.26 (CH), 133.98 (C), 135.98 (C), 138.39 (C), 155.68 (C), 156.05 (C), 157.74 (C); ESI (m/z) 323 [M+Na]$^+$ESI (m/z) 351 [M+H]$^+$. *3-{4-[5-(2-Hydroxy-ethoxy)-naphthalen-1-yloxy]-phenyl}-but-2-en-1-ol* (**11b**). Yield 86%, white solid, mp 114–117 °C; IR (KBr, cm^{-1}) 1594, 3233; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H), 3.87 (q, 2H, J = 5.3 Hz), 4.14 (t, 2H J = 5.7 Hz), 4.18 (t, 2H, J = 4.7 Hz), 4.72 (t, 1H, J = 5.4 Hz), 5.02 (t, 1H, J = 5.7 Hz), 5.85-5.88 (m, 1H), 6.96 (d, 2H, Ar, J = 8.7 Hz), 7.04 (d, 1H, Ar, J = 7.6 Hz), 7.07 (d, 1H, Ar, J = 7.5 Hz), 7.42-7.49 (m, 4H, Ar), 7.58 (d, 1H, Ar, J = 8.4 Hz), 8.09 (d, 1H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.25 (CH3), 60.17 (CH2), 61.83 (CH2), 69.84 (CH2), 105.97 (CH), 114.93 (CH), 115.04 (CH), 117.67 (CH), 118.17 (CH), 125.45 (CH), 125.90 (CH), 126.22 (CH), 127.33 (CH), 128.29 (CH), 137.41 (C), 137.83 (C), 152.83 (C), 154.51 (C), 157.61 (C);ESI (m/z) 351[M+H]$^+$. *3-{4-[4-(2-Hydroxy-ethoxy)-phenoxy]-phenyl}-but-2-en-1-ol* (**11c**). Yield 84%, white solid, mp 92–93 °C; IR (KBr, cm^{-1}) 1597, 3342; 1H NMR (400 MHz, Acetone-d_6) δ 2.01 (d, 3H, J = 1.1 Hz), 2.92 (brs, 1OH), 3.76 (t, 1OH, J = 5.4 Hz), 3.87 (q, 2H, J = 5.4 Hz), 4.27 (t, 2H, J = 4.6 Hz), 5.94–5.90 (m, 1H), 6.88 (d, 2H, Ar, J = 8.9 Hz), 6.97 (s, 4H, Ar), 7.41 (d, 2H, Ar, J = 8.8 Hz); ^{13}C NMR (100 MHz, Acetone-d_6) δ 16.01 (CH3), 59.83 (CH2), 61.42 (CH2), 71.04 (CH2), 116.53 (CH), 118.01 (CH), 121.64 (CH), 127.80 (CH), 128.46 (CH), 135.47 (C), 138.42 (C), 150.96 (C), 156.56 (C), 158.70 (C);ESI (m/z) 323 [M+Na]$^+$. General procedure for the preparation 1,2,4-trioxanes: preparation of *trioxane* **13a1**. A solution of allylic alcohol **11a** (1 g, 2.85 mmol) and methylene blue (5 mg) was taken in 250 mL double jacket flask, in a mixture of acetonitrile (100 mL) and THF (100 mL) was irradiated with 500 W tungsten–halogen lamp at -0 °C to -10 °C, while a slow stream of O_2 was bubbled into the reaction mixture for 6 h. The reaction mixture was concentrated on a rotatory evaporator at room temperature and then dissolved in acetonitrile (20 mL), cyclopentanone (1.44 mL, 17.14 mmol, 6.0 equiv) and conc. HCl (0.05 mL) were added and the reaction mixture was stirred for 1 h at rt. The reaction mixture was concentrated under vacuum at the room temperature, and the crude product was purified by column chromatography over silica gel (60-120 mesh) using EtOAc/Hexane (5:95) as eluent furnished trioxane **13a1** (691 mg, 54% yield) as a white crystalline solid, mp 76–80 °C. Trioxanes **13b1**, **13c1**, were prepared from allylic alcohols **11b–c** using the above procedure and trioxanes **13a2–c2** and **13a3–13c3** were prepared from allylic alcohols **11a–c** by replacing cyclopentanone with cyclohexanone and 2-admantanone, respectively. *2-(7-{4-[1-(6,7,10-Trioxa-spiro [4.5]dec-8-yl)-vinyl]-phenoxy}-naphthalen-2-yloxy)-ethanol* (**13a1**). Yield 54%, white solid, mp 76–80 °C; IR (KBr, cm^{-1}) 1593, 3510; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66–1.95 (m, 7H), 2.04 (brs, OH), 2.46–2.52 (m, 1H), 3.87 (d, 2H, J = 6.4 Hz), 4.01 (brs, 2H), 4.17 (t, 2H, J = 4.2 Hz), 5.30-5.26 (m, 2H), 5.48 (s, 1H), 7.04–7.01 (m, 3H, Ar), 7.08 (t, 1H, Ar, J =2.5 Hz), 7.11 (t, 1H, Ar, J =2.3 Hz), 7.21 (d, 1H, Ar, J = 2.3 Hz), 7.38 (d, 2H, Ar, J = 8.7 Hz), 7.73 (t, 2H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.57 (CH2), 24.98 (CH2), 33.01 (CH2), 37.23 (CH2), 61.66 (CH2), 65.24 (CH2), 69.40 (CH2), 80.48 (CH), 106.5 (CH), 113.74 (CH), 114.82 (C), 116.10 (CH2), 117.85 (CH), 119.18 (CH), 126.07 (C), 128.11 (CH), 129.60 (CH), 129.9 (CH), 133.89 (C), 135.80 (C), 142.71 (C), 155.64 (C), 157.47 (C); ESI (m/z) 471 [M+Na]$^+$; HRMS calcd for $C_{27}H_{28}O_6$ 448.1885; found, 488.1884. *2-(5-{4-[1-(6,7,10-Trioxa-spiro[4.5]dec-8-yl)-vinyl]-phenoxy}-naphthalen-1-yloxy)-ethanol* (**13b1**). Yield 59%, oil; IR (Neat, cm^{-1}) 1504, 3409; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72–1.94 (m, 7H), 2.49–2.58 (m, 1H), 2.78 (brs, OH), 3.88 (d, 2H, J = 6.1 Hz), 4.10 (t, 2H, J = 4.3 Hz), 4.25 (t, 2H, J = 4.3 Hz), 5.28–5.33 (m, 2H), 5.47 (s, 1H), 6.85 (d, 1H, Ar, J = 7.7 Hz), 6.98 (d, 2H, Ar, J = 8.8 Hz), 7.05 (d, 1H, Ar, J = 7.5 Hz), 7.34-7.42 (m, 4H, Ar), 7.76 (d, 1H, Ar, J = 8.5 Hz), 8.13 (d, 1H, Ar, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.79 (CH2), 25.2 (CH2), 33.23 (CH2), 37.45 (CH2), 61.89 (CH2), 65.45 (CH2), 70.16 (CH2), 80.7 (CH), 106.28 (CH), 115.03 (C), 115.11 (CH), 115.58 (CH), 116.17 (CH2), 118.42 (CH), 118.94 (CH), 125.61 (CH), 126.59 (CH), 127.63 (C), 128.29 (CH), 128.56 (C), 133.63 (C), 142.91 (C), 152.65 (C), 154.86 (C), 158.66 (C); FAB-MS (m/z) 449 [M+H]$^+$; HRMS. calcd for $C_{27}H_{28}O_6$ 448.1886; found, 448.1867. *2-(4-{4-[1-(6,7,10-Trioxa-spiro[4.5]dec-8-yl)-vinyl]-phenoxy}-phenoxy)-ethanol* (**13c1**). Yield 63%, oil; IR (Neat, cm^{-1}) 1598, 3446; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68–1.93 (m, 7H), 2.32 (brs, OH), 2.48–2.56 (m, 1H), 3.86 (d, CH2, J = 6.2 Hz), 3.98 (d, 2H, J = 4.2 Hz), 4.09 (t, 2H, J = 4 Hz), 5.26–5.30 (m, 2H), 5.49 (s,1H), 6.91 (dd, 4H, Ar, J = 9.3 and 2.9 Hz), 7.0 (d, 2H, Ar, J = 9.2 Hz), 7.34 (d, 2H, Ar, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) d 23.53 (CH2), 24.94 (CH2), 32.96 (CH2), 37.19 (CH2), 61.63 (CH2), 65.22 (CH2), 69.92 (CH2), 80.48 (CH), 114.75 (C), 115.77 (CH2), 115.88 (CH), 117.61 (CH), 121.18 (CH), 127.92 (CH), 132.96 (C), 142.7 (C), 150.28 (C), 155.3 (C), 158.69 (C); ESI (m/z) 399 [M+H]$^+$; HRMS calcd for $C_{23}H_{26}O_6$ 398.1729; found, 398.17. *2-(7-{4-[1-(1,2,5-Trioxa-spiro[5.5]undec-3-yl)-vinyl]-phenoxy}-naphthalen-2-yloxy)-ethanol* (**13a2**). Yield 60%, white solid, mp 107–109 °C; IR (KBr, cm^{-1}) 1598, 3516; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.64 (m, 8H), 1.96–2.03 (m, 2H), 2.17–2.2 (m, 1H), 3.77 (dd, 1H, J = 11.9 and 2.9 Hz), 3.95–4.01 (m, 3H), 4.18 (t, 2H, J = 4.3 Hz), 5.20–5.27 (m, 3H), 5.28 and 5.47 (2 × s, 2H), 7.00–7.02 (m, 3H, Ar), 7.06–7.10 (m, 2H, Ar), 7.19 (d, 1H, Ar, J = 2.3 Hz), 7.37 (d, 2H, Ar, J = 8.8 Hz), 7.70 (d, 1H, Ar, J = 9 Hz), 7.73 (d, 1H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.50 (CH2), 22.54 (CH2) 25.74 (CH2), 29.21 (CH2), 34.85 (CH2), 61.67 (CH2), 62.86 (CH2), 69.39 (CH2), 80.46 (CH), 102.87 (C), 106.47 (CH), 113.67 (CH), 116.02 (CH2), 117.84 (CH), 119.23 (CH), 126.05 (C), 128.10 (CH), 129.61 (CH), 129.90 (CH), 134.02 (C), 135.79 (C), 142.90 (C), 155.68 (C), 157.42 (C), 157.46 (C); ESI (m/z) 485 [M+Na]$^+$; HRMS calcd for $C_{28}H_{30}O_6$ 462.2042; found, 462.2040. *2-(5-{4-[1-(1,2,5-Trioxa-spiro[5.5]undec-3-yl)-vinyl]-phenoxy}-naphthalen-1-yloxy)-ethanol* (**13b2**). Yield 48%, oil; IR (Neat, cm^{-1}) 1598, 3421; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.65 (m, 9H), 1.98-2.07 (m, 1H), 2.18–2.28 (m, 1H), 3.79 (dd, 1H, J = 11.9 and 3 Hz), 4.0 (dd, 1H, J = 11.9 and 10.4 Hz), 4.13 (t, 2H, J = 4.8 Hz), 4.31 (t, 2H, J = 4.2 Hz), 5.23 (dd, 1H, J = 10.7 and 2.6 Hz), 5.29 and 5.48 (2 × s, 2H), 6.9 (d, 1H, Ar, J = 7.5 Hz), 6.98 (dd, 2H, Ar, J = 6.7 and 2 Hz), 7.05 (dd, 1H, Ar, J = 7.5 and 0.7 Hz), 7.35-7.44 (m, 4H, Ar), 7.76 (d, 1H, Ar, J = 8.5 Hz), 8.10 (d, 1H, Ar, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.48 (CH2), 22.52 (CH2), 25.75 (CH2), 29.24 (CH2), 34.86 (CH2), 61.77 (CH2), 62.85 (CH2), 69.91 (CH2), 80.5 (CH), 102.83 (C), 106.09 (CH), 114.98 (CH), 115.31 (CH), 115.83 (CH2), 118.01 (CH), 118.22 (CH), 125.43 (CH), 126.34 (CH), 127.49 (C), 128.12 (CH), 128.36 (C), 133.63 (C), 142.99 (C), 152.53 (C), 154.6 (C), 158.43 (C); FAB-MS (m/z) 463 [M+H]$^+$; HRMS calcd for $C_{28}H_{30}O_6$ 462.2042; found, 462.2040. *2-(4-{4-[1-(1,2,5-Trioxa-spiro[5.5]undec-3-yl)-vinyl]-phenoxy}-phenoxy)-ethanol* (**13c2**). Yield 69%, oil; IR (Neat, cm^{-1}) 1599, 3447; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41–1.60 (m, 8H), 1.95–1.99 (m, 2H), 2.16–2.21 (m, 1H), 3.73 (dd, 1H, J = 11.9 and 3 Hz), 3.92–.97 (m, 3H), 4.06 (t, 2H, J = 4.2 Hz), 5.19 (dd, 1H, J = 10.4 and 2.8 Hz), 5.24 and 5.42 (2 × s, 2H), 6.87 (d, 2H, Ar, J = 6.3 Hz), 6.89 (d, 2H, Ar, J = 6.3 Hz), 6.96 (d, 2H, Ar, J = 9.1 Hz), 7.30 (d, 2H, Ar, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.50 (CH2), 22.54 (CH2), 25.75 (CH2), 29.21 (CH2), 34.87 (CH2), 61.74 (CH2), 62.89 (CH2), 69.89 (CH2), 80.50 (CH), 102.83 (C), 115.71 (CH2), 115.89 (CH), 117.67 (CH), 121.22 (CH), 127.95 (CH), 133.11 (C), 142.93 (C), 150.35 (C), 155.30 (C), 158.70 (C); ESI (m/z) 413 [M+H]$^+$; HRMS calcd for $C_{24}H_{28}O_6$ 412.1886; found, 412.1886. *Trioxane* (**13a3**). Yield 62%, white solid, mp 60–63 °C; IR (KBr, cm^{-1}) 1599, 3435; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12–1.60 (m, 13H), 2.24 (brs, OH), 2.98 (brs, 1H), 3.82 (dd, 1H, J = 11.9 and 3 Hz), 3.98–4.05 (m, 3H), 4.17 (t, 2H, J = 4.1 Hz), 5.26-5.31 (m, 2H), 5.51 (s, 1H), 7.04 (d, 3H, Ar, J = 8.7 Hz), 7.09-7.14 (m, 2H, Ar), 7.23 (d, 1H, Ar, J = 2.3 Hz), 7.41 (d, 2H, Ar, J = 8.6 Hz), 7.74 (dd, 2H, Ar, J = 10.5 and 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3 (CH), 29.55 (CH), 33.15 (CH2), 33.39 (CH2) 33.62 (CH2), 33.73 (CH2), 36.38 (CH), 37.33 (CH2), 61.55 (CH2), 62.28 (CH2), 69.38 (CH2), 80.22 (CH), 104.87 (C), 106.43 (CH), 113.62 (CH), 115.9 (CH2), 117.76 (CH), 117.79 (CH), 119.18 (CH), 125.99 (C), 128.01 (CH), 129.54 (CH), 129.84 (CH), 134.02 (C), 135.75 (C), 142.86 (C), 155.62 (C), 157.35 (C), 157.43 (C); ESI (m/z) 537 [M+Na]$^+$; Anal. calcd for $C_{32}H_{34}O_6$ C, 74.69, H, 6.66; found, C, 74.49, H, 6.78. HRMS (EI+) calcd for $C_{32}H_{34}O_6$ 514.2357; found, 514.2357. *Trioxane* (**13b3**). Yield 66%, oil; IR (Neat, cm^{-1}) 1598, 3421; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65–2.09 (m, 13H), 2.42 (brs, OH), 2.97 (brs, 1H), 3.8 (dd, 1H, J = 11.9 and 2.9 Hz), 3.99 (dd, 1H, J = 11.8 and 10.7 Hz), 4.12 (t, 2H, J = 4.7 Hz), 4.28 (t, 2H, J = 4.3 Hz), 5.24-5.29 (m, 2H), 5.48 (s, 1H), 6.87 (d, 1H, Ar, J = 7.7 Hz), 6.98 (d, 2H, Ar, J = 8.7 Hz), 7.05 (d, 1H, Ar, J = 7.4 Hz), 7.36-7.4 (m, 4H, Ar), 7.76 (d, 1H, Ar, J = 8.5 Hz), 8.11 (d, 1H, Ar, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.31 (2 × CH), 29.57 (CH), 33.15 (CH2), 33.4 (CH2), 33.63 (CH2), 33.73 (CH2), 36.38 (CH), 37.35 (CH2), 61.69 (CH2), 62.31 (CH2), 69.88 (CH2), 80.25 (CH), 104.84 (C), 106.02 (CH), 114.91 (CH), 115.26 (CH), 115.7 (CH2), 117.99 (CH), 118.19 (CH), 125.36 (CH), 126.28 (CH), 127.36 (C), 128.3 (CH), 133.57 (C), 142.9 (C), 152.45 (C), 154.56 (C), 158.36 (C); ESI (m/z) 537 [M+Na]$^+$; Anal. calcd for $C_{32}H_{34}O_6$ C, 74.69, H, 6.66; found, C, 74.49, H, 6.78; HRMS (EI+) calcd for $C_{32}H_{34}O_6$ 514.2357; found, 514.2357. *Trioxane* (**13c3**). Yield 53%, whit solid, mp 95–98 °C; IR (KBr, cm^{-1}) 1601, 3463; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60–2.07 (m, 13H), 2.32 (brs, OH), 2.96 (brs, 1H), 3.78 (dd, 1H, J = 11.9 and 2.7 Hz), 3.94-4.01 (m, 3H), 4.08 (t, 2H, J = 4 Hz), 5.22–5.27 (m, 2H), 5.46 (s, 1H), 6.91 (dd, 4H, Ar, J = 9.3 and 2.8 Hz), 6.99 (d, 2H, Ar, J = 7.8 Hz), 7.35 (d, 2H, Ar, J = 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.33 (2 × CH), 29.58 (CH), 33.17 (CH2), 33.41 (CH2), 33.65 (CH2), 33.74 (CH2), 36.40 (CH), 37.37 (CH2), 61.63 (CH2), 62.32 (CH2), 69.94 (CH2), 80.29 (CH), 104.83 (C), 115.58 (CH2), 115.89 (CH), 117.65 (CH), 121.13 (CH), 127.88 (CH), 133.16 (C), 142.95 (C), 150.34 (C), 155.29 (C), 158.64 (C); ESI (m/z) 465 [M+H]$^+$; HRMS calcd for $C_{28}H_{32}O_6$ 464.2199; found, 464.2169. General procedure for the preparation of hemisuccinates **14a1**–**14c3**: *Preparation of hemisuccinates* **14a1**. A solution of trioxane **13a1** (150 mg, 0.33 mmol), Et_3N (0.1 mL, 0.99 mmol, 3.0 equiv), succinic anhydride (100 mg, 1.0 mmol 3.0 equiv) and DMAP (2 mg) in DCM (20 mL) was stirred for 3 h at room temperature. Reaction mixture was quenched by adding 10% HCl solution and extracted with DCM (3 × 25 mL). Solvent was evaporated and crude product was purified by the column chromatography over silica gel (60-120 mesh) using EtOAc/Hexane (1:4) as eluent furnished hemisuccinate 14a1 (161 mg, 88% yield) as a white solid, mp 85–90 °C. Hemisuccinates **14a2–a3**, **14b1–b3** and **14c1–c3** were prepared by the above procedure. *Succinic acid mono-[2-(7-{4-[1-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-vinyl]-phenoxy}-naphthalen-2-yloxy)-ethyl] ester* (**14a1**). Yield 88%, white solid, mp 85–90 °C; IR (KBr, cm^{-1}) 1508, 1690, 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69–1.91 (m, 7H), 2.46–2.52 (m, 1H), 2.64 (s, 4H), 3.84–3.87 (m, 2H), 4.22 (t, 2H, J = 4.7 Hz), 4.48 (t, 2H, J = 4.3 Hz), 5.26–5.29 (m, 2H), 5.46 (s, 1H), 7.97 (d, 1H, Ar, J = 2.3 Hz), 7.0 (d, 2H, Ar, J = 8.8 Hz), 7.07 (td, 2H, Ar, J = 8.8 and 2.3 Hz), 7.18 (d, 1H, Ar, J = 2.3 Hz), 7.38 (d, 2H, Ar, J = 8.8 Hz), 7.69 (d, 1H, Ar, J = 8.8 Hz), 7.73 (d, 1H, Ar, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.57 (CH2), 24.98 (CH2), 28.87 (CH2), 28.97 (CH2), 33.0 (CH2), 37.22 (CH2), 63.25 (CH2), 65.24 (CH2), 65.97 (CH2), 80.45

(CH), 106.43 (CH), 113.71 (CH), 114.83 (C), 116.10 (CH2), 117.88 (CH), 119.18 (CH), 126.10 (C), 128.10 (CH), 129.60 (CH), 129.88 (CH), 133.87 (C), 135.72 (C), 142.65 (C), 155.63 (C), 157.28 (C), 157.43 (C), 172.31 (C), 177.16 (C); FAB-MS (m/z) 549 $[M+H]^+$; HRMS calcd for $C_{31}H_{32}O_9$ 548.2046; found, 548.1845. *Succinic acid mono-[2-(5-{4-[1-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-vinyl]-phenoxy}-naphthalen-1-yloxy)-ethyl] ester* (**14b1**). Yield 86%, oil; IR (Neat, cm-1) 1504, 3409; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68–1.96 (m, 7H), 2.48–2.57 (m, 1H), 2.71 (s, 4H), 3.87 (d, 2H, $J = 6$ Hz), 4.37 (t, 2H, $J = 4.7$ Hz), 4.64 (t, 2H, $J = 4.3$ Hz), 5.28–5.31 (m, 2H), 5.47 (s, 1H), 6.86 (d, 1H, Ar, $J = 7.6$ Hz), 6.97 (d, 2H, Ar, $J = 8.7$ Hz), 7.06 (d, 1H, Ar, $J = 7.5$ Hz), 7.35–7.45 (m, 4H, Ar), 7.74 (d, 1H, Ar, $J = 8.5$ Hz), 8.08 (d, 1H, Ar, $J = 8.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.55 (CH2), 24.96 (CH2), 29.04 (CH2), 33.0 (CH2), 37.22 (CH2), 63.27 (CH2), 65.25 (CH2), 66.52 (CH2), 80.5 (CH), 105.92 (CH), 115.05 (C), 115.48 (CH), 115.93 (CH2), 118.15 (CH), 118.32 (CH), 125.48 (CH), 126.24 (CH), 127.46 (C), 128.07 (CH), 128.36 (C), 133.4 (C), 142.74 (C), 152.34 (C), 154.52 (C), 158.5 (C), 172.37 (C), 177.51 (C); FAB-MS (m/z) 549 $[M+H]^+$; HRMS. calcd for $C_{31}H_{32}O_9$ 548.2046; found, 548.2046. *Succinic acid mono-[2-(4-{4-[1-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-vinyl]-phenoxy}-phenoxy)-ethyl] ester* (**14c1**). Yield 90%, white solid, mp 72–75 °C; IR (KBr, cm^{-1}) 1596, 3434; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70–1.86 (m, 7H), 2.49–2.53 (m, 1H), 2.71 (s, 4H), 3.86 (d, 2H, $J = 6.2$ Hz), 4.18 (t, 2H, $J = 5$ Hz), 4.47 (t, 2H, $J = 4.6$ Hz), 5.26-5.3 (m, 2H), 5.45 (s,1H), 6.89-7.01 (m, 6H, Ar), 7.34 (dd, 2H, Ar, $J = 6.7$ and 2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.54 (CH2), 24.95 (CH2), 28.9 (CH2), 28.98 (CH2), 32.98 (CH2), 37.21 (CH2), 61.37 (CH2), 65.24 (CH2), 66.6 (CH2), 80.51 (CH), 114.78 (C), 115.78 (CH2), 116.05 (CH), 117.66 (CH), 121.18 (CH), 127.95 (CH), 133.02 (C), 142.75 (C), 150.44 (C), 155.13 (C), 158.69 (C) 172.26 (C), 177.19 (C); ESI (m/z) 516 $[M+NH_4]^+$; HRMS calcd for $C_{27}H_{30}O_9$ 498.1890; found, 498.1884. *Succinic acid mono-[2-(7-{4-[1-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-vinyl]-phenoxy}-naphthalen-2-yloxy)-ethyl] ester* (**14a2**).Yield 79%, white solid, mp 115–120 °C; IR (KBr, cm^{-1}) 1508, 1717, 3420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41–1.61 (m, 8H), 1.96–2.01 (m, 1H), 2.17–2.20 (m, 1H), 2.64 (s, 4H), 3.77 (dd, 1H, $J = 11.9$ and 2.9 Hz), 3.98 (dd, 1H, $J = 11.9$ and 10.5 Hz), 4.25 (t, 2H, $J = 4.8$ Hz), 4.48 (t, 2H, $J = 4.5$ Hz), 5.22 (dd, 1H, $J = 10.5$ and 2.8 Hz), 5.27 and 5.47 (2 × s, 2H), 6.97 (d, 1H, Ar, $J = 2.4$ Hz), 7.0 (d, 2H, Ar, $J = 8.8$ Hz), 7.07 (dt, 2H, Ar, $J = 8.8$ and 2.4 Hz), 7.18 (d, 1H, Ar, $J = 2.3$ Hz), 7.37 (d, 2H, Ar, $J = 8.8$ Hz), 7.70 (d, 1H, Ar, $J = 8.9$ Hz), 7.72 (d, 1H, Ar, $J = 8.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.46 (CH2), 22.50 (CH2), 25.7 (CH2), 28.95 (CH2) 29.22 (CH2), 34.79 (CH2), 62.79 (CH2), 63.21 (CH2), 66.01 (CH2), 80.43 (CH), 102.85 (C), 106.55 (CH), 113.70 (CH), 115.95 (CH2), 117.86 (CH), 119.16 (CH), 126.08 (C), 128.07 (CH), 129.56 (CH), 129.83 (CH), 134.0 (C), 135.74 (C), 142.92 (C), 155.63 (C), 157.29 (C), 157.41 (C), 172.23 (C), 177.8 (C); ESI (m/z) 585 $[M+Na]^+$; HRMS calcd for $C_{32}H_{34}O_9$ 562.2203; found, 562.2203. *Succinic acid mono-[2-(5-{4-[1-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-vinyl]-phenoxy}-naphthalen-1-yloxy)-ethyl] ester* (**14b2**). Yield 86%, oil; IR (Neat, cm^{-1}) 1503, 1725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45–1.65 (m, 8H), 2.00–2 09 (m, 1H), 2.19–2.28 (m, 1H), 2.71 (s, 4H), 3.79 (dd, 1H, $J = 11.9$ and 3 Hz), 4.0 (dd, 1H, $J = 11.8$ and 10.5 Hz), 4.37 (t, 2H, $J = 4.9$ Hz), 4.63 (t, 2H, $J = 4.3$ Hz), 5.23 (dd, 1H, $J = 10.5$ and 2.7 Hz), 5.29 and 5.47 (2 × s, 2H), 6.86 (d, 1H, Ar, $J = 7.6$ Hz), 6.98 (d, 2H, Ar, $J = 8.8$ Hz), 7.05 (d, 1H, Ar, $J = 7.3$ Hz), 7.35-7.44 (m, 4H, Ar), 7.75 (d, 1H, Ar, $J = 8.5$ Hz), 8.08 (d, 1H, Ar, $J = 8.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.47 (CH2), 22.51 (CH2), 25.71 (CH2), 29.01 (CH2), 29.2 (CH2), 34.82 (CH2), 62.84 (CH2), 63.24 (CH2), 66.50 (CH2), 80.47 (CH), 102.83 (C), 105.89 (CH), 115.06 (CH), 115.46 (CH), 115.83 (CH2), 118.17 (CH), 118.31 (CH), 125.46 (CH), 126.22 (CH), 127.45 (C), 128.03 (CH), 128.34 (C), 133.51 (C), 142.9 (C), 152.35 (C), 154.49 (C), 158.47 (C), 172.38 (C), 177.79 (C); ESI (m/z) 585 $[M+Na]^+$; HRMS calcd for $C_{32}H_{34}O_9$ 562.2203; found, 562.2203. *Succinic acid mono-[2-(4-{4-[1-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-vinyl]-phenoxy}-phenoxy)-ethyl] ester* (**14c2**). Yield 85%, white solid, mp 52–55 °C; IR (KBr, cm^{-1}) 1596, 3434; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43–1.65 (m, 8H), 1.97–2.06 (m, 1H), 2.19–2.27 (m, 1H), 2.71 (s, 4H), 3.77 (dd, 1H, $J = 11.9$ and 2.9 Hz), 4.18 (t, 2H, $J = 4.9$ Hz), 4.47 (t, 2H, $J = 4.5$ Hz), 5.22 (dd, 1H, $J = 10.3$ and 2.7 Hz), 5.28 and 5.46 (2 × s, 2H), 6.91 (d, 4H, Ar, $J = 8.7$ Hz), 6.99 (d, 2H, Ar, $J = 9.2$ Hz), 7.34 (d, 2H, Ar, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.52 (CH2), 22.56 (CH2), 28.94 (CH2), 29.03 (CH2), 29.27 (CH2), 34.88 (CH2), 62.9 (CH2), 63.41 (CH2), 66.67 (CH2), 80.55 (CH), 102.86 (C), 115.71 (CH2), 116.12 (CH), 117.75 (CH), 121.18 (CH), 127.99 (CH), 133.21 (C), 143.03 (C), 150.55 (C), 155.17 (C), 158.7 (C), 172.27 (C), 177.2 (C); ESI (m/z) 530 $[M+NH_4]^+$; HRMS calcd for $C_{28}H_{32}O_9$ 512.2046; found, 512.2086. *Hemisuccinate* (**14a3**). Yield 76%, oil; IR (Neat, cm^{-1}) 1506, 1629, 3421; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60–2.11 (m, 13H), 2.67 (s, 4H), 2.96 (brs, 1H), 3.81 (dd, 1H, $J = 11.9$ and 3 Hz), 4.0 (dd, 1H, $J = 11.8$ and 10.6 Hz), 4.26 (t, 2H, $J = 4.9$ Hz), 4.51 (t, 2H, $J = 4.4$ Hz), 5.27 (dd, 1H, $J = 10.7$ and 2.7 Hz), 5.31 and 5.50 (2 × s, 2H), 7.01-7.13 (m, 5H, Ar), 7.22 (d, 1H, Ar, $J = 2.2$ Hz), 7.40 (d, 2H, Ar, $J = 8.7$ Hz), 7.74 (t, 2H, Ar, $J = 8.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.39 (2 × CH), 29.04 (2 × CH2), 29.67 (CH), 33.24 (CH2), 33.48 (CH2), 33.71 (CH2), 33.81 (CH2), 36.45 (CH), 37.43 (CH2), 62.36 (CH2), 63.27 (CH2), 66.08 (CH2), 80.34 (CH), 104.94 (C), 106.63 (CH), 113.73 (CH), 115.93 (CH2), 117.91 (CH), 119.22 (CH), 126.13 (C), 128.10 (CH), 129.62 (CH), 129.88 (CH), 134.15 (C), 135.8 (C), 143.03 (C), 155.71 (C), 157.35 (C), 157.45 (C), 172.28 (C), 177.23 (C); ESI (m/z) 637 $[M+Na]^+$; Anal. calcd for $C_{36}H_{38}O_9$ C, 70.34, H.6.23; found, C, 70.14, H.6.74. *Hemisuccinate* (**14b3**). Yield 98%, oil; IR (Neat, cm^{-1}) 1598, 1734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59–2.11 (m, 13H), 2.70 (s, 4H), 2.96 (brs, 1H), 3.80 (dd, 1H, $J = 11.9$ and 3 Hz), 3.98 (dd, 1H, $J = 11.8$ and 10.6 Hz), 4.36 (t, 2H, $J = 4.9$ Hz), 4.63 (t, 2H, $J = 4.4$ Hz), 5.23-5.28 (m, 2H), 5.47 (s, 1H), 6.85 (d, 1H, Ar, $J = 7.6$ Hz), 6.97 (d, 2H, Ar, $J = 8.8$ Hz), 7.05 (dd, 1H, Ar, $J = 7.5$ and 0.7 Hz), 7.35-7.44 (m, 4H, Ar), 7.75 (d, 1H, Ar, $J = 8.5$ Hz), 8.08 (d, 1H, Ar, $J = 8.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.35 (2 × CH), 29.01 (CH2), 29.03 (CH2), 29.60 (CH), 33.19 (CH2), 33.43 (CH2), 33.67 (CH2), 33.77 (CH2), 36.42 (CH), 37.39 (CH2), 62.35 (CH2), 63.25 (CH2), 66.51 (CH2), 80.29 (CH), 104.88 (C), 105.91 (CH), 115.05 (CH), 115.41 (CH), 115.72 (CH2), 118.18 (CH), 118.28 (CH), 125.47 (CH), 126.22 (CH), 127.45 (C), 128.01 (CH), 133.58 (C), 142.95 (C), 152.36 (C), 154.50 (C), 158.44 (C), 172.35 (C), 177.62 (C); ESI (m/z) 637 $[M+Na]^+$; Anal. calcd for $C_{36}H_{38}O_9$ C, 70.34, H.6.23; found, C, 70.16, H.6.67. *Hemisuccinate* (**14c3**). Yield 95%, oil; IR (Neat, cm-1) 1601, 3463; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58–2.09 (m, 13H), 2.69 (s, 4H), 2.95 (brs, 1H), 3.78 (dd, 1H, $J = 11.9$ and 3 Hz), 3.97 (dd, 1H, $J = 11.9$ and 10.5 Hz), 4.17 (t, 2H, $J = 4.8$ Hz), 4.46 (t, 2H, $J = 4.5$ Hz), 5.22-5.26 (m, 2H), 5.45 (s, 1H), 6.9 (dd, 4H, Ar, $J = 6.8$ and 2.2 Hz), 6.99 (d, 2H, Ar, $J = 9.1$ Hz), 7.34 (d, 2H, Ar, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3 (2 × CH), 28.93 (CH2), 28.98 (CH2), 29.55 (CH), 33.13 (CH2), 33.38 (CH2), 33.62 (CH2), 33.71 (CH2), 36.36 (CH), 37.34 (CH2), 62.29 (CH2), 63.32 (CH2), 66.54 (CH2), 80.24 (CH), 104.83 (C), 115.56 (CH2), 116 (CH), 117.64 (CH), 121.10 (CH), 127.86 (CH), 133.14 (C), 142.91 (C), 150.40 (C), 155.06 (C), 158.6 (C), 172.27 (C), 177.83 (C); ESI (m/z) 565 $[M+H]^+$; Anal. calcd for $C_{32}H_{36}O_9$ C, 68.07, H, 6.43; found, C, 68.01, H, 6.67.

25 The animals used for the present experiments were duly notedand approved by the Institutional Animal Ethics Committee of Central drug research institute (CDRI), Lucknow, UP, India and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India (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 X 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 **13a1-c1**, **13a2-c2**, **13a3-c3**, **14a1-c1**, **14a2-c2**, and **14a3-c3** 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 and 0.3 mg for a dose of 24 mg/kg) in 0.1 ml and administered orally for each dose. Parasitaemia levels were recorded from thin blood smears between days 4 and 28. The animals which did not develop patent infection till day 28 were recorded as cured.[27] Mice treated with β-arteether served as positive control. Multidrug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine.

26 (a) One hundred percent protection means none of the treated mice developed patent infection during the 28 days observation period and hence recorded as cured. Similarly, 20% protection means only one out of five mice was cured. (b) One hundred percent suppression of parasitaemia 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 days survival assay.

27 Puri SK, Singh N. Azithromycin: antimalarial profile against blood- and sporozoite-induced infections in mice and monkeys. *Expl Parasitol*. 2000;94:8–14.