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Syntheses and Biological Evaluation of Alkanediamines as Antioxidant and Hypolipidemic Agents☆

Sanjay Batra,[a,*] Amiya P. Bhaduri,[a] Bhawani S. Joshi,[b] Raja Roy,[b] Ashok K. Khanna[c] and Ramesh Chander[c]

[a]*Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India*
[b]*RSIC Division, Central Drug Research Institute, Lucknow 226 001, India*
[c]*Biochemistry Division, Central Drug Research Institute, Lucknow 226 001, India*

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Abstract—A new series of compounds belonging to *N*,*N*′- [bis (1-aryl-6-hydroxy-hex-2-ene-1-one-3-yl)-1,*n*-alkanediamines (**2–5a–f**) have been synthesized and evaluated for antioxidant and hypolipidemic activities. Amongst all the synthesized compounds, seven compounds namely **2c**, **2e**, **4c**, **5b**, **5c**, **5e** and **5f** exhibit potent antioxidant activity. These compounds have also been evaluated for hypolipidemic activity.

Atherosclerosis and its thrombotic complications, which has been the major cause of coronary artery disease, is associated with elevated levels of serum cholesterol and low density lipoproteins along with free radical oxidative stress. It is now well documented that the low density lipoprotein (LDL) cholesterol, which has undergone oxidative damage due to the hydroxyl radicals (·OH) generated by the alterations in the oxidation states of metal ions, mainly iron and copper, is relatively more atherogenic than the native LDL.[2] Therefore, it is envisaged that, beside a cholesterol lowering property, a hypolipedimic agent that incorporates antioxidant activity will be able to protect endothelial and myocardial function and would be a better antiatherosclerotic agent. With an objective to explore newer molecular structures for such activity, we have earlier reported the synthesis and biological evaluation of 3-amino and substituted amino-1-aryl-6-hydroxy-hex-2-ene-1-ones.[3] In our continued efforts to further modify these molecules, it was envisaged that, instead of a primary amine, if a diamine is used it may result in 1-aryl-6-hydroxy-hex-2-ene-1-one moiety on both the ends of the amine, thereby resulting in a better activity profile. Indeed, it was observed that some of the *N*,*N*′- [bis (1-aryl-6-hydroxy-hex-2-ene-1-one-3-yl)-1,*n*-alkanediamines (**2–5a–f**) show potent antioxidant and hypolipidemic activities. The details of their synthesis and biological activity are reported herein.

Chemistry

The synthesis of various diamines is outlined in Scheme 1. The starting substrates **1 a–f** were obtained as reported earlier.[4] These compounds, on reaction with various 1,*n*-diamines (where $n = 2$, 3, 4 and 8) in the presence of boron trifluoride etherate, furnished the diamino derivatives **2–5a–f.** The structure of these products was established on the basis of Hetero multiple bond correlation (HMBC) and Heteromultiple Quantum COSY experiments. These compounds could also be obtained by reacting the bromo derivatives **6a–f** with appropriate diamines as described earlier.[3]

Antioxidant activity

Oxidation of low-density lipoprotein by Cu^{2+}. Human serum was separated from the blood of normolipidemic donors who have been fasted overnight. LDL was isolated by sequential ultracentrifugation using Beckman ultra-centrifuge model LE-80K.[5] LDL preparation (d, 1.063) was dialyzed against 0.15 M NaCl solution containing EDTA (0.02% w/v) in cold and the purity was checked by polyacrylamide gel electrophoresis. LDL (0.71 mg) and $CuCl_2$. $2H_2O$ (10 μM) in the absence or presence of test compounds (2.5 or 5 μmol/mL) listed in

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*Corresponding author. Tel.: +091-522-212411-18 (EPBAX 4368, 4383); fax: +91-522-224305, 223938; e-mail: batra_san@yahoo.co.uk, root@cscdri.ren.nic.in

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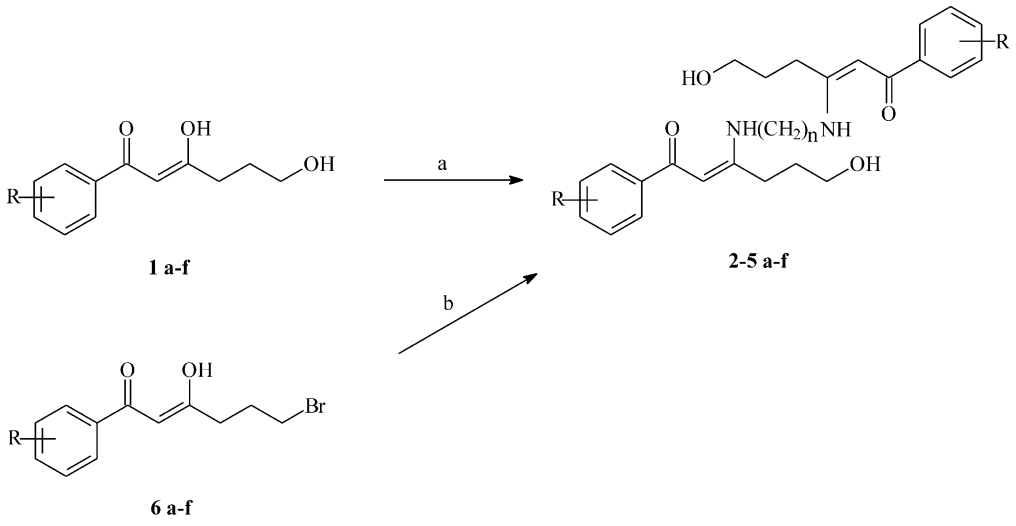

Compd no.	R
a	H
b	4-CH_3
c	4-OCH_3
d	4-F
e	4-Cl
f	4-Br

Compd. No.	n
2	2
3	3
4	4
5	8

Scheme 1. Reagents and conditions: (a) BF_3. Et_2O, 1,*n*-alkanediamine, dry diethylether/dichloromethane (50:50, v/v), 8–24 h; (b) 1,*n*-alkanediamine, methanol, steel bomb, 2–3 h.

Table 1 in 0.05 M phosphate buffer (pH 7.4) to a final volume of 1.5 mL, was incubated at 37 °C for 90 min. The lipid peroxidation products in oxidized LDL, oxidized LDL with Cu^{2+} in the absence or presence of test compounds was assayed as thiobarbituric acid reactive substances (TBARS).[6] Briefly, the incubation mixture was added 0.5 mL SDS (8% w/v), 0.5 mL glacial acetic acid and 1.5 mL TBA (0.8% w/v) in the above sequence with stirring each time at room temperature. This reaction mixture was heated in a boiling water bath in the dark for 30 min. The tubes were cooled, pink coloured chromogen was extracted with 8 mL of mixture of *n*-butanol/pyridine (7:1 v/v) and the optical density was measured on a spectrophotometer at 532 nm against a reagent blank. An appropriate standard of malonaldehyde (MDA) was tested simultaneously.

Generation of hydroxyl radicals and degeneration of deoxyribose. The •OH were generated in a non-enzymic system comprising of $FeSO_4 \cdot H_2O$ (2 mM), EDTA (2 mM), sodium ascorbate (2 mM), H_2O_2 (2.8 mM), deoxyribose (2.8 mM) added with the test drugs (1, 2 or 5 μmol) and probucol in 0.05 M KH_2PO_4–KOH buffer (pH 7.4) made up to the final volume of 2 mL.[7] The reaction mixture was incubated at 37 °C for 90 min. Similarly separate tubes containing the above reagents for generation of •OH and various concentrations of test samples to serve as corresponding references. MDA contents in both sets were measured by TBA method.[6] The influence of the test substances on the formation of lipid peroxides was calculated after subtracting the values of reference tubes from those of their respective experimental values.

Hypolipidemic activity

Adult male Charles Foster rats (200–225 g) bred in the animal house of the institute were divided in control, triton and triton plus drug treated groups containing six rats in each. Triton WR-1339 (Sigma, USA) was administered (200 mg/kg b.wt.) by intraperitoneal injection. The compounds **2c**, **2e**, **4c**, **5b**, **5c**, **5e** and **5f** and guggulipid were macerated with 2% aqueous gum acacia suspension and fed orally (100 mg/kg b.wt.) simultaneously with triton. At the end of the experiment, rats were fasted overnight and blood was withdrawn from retro-orbital plexus. Serum was separated by centrifugation at low speed and assayed for total cholesterol (TC), phospholipid (PL) and triglycerides (Tg) by the standard procedure reported earlier.[3] The compounds **2c** and **2e** showing significant lipid lowering activity were further tested in the above test model for assay of post heparin lipolytic activity (PHLA).[8] At the end of the experiment before withdrawal of blood, rats were given intravenously heparin solution in normal saline (10 mg/kg b.wt.) through the tail vein. After 15 min, blood was

withdrawn and collected in a tube containing 0.1 mL sodium citrate solution (380 mg/ml w/v) for 0.9 mL of blood. After 20 min in cold, blood was centrifuged and plasma was used for assay of PHLA. The reaction mixture containing 0.2 mL plasma, 0.01 mL intralipid emulsion (Vitram Chemico, Stockholm, Sweden), 1.0 mL BSA (2.5%) in 0.1 Tris–HCl buffer (pH 7.4) to a final volume of 2.0 mL was incubated at 37 °C for 90 min. The amount of fatty acid released was measured. Protein was estimated by the method of reported in the literature.[9]

Results

Primary screening of compounds for antioxidant and lipid lowering activities

It has been already reported earlier[3] that the oxidation of LDL in the presence of Cu^{2+} caused a marked formation of lipid peroxides. All the test compounds when added to this reaction mixture at 2.5 and 5 μmol/mL concentration protected the Cu^{2+} mediated oxidation of lipids to varying extents as shown in Table 1. Of all the test compounds, **2c**, **2e**, **4c**, **5b**, **5c**, **5e** and **5f** significantly inhibited this oxidation. These potent antioxidants were further tested for their cholesterol lowering activity at the dose of 100 mg/kg po in triton model in rats, which has also been reported simultaneously in Table 1.

Effect of compounds on generation of hydroxyl radical in vitro

The most active compounds were further tested against the generation of hydroxyl radicals in non-enzymic system of Fe^{2+}, sodium ascorbate and H_2O_2. Addition of the above compounds at 1.0, 2.5 and 5.0 μmol/mL into the above reaction mixture inhibited the formation of hydroxyl radicals in concentration-dependent manner and their antioxidant potential corresponded with that of the LDL oxidation when compared individually. However, only compounds **4c**, **5b, 5e** and **5f** show comparable IC_{50} values to that of probucol, while all the others had higher IC_{50} values as shown in Table 2.

Effect of compounds in Triton induced hyperlipidemia in rats

The data in Table 3 showed that the administration of Triton WR-1339 increased the animal plasma level of TC, PL and Tg by 3.9-, 2.06- and 1.94-fold, respectively, followed by a 42% reduction (inhibition) of PHLA activity. Oral feeding of the abovementioned compounds and guggulipid (a positive control) at the dose of 100 mg/kg simultaneously with Triton caused lowering

Table 1. Screening of compounds for antioxidant and lipid lowering activity[a,b]

Compound no.	Inhibition of oxidized-LDL		Cholesterol lowering activity (% decrease) in triton model in rats (dose 100 mg/kg)
	2.5 mM	5 mM	
Probucol	$58\pm3.80^{**b}$	$72\pm6.75^{***}$	$32\pm2.26^{**}$
Guggulipid[c]	NA	NA	$35\pm1.90^{**}$
2a	$33\pm2.58^{*}$	$49\pm1.87^{**}$	15 ± 4.8
2b	17 ± 3.88^{NS}	$22\pm1.25^{*}$	16 ± 5.5
2c	$46\pm1.85^{*}$	$68\pm1.45^{***}$	31 ± 3.85
2d	34 ± 0.60^{NS}	$52\pm0.42^{*}$	17 ± 2.2
2e	$55\pm4.18^{**}$	$77\pm4.90^{***}$	30 ± 4.08
2f	$53\pm4.95^{*}$	$68\pm2.87^{**}$	15 ± 3.52
3a	24 ± 2.25^{NS}	$38\pm3.75^{*}$	20 ± 2.5
3b	—	—	17 ± 6.9
3c	2 ± 0.98^{NS}	$21\pm1.53^{*}$	19 ± 6.4
3d	15 ± 1.71^{NS}	$44\pm3.25^{*}$	17 ± 4.6
3e	23 ± 4.08^{NS}	$51\pm1.31^{*}$	11 ± 3.7
3f	11 ± 1.51^{NS}	35 ± 0.53^{NS}	14 ± 5.5
4a	13 ± 1.94^{NS}	$22\pm0.94^{*}$	10.26 ± 3.18
4b	24 ± 2.48^{NS}	$50\pm2.26^{*}$	11 ± 1.7
4c	$60\pm2.12^{***}$	$70\pm1.54^{***}$	22 ± 4.0
4d	2 ± 0.32^{NS}	3 ± 0.27^{NS}	11 ± 0.22
4e	3 ± 0.36^{NS}	10 ± 0.60^{NS}	17 ± 1.01
4f	2 ± 0.21^{NS}	8 ± 0.48^{NS}	12 ± 2.21
5a	—	—	—
5b	$62\pm3.69^{**}$	$74\pm1.66^{***}$	24 ± 1.85
5c	$44\pm1.53^{**}$	$61\pm4.04^{***}$	25 ± 4.20
5d	—	—	—
5e	$53\pm0.94^{**}$	$82\pm0.214.04^{***}$	19 ± 2.55
5f	$52\pm2.95^{**}$	$71\pm1.20^{***}$	22 ± 3.05

[a]The percent reversal and its significance against protection of LDL oxidation was deduced by comparing the values of n mol MDA formed/ mg protein±S.D. of four separate observations with LDL in absence or presence of test compounds. Similarly cholesterol lowering activity and its significance was deduced by comprising the levels of cholesterol±S.D. of six hypolipidemic rats in both; with drug and without drug treatment groups.

[b]$P^{*}<0.5$; $^{**}<0.01$; $^{***}<0.001$; NS, not significant.

[c]0.5 and 1.0 mg/mL.

Table 2. Inhibition of ·OH generation by compounds

Compound no.	% inhibition by concn used (mM)			IC_{50}
	1.0	2.5	5.0	
2c	15±3.0	46±5.2	68±7.8	3.4
2e	47±5.3	55±4.0	77±9.5	3.2
4c	43±2.2	61±2.2	70±1.5	1.6
5b	43±3.2	62±1.0	74±2.1	1.5
5c	30±0.3	44±1.5	61±7.4	3.0
5e	19±3.5	53±1.0	82±1.0	1.9
5f	43±2.1	61±3.8	70±1.5	1.6
Probucol	40±5.8	62±5.9	74±6.2	1.6

The percent inhibition and its significance against generation of ·OH was deduced by comparing the values of n mol MDA formed/h ± S.D. of four separate observation with OH formed in the absence or presence of test compounds.

Table 3. Lipid lowering activity of test compounds in triton induced hyperlipidemic rats

Test compounds	Total cholesterol[a]	Phospholipid[a]	Triglyceride[a]	PHLA activity[b]
Control	87.30±7.85	80.55±9.00	92.18±11.52	253.05±20.7
Triton fed	278.73±29.39***	166.18±5.80***	179.30±9.75***	145.67±19.8***(R = -42%)
Triton + **2c**	165.49±12.77***(40.59)	120.65±8.81**(27.39)	126.66±10.00***(29.35)	210.05±8.76(R = 60%)
Triton + **2e**	167.21±11.66***(40.01)	121.11±7.66**(27.12)	123.88±7.96***(30.90)	203.00±10.29(R = 53%)
Triton + **2f**	196.58±14.90***(29.47)	146.00±11.21^{NS}(12.14)	158.44±8.77***(16.09)	—
Triton + **4c**	234.83±21.91*(15.75)	124.15±9.66**(25.29)	129.71±8.97**(27.65)	—
Triton + **5b**	221.99±24.12**(20.35)	107.99±5.33***(35.01)	131.32±13.39**(26.75)	—
Triton + **5c**	220.28±21.71**(20.97)	109.53±10.09***(36.49)	131.23±9.10**(26.80)	—
Triton + **5e**	239.03±24.35^{NS}(14.24)	134.33±11.78*(19.16)	136.85±8.38**(23.67)	—
Triton + **5f**	228.47±11.54*(18.03)	120.45±7.68**(27.51)	129.04±8.60**(28.03)	—
Triton + Guggulipid	181.17±17.45***(35.00)	114.66±10.42***(31.25)	116.00±19.30***(35.30)	218.51±7.09(R = 68%)

Values are mean ± S.D. of six rats. Triton fed group was compared with control and triton plus compound treated. $P^{*} < 0.05$; $^{**} < 0.01$; ***,0.001; ^{NS}, not significant.
[a]mg/dl.
[b]μmol FFA/h/dl.

of plasma lipids to varying extents. Compounds **2c** and **2e** showed significant lowering of TC by 40%, PL by 27% and Tg by 29–31%. The plasma of the hyperlipidemic animals treated with compounds **2c** and **2e** and guggulipid was further analyzed for PHLA activity and it was found that these compounds potentially reactivated the enzyme activity by 53 and 60%, respectively, though these were lower than that observed by guggulipid (68%).

Discussion

Since the major aim of the present study was to further optimize the lead obtained from earlier reported 1,3-hexanedione derivatives, in the first instance all the compounds were screened for in vitro antioxidant activity against Cu^{2+}-induced LDL oxidation as described earlier. Of all the test compounds, **2c**, **2e**, **4c**, **5b**, **5c**, **5e** and **5f** exhibited potent prevention against the Cu^{2+}-induced LDL oxidation. However, the IC_{50} of compounds **4c**, **5b, 5e** and **5f** were only comparable to that of the standard, namely probucol, but as we were interested in compounds with antioxidant as well as hypolipidemic activity, all potent antioxidants were evaluated for their cholesterol lowering property in Triton-induced hyperlipidemia. Out of all the test compounds only compounds **2c** and **2e** showed promising activity while no other compound elicited significant biological response. The analysis of the structure–activity relationship indicates that, although compounds possessing substituted amino octyl amino skeleton in this series of compounds show better antioxidant activity than their corresponding amino ethyl amino analogues, the lipid lowering activity is associated only with compounds having an amino ethyl amino skeleton. This further endorses our earlier findings that in this series of compounds amino ethyl amino group elicit better biological response. To further investigate the possible mode of action of these synthetic derivatives, we have assayed the PHLA in experimental hyperlipidemia induced by Triton. Triton caused lowering of PHLA by 42% that was shown to be reactivated by the test compounds. It is remarkable that lowering of lipids was directly related with stimulation of PHLA activity in drug treated hyperlipidemic animals. Triton is known to inhibit lipoprotein lipase activity by the modification of the circulatory lipids such that the enzyme can no longer act.[10] It has also been reported that the main cause of Triton hyperlipidemia is coating of the plasma lipoproteins by Triton, resulting in their faulty catabolism by preventing the occurrence of the interaction between lipid and lipoprotein lipases in the body.[11] Thus, it is presumed that these compounds may be acting both by the modification of lipids as well as stimulation of lipases under experimental conditions.

Conclusion

The synthesis and biological evaluation of various *N*,*N*′-[bis (1-aryl-6-hydroxy-hex-2-ene-1-one-3-yl)-1,*n*-alkane-

diamines included in the present study represent the extension of our earlier work on 1,3-hexanedione derivatives. The preliminary biological screening data of these compounds endorse our earlier findings that the amino ethyl amino moiety is an optimum requirement to generate both antioxidant and hypolipidemic activity in this series of compounds.

Experimental

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Shimadzu FTIR-8201PC spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance DRX-300 or Bruker DPX-200 FT spectrometers, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on JEOL/SX-102 spectrometer. Elemental analyses were performed by a Carlo Erba 1108 microanalyzer. Basic aluminum oxide (100 mesh, pH 9.5) was used for column chromatography of various amines.

General method for preparation of *N*,*N*′- [bis (1-aryl-6-hydroxy-hex-2-ene-1-one-3-yl) 1, *n*-alkanediamines

Method A. To a stirred solution of appropriate compound from **1a**–**e** (5 mmol) in 25 mL of dry ether was added boron trifluoride etherate (0.13 mL, 10 mmol) at room temperature. After 15–25 min, solid separates out to which was added dropwise a solution of suitable diaminoalkane (10 mmol) in 20 mL of dichloromethane with stirring at 0 °C (maintained by ice–salt mixture). The reaction was allowed to stir at room temperature for 8–10 h. On completion the excess solvent was evaporated and the reaction mixture was extracted with ethyl acetate (2×50 mL). The organic layers were combined, dried over sodium sulphate and evaporated to yield a residue, which upon trituration with cold dry diethylether or purification using column chromatography over basic alumina using chloroform/methanol (249:1,v/v) as eluent yielded the diaminoalkane derivatives.

Method B. As described in method A of ref 3.

***N*,*N*-[bis(1-Phenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1,2-ethanediamine (2a).** (85%, 133–134 °C): IR (KBr) 3432, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H, 2×CH_2), 2.52 (t, 4H, *J*= 8 Hz, 2×CH_2), 3.62 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 5.73 (s, 2H, 2×=CH), 7.38 (m, 6H, Ar–H), 7.81 (m, 4H, Ar–H); Mass (FAB) 436 (M^+). Anal. calcd for $C_{26}H_{32}N_2O_4$ C, 71.53, H, 7.38, N, 6.41. Found C, 71.51, H, 7.56, N, 6.39%.

***N*,*N*′- [bis (1-(4-Methylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 2-ethanediamine (2b).** (65%, 160–161 °C): IR (KBr) 3384, 1566 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 4H, 2×CH_2), 2.42 (s, 6H, 2×Ar-CH_3), 2.50 (t, 4H, *J*=8×Hz, 2×CH_2), 3.57 (m, 4H, *J*=6 Hz, 2×CH_2OH), 3.70 (m, 4H, 2×NH-CH_2), 5.61 (s, 2H, 2×=CH), 7.17, 7.21 (d, 4H, *J*=8 Hz, Ar–H), 7.70, 7.74 (d, 4H, *J*=8 Hz, Ar–H); Mass (FAB) 464 (M^+). Anal. calcd for $C_{28}H_{36}N_2O_4$ C, 72.37, H, 7.80, N, 6.02. Found C, 72.44, H, 7.64, N, 6.12%.

***N*,*N*′- [bis (1-(4-Methoxylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 2-ethanediamine (2c).** (54%, 148–149 °C): IR (KBr) 3410, 1588 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H, 2×CH_2), 2.48 (t, 4H, *J*=8 Hz, 2×CH_2), 3.60 (m, 4H, *J*=6 Hz, 2×CH_2OH), 3.68 (m, 4H, 2×NH–CH_2), 3.82 (s, 6H, 2Ar–OCH_3), 5.68 (s, 2H, 2×=CH), 7.26, 7.31 (d, 4H, *J*=8 Hz, Ar–H), 7.78, 7.82 (d, 4H, *J*=8 Hz, Ar–H); Mass (FAB) 496 (M^+). Anal. calcd for $C_{28}H_{36}N_2O_6$ C, 67.72, H, 7.30, N, 5.64. Found C, 67.41, H, 7.39, N, 5.39%.

***N*,*N*′- [bis (1- (4-Fluorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 2-ethanediamine (2d).** (77%, 150–151 °C): IR (KBr) 3408, 1572 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H, 2×CH_2), 2.51 (t, 4H, *J*=8 Hz, 2×CH_2), 3.62 (m, 4H, *J*=6 Hz, 2×CH_2OH), 3.73 (m, 4H, 2×NH–CH_2), 5.67 (s, 2H, 2×=CH), 7.01 (t, 4H, *J*=10 Hz, Ar–H), 7.82 (dd, 4H, *J*=6 Hz, Ar–H); Mass (FAB) 472 (M^+). Anal. calcd for $C_{26}H_{30}F_2N_2O_4$ C, 64.99, H, 6.29, N, 5.83. Found C, 65.26, H, 6.36, N, 5.70%.

***N*,*N*′- [bis (1-(4-Chlorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 2-ethanediamine (2e).** (58%, 180–181 °C): IR (KBr) 3434, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H, 2×CH_2), 2.51 (t, 4H, *J*=8 Hz, 2×CH_2), 3.62 (m, 4H, *J*= 6 Hz, 2×CH_2OH), 3.72 (m, 4H, 2 NH–CH_2), 5.68 (s, 2H, 2×=CH), 7.37, 7.41(d, 4H, *J*=8 Hz, Ar–H), 7.74, 7.78 (d, 4H, *J*=8 Hz, Ar–H); Mass (FAB) 504, 506 (M^+). Anal. calcd for $C_{26}H_{30}Cl_2N_2O_4$ C, 61.78, H, 5.98, N, 5.54. Found C, 62.05, H, 5.69, N, 5.72%.

***N*,*N*′-[bis (1- (4-Bromophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 2-ethanediamine (2f).** (62%, 183–184 °C): IR (KBr) 3434, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H, 2×CH_2), 2.55 (t, 4H, *J*=8 Hz, 2×CH_2), 3.61 (m, 4H, *J*=6 Hz, 2×CH_2OH), 3.74 (m, 4H, 2×NH–CH_2), 5.68 (s, 2H, 2×=CH), 7.50, 7.54 (d, 4H, *J*=8 Hz, Ar–H), 7.67, 7.71 (d, 4H, *J*= 8 Hz, Ar–H); Mass (FAB) 592, 596 (M^+). Anal. calcd for $C_{26}H_{30}Br_2N_2O_4$ C, 52.54, H, 5.09, N, 4.71. Found C, 52.33, H, 5.07, N, 4.57%.

***N*,*N*′-[bis(1-Phenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1,3-propanediamine (3a).** (72%, 143–144 °C): IR (KBr) 3406, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 4H, 2×CH_2), 2.04 (m, 2H, CH_2), 2.52 (t, 4H, *J*=8 Hz, 2×CH_2), 3.65 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 5.74 (s, 2H, 2×=CH), 7.39 (m, 6H, Ar–H), 7.82 (m, 4H, Ar–H); Mass (FAB) 450 (M^+). Anal. calcd for $C_{27}H_{34}N_2O_4$ C, 71.97, H, 7.60, N, 6.21. Found C, 72.21, H, 7.51, N, 5.95%).

***N*,*N*′- [bis (1-(4-Methylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-propanediamine (3b).** (70%, oil): IR (neat) 3376, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H, 2×CH_2), 2.06 (m, 2H, CH_2), 2.37(s, 6H, 2×Ar–CH_3), 2.44 (t, 4H, *J*=8 Hz, 2×CH_2), 3.67 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 5.72 (s, 2H, 2×=CH), 7.18, 7.22 (d, 4H, *J*=8 Hz, Ar-H), 7.72, 7.76 (d, 4H, *J*=8 Hz, Ar–H);

Mass (FAB) 478 (M^+). Anal. calcd for $C_{29}H_{38}N_2O_4$ C, 72.77, H, 7.80, N, 6.02. Found C, 72.44, H, 7.64, N, 6.12%.

***N,N′*- [bis (1-(4-Methoxylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-propanediamine (3d).** (50%, 121–122 °C): IR (KBr) 3390, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (m, 4H, 2×CH_2), 2.04 (m, 2H, CH_2), 2.49 (t, 4H, J = 8 Hz, 2×CH_2), 3.60 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 3.83 (s, 6H, 2×Ar–OCH_3), 5.69 (s, 2H, 2×=CH), 6.88, 6.92 (d, 4H, J = 8 Hz, Ar–H), 7.80, 7.84 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 510 (M^+). Anal. calcd for $C_{29}H_{38}N_2O_6$ C, 68.23, H, 7.45, N, 5.49. Found C, 68.34, H, 7.57, N, 5.49%.

***N,N′*- [bis (1-(4-Fluorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-propanediamine (3d).** (50%, 82–83 °C): IR (KBr) 3438, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (m, 4H, 2×CH_2), 2.07 (m, 2H, CH_2), 2.52 (t, 4H, J = 8 Hz, 2×CH_2), 3.63 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 5.69 (s, 2H, 2× = CH), 7.07 (t, 4H, J = 10 Hz, Ar–H), 7.85 (dd, 4H, J = 6 Hz, Ar–H); Mass (FAB) 486 (M^+). Anal. calcd for $C_{27}H_{32}F_2N_2O_4$ C, 65.57, H, 6.52, N, 5.66. Found C, 65.78, H, 6.59, N, 5.98%.

***N,N′*- [bis (1-(4-Chlorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-propanediamine (3e).** (73%, 118–119 °C): IR (KBr) 3374, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (m, 4H, 2×CH_2), 2.09 (m, 2H, CH_2), 2.54 (t, 4H, J = 8 Hz, 2×CH_2), 3.66 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 5.72 (s, 2H, 2×=CH), 7.38, 7.42(d, 4H, J = 8 Hz, Ar–H), 7.76, 7.80 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 518, 519 (M^+). Anal. calcd for $C_{27}H_{32}Cl_2N_2O_4$ C, 62.43, H, 6.21, N, 5.39. Found C, 62.05, H, 6.19, N, 5.42%.

***N,N′*- [bis (1-(4-Bromophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-propanediamine (3f).** (56%, 129–130 °C): IR (KBr) 3450, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 4H, 2×CH_2), 2.06 (m, 2H, CH_2), 2.51 (t, 4H, J = 8 Hz, 2×CH_2), 3.62 (m, 8H, 2×NH–CH_2 and 2×CH_2OH), 5.67 (s, 2H, 2×=CH), 7.40, 7.44 (d, 4H, J = 8×Hz, Ar–H), 7.67, 7.71 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 604, 608 (M^+). Anal. calcd for $C_{26}H_{30}Br_2N_2O_4$ C, 53.30, H, 5.30, N, 4.60. Found C, 53.35, H, 5.04, N, 4.71%.

***N,N′*-[bis(1-Phenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 4-butanediamine (4a).** (81%, 134–135 °C): IR (KBr) 3350, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, 8H, 4×CH_2), 2.48 (t, 4H, J = 8 Hz, 2×CH_2), 3.30 (m, 4H, 2×NH–CH_2), 3.68 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.68 (s, 2H, 2×=CH), 7.57 (m, 6H, Ar–H), 7.81 (m, 4H, Ar–H); Mass (FAB) 464 (M^+). Anal. calcd for $C_{28}H_{36}N_2O_4$ C, 72.38, H, 7.81, N, 6.03. Found C, 72.31, H, 7.94, N, 6.26%.

***N,N′*- [bis (1-(4-Methylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 4-butanediamine (4b).** (78%, 128–129 °C): IR (KBr) 3352, 1572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (m, 8H, 4×CH_2), 2.30(s, 6H, 2×Ar–CH_3), 2.40 (t, 4H, J = 8 Hz, 2×CH_2), 3.36 (m, 4H, 2×NH–CH_2), 3.63 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.60 (s, 2H, 2×=CH), 7.10, 7.14 (d, 4H, J = 8 Hz, Ar–H), 7.74, 7.78 (d, 4H, J = 8 Hz, Ar–H); mass (FAB) 492 (M^+). Anal. calcd for $C_{30}H_{40}N_2O_4$ C, 73.14, H, 8.18, N, 5.68. Found C, 73.44, H, 7.94, N, 5.62%.

***N,N′*-[bis (1-(4-Methoxylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-butanediamine (4c).** (59%, 148–149 °C): IR (KBr) 3430, 1584 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 8H, 2×CH_2), 2.35 (t, 4H, J = 8 Hz, 2×CH_2), 3.43 (m, 4H, 2×NH–CH_2), 3.67 (t, 4H, J = 6 Hz, 2×CH_2OH), 3.83 (s, 6H, 2×Ar–OCH_3), 5.64 (s, 2H, 2×=CH), 6.87, 6.91 (d, 4H, J = 8 Hz, Ar–H), 7.79, 7.83 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 524 (M^+). Anal. calcd for $C_{30}H_{40}N_2O_6$ C, 68.67, H, 7.68, N, 5.33. Found C, 69.44, H, 7.57, N, 5.49%.

***N,N′*- [bis (1-(4-Fluorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 4-butanediamine (4d).** (85%, 128–129 °C): IR (KBr) 3474, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 8H, 4×CH_2), 2.47 (t, 4H, J = 8 Hz, 2×CH_2), 3.46 (m, 4H, 2×NH–CH_2), 3.69 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.63 (s, 2H, 2×=CH), 7.05 (m, 4H, Ar–H), 7.84 (dd, 4H, J = 6 Hz, Ar–H); Mass (FAB) 528 (M^+). Anal. calcd for $C_{28}H_{34}F_2N_2O_4$ C, 66.13, H, 6.74, N, 5.51. Found C, 66.38, H, 6.68, N, 5.41%.

***N,N′*- [bis (1-(4-Chlorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 4-butanediamine (4e).** (64%, 154–156 °C): IR (KBr) 3440, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (m, 8H, 4×CH_2), 2.47 (t, 4H, J = 8 Hz, 2 CH_2), 3.44 (m, 4H, 2×NH–CH_2), 3.68 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.63 (s, 2H, 2×=CH), 7.33, 7.37(d, 4H, J = 8 Hz, Ar–H), 7.73, 7.77 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 532, 534 (M^+). Anal. calcd for $C_{28}H_{34}Cl_2N_2O_4$ C, 63.04, H, 6.42, N, 4.50. Found C, 63.05, H, 6.19, N, 4.42%.

***N,N′*- [bis (1- (4-bromophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 4-butanediamine (4f).** (69%, 162–163 °C): IR (KBr) 3450, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 8H, 4×CH_2), 2.47 (t, 4H, J = 8 Hz, 2×CH_2), 3.44 (m, 4H, 2×NH–CH_2), 3.68 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.63 (s, 2H, 2×=CH), 7.50, 7.54 (d, 4H, J = 8 Hz, Ar–H), 7.67, 7.71 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 618, 622 (M^+). Anal. calcd for $C_{28}H_{34}Br_2N_2O_4$ C, 54.03, H, 5.51, N, 4.50. Found C, 54.25, H, 5.44, N, 4.71%.

***N,N′*-[bis(1-Phenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 8-octanediamine (5a).** (88%, 134–135 °C): IR (KBr) 3350, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, 8H, 4×CH_2), 2.48 (t, 4H, J = 8 Hz, 2 × CH_2), 3.30 (m, 4H, 2×NH–CH_2), 3.68 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.68 (s, 2H, 2×=CH), 7.57 (m, 6H, Ar–H), 7.81 (m, 4H, Ar–H); Mass (FAB) 520 (M^+). Anal. calcd for $C_{28}H_{36}N_2O_4$ C, 72.38, H, 7.81, N, 6.03. Found C, 72.31, H, 7.94, N, 6.26%.

***N, N′*- [bis (1-(4-Methylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 8-octanediamine (5b).** (84%, 118–119 °C): IR (KBr) 3428, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (m, 16H, 8×CH_2), 2.37 (s, 6H, 2×Ar–CH_3), 2.44 (t, 4H, J = 8×Hz, 2×CH_2), 3.36 (m, 4H, 2×NH–CH_2), 3.72 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.65 (s, 2H, 2×=CH), 7.17, 7.21 (d, 4H, J = 8 Hz, Ar–H), 7.72, 7.76 (d, 4H, J = 8×Hz, Ar–H); Mass (FAB) 548 (M^+). Anal. calcd for $C_{34}H_{48}N_2O_4$ C, 74.42, H, 8.81, N, 5.10. Found C, 74.44, H, 8.64, N, 5.02%.

***N,N′*- [bis (1-(4-methoxylphenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 3-octanediamine (4c).** (75%, 117–118 °C): IR (KBr) 3402, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (m, 16H, 8×CH_2), 2.42 (t, 4H, J = 8 Hz, 2×CH_2), 3.33 (m, 4H, 2×NH–CH_2), 3.71 (t, 4H, J = 6 Hz, 2×CH_2OH), 3.83 (s, 6H, 2×Ar–OCH_3), 5.63 (s, 2H, 2×=CH), 6.87, 6.91 (d, 4H, J = 8 Hz, Ar–H), 7.80, 7.84 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 580 (M^+). Anal. calcd for $C_{34}H_{48}N_2O_6$ C, 70.31, H, 8.33, N, 4.82. Found C, 70.34, H, 8.57, N, 4.49%.

***N,N′*- [bis (1-(4-Fluorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 8-octanediamine (4d).** (79%, 131–132 °C): IR (KBr) 3330, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (m, 16H, 8×CH_2), 2.45 (t, 4H, J = 8 Hz, 2×CH_2), 3.33 (m, 4H, 2×NH–CH_2), 3.73 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.62 (s, 2H, 2×=CH), 7.07 (t, 4H, J = 10 Hz, Ar–H), 7.85 (dd, 4H, J = 6 Hz, Ar–H); Mass (FAB) 554 (M^+). Anal. calcd for $C_{27}H_{32}F_2N_2O_4$ C, 65.57, H, 6.52, N, 5.66. Found C, 65.78, H, 6.59, N, 5.98%.

***N,N′*- [bis (1- (4-Chlorophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 8-octanediamine (5e).** (74%, 131–132 °C): IR (KBr) 3330, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (m, 16H, 8×CH_2), 2.45 (t, 4H, J = 8 Hz, 2×CH_2), 3.33 (m, 4H, 2×NH–CH_2), 3.73 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.62 (s, 2H, 2×=CH), 7.33, 7.37 (d, 4H, J = 8 Hz, Ar–H), 7.75, 7.79 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 586, 588 (M^+). Anal. calcd for $C_{32}H_{40}Cl_2N_2O_4$ C, 65.41, H, 6.86, N, 4.76. Found C, 65.19, H, 6.79, N, 4.42%.

***N,N′*- [bis (1- (4-Bromophenyl-6-hydroxy-hex-2-ene-1-one-3-yl)-1, 8-octanediamine (5f).** (81%, 132–133 °C): IR (KBr) 3416, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (m, 16H, 8×CH_2), 2.45 (t, 4H, J = 8 Hz, 2×CH_2), 3.37 (m, 4H, 2×NH–CH_2), 3.73 (t, 4H, J = 6 Hz, 2×CH_2OH), 5.61 (s, 2H, 2×=CH), 7.49, 7.53 (d, 4H, J = 8 Hz, Ar–H), 7.69, 7.73 (d, 4H, J = 8 Hz, Ar–H); Mass (FAB) 672, 676 (M^+). Anal. calcd for $C_{32}H_{40}Br_2N_2O_4$ C, 56.68, H, 5.96, N, 4.14. Found C, 56.35, H, 5.84, N, 4.17%.

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