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Syntheses and Biological Evaluation of 3-Substituted Amino-1-aryl-6-hydroxy-hex-2-ene-1-ones as Antioxidant and Hypolipidemic Agents[1]†

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Abstract—A new series of compounds belonging to 3-substituted amino-1-aryl-6-hydroxy-hex-2-ene-1-ones (**4–12a–e**) have been synthesized and evaluated for antioxidant and hypolipidemic activities. Amongst all the synthesized compounds, seven compounds, namely **5b**, **5d**, **6e**, **8a**, **8b**, **10b** and **11a**, exhibit better antioxidant activity than probucol. Two compounds, **5d** and **10b**, have been evaluated in detail for antioxidant and hypolipidemic activities and show comparable activity profile to that of probucol and guggulipid. From the present study it may be postulated that the mechanism of action of these compounds could be through activation of lecithin cholesterol acyltransferase (LCAT), liver lipolytic activity, increased faecal bile acid secretion and inhibition of hepatic cholesterol biosynthesis.

Cardiovascular disease is the leading cause of death in both the industrialized and developing nations. A recent survey, carried out by WHO, indicates that the coronary heart disease (CHD) alone accounts for more than half of the total mortalities associated with cardiovascular diseases.[2] Atherosclerosis is the focal point to pathogenesis of these diseases. It is a condition involving arterial damage and is associated with some other vascular pathogenic states such as angina pectoris, myocardial infarction and cerebral thrombosis. Since atherosclerosis is considered to be a multicentric disease, it involves various factors and different cell types. However, the endothelial damages, which ultimately generate atheroma[3] and plaque formation, are characterized by high cholesterol and lipid concentrations along with free radical oxidative stress. Perhaps the involvement of hydroxyl radicals (·OH) is a major causative factor for the peroxidative modifications in circulatory LDL that is responsible for initiation and progression of atherosclerosis.[4,5] The oxidation of LDL is a lipid peroxidation chain reaction that transforms the polyunsaturated fatty acid and cholesterol into lipid hydroperoxides and oxycholesterol, respectively thereby causing damage of arterial endothelial cells and promoting the formation and deposition of atherosclerotic plaque.[6] Thus, it may be envisioned that any drug which is aimed towards lowering of the increased levels of cholesterol and low density lipoproteins (LDL)[7,8] and possesses antioxidant activity[9,10] will prove effective in the treatment of atherosclerosis. At present, therapy of disorders of the lipid metabolism is based on the use of drugs having hypolipidemic activity like fibric acid derivatives, anion exchange resins which sequester the bile acid, the inhibitors of HMG Co-A, an enzyme involved in the de novo synthesis of sterols, probucol, lifibrol and many others.[11–15] Recently, analogues of alkylaminophenones have been reported to possess potential hypolipidemic activity.[16] In our objectives towards development of newer antiatherosclerotic agents, we were simultaneously working upon 3-substituted amino-1-aryl-6-hydroxy-hex-2-ene-1-ones, which have a similar skeletal framework and were found to be potent antioxidant and hypolipidemic agents. The details of their synthesis and biological evaluation are reported herein.

Chemistry

The synthesis of various enaminones is outlined in Scheme 1. The starting substrates for the present study

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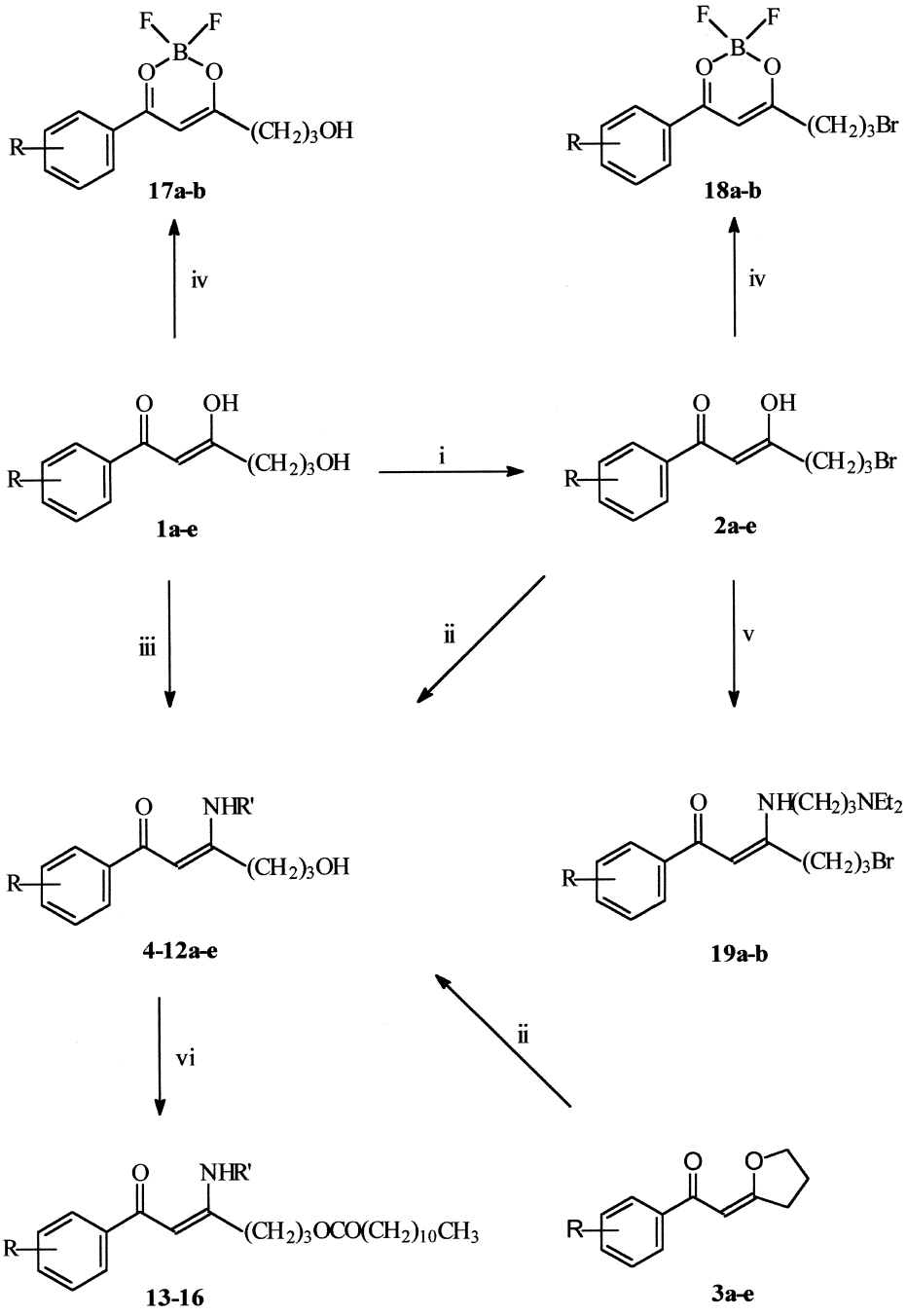

R' / R	H	$(CH_2)_2NEt_2$	$(CH_2)_2$-(pyrrolidin-1-yl)	$(CH_2)_2$-(morpholin-4-yl)	$(CH_2)_2$-(piperanin-1-yl)	CH_2-(piperidin-4-yl)	CH_2-Ph	$(CH_2)_3NEt_2$	$(CH_2)_3$-(pyrrolidin-2-one-1-yl)
H	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**
4-Br	**4b**	**5b**	**6b**	**7b**	**8b**	**9b**	**10b**	**11b**	**12b**
4-CH_3	**4c**	**5c**	**6c**	**7c**	**8c**	**9c**	**10c**	**11c**	**12c**
4-Cl	**4d**	**5d**	**6d**	**7d**	**8d**	**9d**	**10d**	**11d**	**12d**
4-F	**4e**	**5e**	**6e**	**7e**	**8e**	**9e**	**10e**	**11e**	**12e**

Scheme 1. (i) PBr_3, CH_2Cl_2, rt, 45 min–1 h; (ii) $R'NH_2$, MeOH, steel bomb, 90–110 °C, 1.5–2.0 h; (iii) $BF_3.Et_2O$, $R'NH_2$, dichloromethane: ether, rt, 8–16 h; (iv) $BF_3.Et_2O$, ether, rt, 20 min; (v) $BF_3.Et_2O$, $NH_2(CH_2)_3NEt_2$, dichloromethane: ether, rt, 10 h; (vi) Lauryl chloride, Et_3N, 0 °C–rt, 45 min–1 h.

were obtained by reacting appropriate acetophenones with γ-butyrolactone in the presence of sodium methoxide.[17] The *Z* stereochemistry of the products was established on the basis of nOe experiments. The reaction of compounds **1a–e** with phosphorous tribromide led to regioselective bromination to yield the bromo derivatives **2a–e** as major products along with minor yields of **3a–e**. Reactions of bromo derivatives **2a-e** with primary amines in a sealed tube furnished the amines **4–12a–e** though the secondary and tertiary amines yielded non-nitrogenous products which were identified as **3a–e**. This observation suggested that under basic conditions once the enolate anion was generated, inversion of geometry occurred and the resulting *E* isomers did undergo ring closure reactions to furnish products **3a–e**. Perhaps, it was observed that compounds **3a–e** on reaction with primary amines in a sealed tube led to the formation of compounds **4–12a–e**. The structure and stereochemistry of the amino derivatives was confirmed by ^{1}H-^{1}H COSY experiment and nOe difference studies. Additional chemical evidence for compounds to be the enaminone derivatives was obtained by the formation of lauryl acetates (**13–16**) of the representative compounds. The *Z* stereochemistry of the amines suggested that probably compounds **2a–e** with primary amines under forceful conditions yielded compounds **3a–e** as the intermediate products. These intermediates then add amines (Fig. 1) and during the ring opening process delivered the thermodynamically stable compounds **4–12a–e**. It may be argued that if the thermodynamic stability was the driving force for the *Z* stereochemistry of the compounds **4–12a–e**, the outcome of the stereochemistry of the same compounds by an alternate route of synthesis could be worked. The literature indicated that structurally similar compounds in the presence of Lewis acids were capable of forming metal enolates.[18–20] This led to the reactions of compounds **1a–b** and **2a–b** with boron trifluoride etherate. The resulting boron derivatives **17a–b** from compounds **1a–b** were hygroscopic and could not be analyzed; however, bromo derivatives **2a–b** yielded solid boron enolates **18a–b**. Reactions of compounds **17a–b** with primary amines furnished compounds **5a–b** while reactions of **18a–b** with amine led to formation of compound **19a–b.**

Biological assays

Antioxidant activity

Oxidation of low-density lipoprotein (LDL) by Cu^{2+}. Human serum was separated from the blood of normolipidemic donors. LDL was isolated by sequential ultracentrifugation using Beckman ultra-centrifuge model LE-80K.[21] 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 on polyacrylamide gel electrophoresis. LDL (0.71 mg) and $CuCl_2.2H_2O$ (10 μM) in the absence or presence of test compounds (5 or 10 μmol/mL) listed in the 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).[22] Compounds **5d** and **10b** having potent antioxidant activities were selected for further in vitro and in vivo studies.

Generation of oxygen free radicals. Super oxide anions (O_2^-) were generated in an in vitro[23] system comprising of NADH (160 μM) phenozine methosulphate (100 μM) and NBT (320 μM) in the absence or presence of compounds **5d**, **10b**, probucol (0.5–2 μmol/mL) and guggulipid (0.25–1.0 mg/mL) in 0.05 M phosphate buffer (pH 8.2) to a final volume of 2.0 mL. After incubation at 37 °C for 30 min, the reaction was checked by 0.5 mL glacial acetic acid and the amount of formazon formed in both sets was estimated spectrophotometrically. In another set of experiments, hydroxyl radicals were generated non-enzymically by $FeSO_4.7H_2O$ (2 mM), sodium ascorbate (2 mM), H_2O_2 (2.8 mM) and deoxyribose (2.8 mM) in 0.05 phosphate buffer (pH 7.4) to a final volume of 2 mL.[24] After reaction in the absence or presence of test drugs (0.5–2 μmol/ml) and guggulipid (0.25–1.0 mg/mL) the incubation mixture was measured for TBARS formed.

Hypolipidemic activity

Triton and cholesterol induced hyperlipidemia was produced in adult male Charles Foster rats (200–225 g) bred

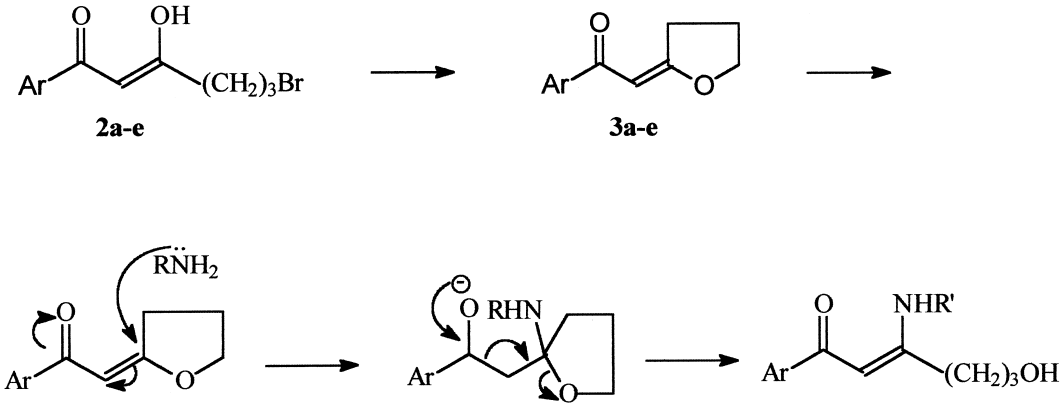

Figure 1.

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)
	5 mM	10 mM	
Probucol	61^{**}	71^{***}	29^{*}
Guggulipid[c]	NA	NA	39^{*}
4a	24^{*}	28^{*}	41^{***}
4b	33^{*}	63^{**}	14^{NS}
4c	35^{*}	35^{*}	—
4d	—	45^{*}	—
4e	20^{NS}	22^{NS}	—
5a	38^{*}	46^{*}	26^{*}
5b	84^{***}	90^{***}	30^{**}
5c	17^{NS}	58^{*}	—
5d	67^{**}	85^{***}	45^{***}
5e	24^{*}	43^{**}	—
6a	36^{*}	71^{***}	34^{***}
6b	43^{*}	51^{*}	—
6c	NA	NA	—
6d	42^{**}	73^{***}	31^{***}
6e	79^{***}	89^{***}	31^{***}
7a	21^{NS}	63^{**}	—
7b	41^{*}	45^{**}	—
7c	50^{**}	83^{**}	14^{*}
7d	43^{*}	51^{**}	—
7e	21^{*}	27^{*}	—
8a	85^{***}	92^{***}	19^{*}
8b	87^{***}	88^{***}	—
8c	42^{**}	41^{*}	—
8d	41^{*}	37^{*}	—
8e	45^{**}	64^{**}	—
9a	42^{*}	50^{**}	—
9b	14^{NS}	15^{NS}	—
9c	2^{NS}	16^{NS}	—
9d	14^{NS}	15^{NS}	—
9e	NA	NA	—
10a	21^{*}	23^{*}	—
10b	83^{***}	86^{***}	45^{***}
10c	45^{**}	62^{**}	20^{*}
10d	44^{**}	50^{**}	—
10e	31^{*}	61^{**}	—
11a	75^{***}	85^{***}	15^{*}
11b	33^{**}	69^{**}	14^{*}
11c	44^{*}	61^{**}	—
11d	34^{*}	50^{**}	—
11e	23^{*}	43^{**}	—
12a	14^{NS}	36^{*}	—
12b	11^{NS}	45^{**}	—
12c	57^{**}	84^{***}	12^{NS}
12d	9^{NS}	21^{*}	—
12e	7^{NS}	36^{*}	—

[a]The percent reversal and its significance against protection of LDL oxidation was deduced by comparing the values of nmol MDA formed/mg protein ±sd of four separate observations with LDL in absence or presence of test compounds. Similarly, cholesterol-lowering activity and its significance was deduced by comparing the levels of cholesterol ±sd of six hyperlipidemic 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.

in the animal house of the institute. Animals 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 for 18h. The compounds **5d**, **10b**, probucol and guggulipid were macerated with 2% aqueous gum acacia suspension and fed orally (50 and 100 mg/kg b.wt) simultaneously with triton. In the chronic experiment hyperlipidemia was produced by feeding of cholesterol (25 mg/kg b.wt) suspended in refined groundnut oil (0.5%, w/v) once a day for 30 days. The compounds and standard drugs were fed orally (50 mg/kg b.wt) simultaneously with cholesterol in drug treated group. In control, animals received same amount of aqueous gumacacia or groundnut oil. At the end of the experiment, rats were fasted overnight and blood was withdrawn from retro-orbital plexus. The animals used for the chronic experiment were sacrificed, liver was promptly excised and homogenized (10%, w/v) in ice-cold 0.1 M phosphate buffer (pH 7.4). Homogenate was centrifuged at $12{,}000 \times g$ for 20 min. The post mitrochondrial supernatant was then spun at $100{,}000 \times g$ for 1 h in ultracentrifuge for sedimentation of microsomes, which were used for the assay of enzymic and non-enzymic lipid peroxidation in vitro.[25]

Biochemical analysis of plasma, serum and liver. Plasma lecithin cholesterol acyltransferase (LCAT) activity[26] and post heparin lipolytic activity (PHLA) was assayed.[27] Very low-density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) were isolated from serum by sequential centrifugation at densities between 1.006 and 1.250 g/ml in ultracentrifuge. These preparations were dialysed against 0.15 M NaCl containing EDTA (0.02%, w/v) in cold. Serum as well as lipoproteins were analyzed for their total cholesterol (TC), phospholipid (PL), triglycerides (Tg) and protein by standard procedures reported earlier.[28] A portion of lipoprotein solution was used for assay of apoproteins.[29] Liver was homogenized (10%, w/v) in cold 0.1 M phosphate buffer (pH 7.2) and used for the assay of total lipolytic activity.[27] The hepatic rate of cholesterol biosynthesis was investigated using [1-C^{14}]-sodium acetate.[30] The lipid extract of each homogenate was used for estimation of TC, PL, Tg and protein. The rat faeces were collected and processed for determination of bile acids.[31]

Enzymic and non-enzymic lipid peroxidation in microsomes. Rat liver microsomes (3 mg protein) from control, cholesterol and cholesterol plus drug treated groups were added with NADPH (100 μM), ADP (500 μM), $FeSO_4.7H_2O$ (2 mM) and EDTA (6 mM) for enzymic induction of lipid peroxidation. In another experiment, lipid peroxidation in microsomes was induced non-enzymically by $FeSO_4.7H_2O$ (2 mM), EDTA (6 mM) and sodium ascorbate (20 mM) in phosphate buffer to a final volume of 2.0 mL. Both sets were incubated at 37 °C for 90 min and the amount of malondialdehyde formed was estimated as TBARS.

Cardioprotective activity

Colony bred male Charles Foster rats, each weighing 200–225 g, were divided into control, ischemic, ischemic plus drug treated groups of six animals in each. Ischemia was produced by intraperitoneal injection of aqueous solution of dl-isoproterenol hydrochloride (85 mg/kg) for five consecutive days.[32] Aqueous suspension of compounds **5d**, **10b**, probucol and guggulipid sonicated

at 30KCS for 2×3 min were administered intraperitoneally at the dose of 50 mg/kg b.wt simultaneously with isoproterenol in drug-treated groups. The control animals received the same amount of normal saline. At the end of the experiment of 5 days, blood was withdrawn 4 h after the last treatment, rats were sacrificed and their hearts were excised immediately. Serum was used for the assay of creatine phosphokinase (CPK),[33] alkaline phosphatase,[34] glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase.[35] Heart homogenate Ca-ATPase,[36] phospholipase,[37] lipid peroxide, glycogen,[38] PL[28] and post mitochondrial superoxide dismutase (SOD)[23] were estimated in all animals.

Statistical analyses

Data were analyzed using Student's *t*-test. Oxidized LDL was compared with oxidized LDL that has been treated with drugs. Similarly, the generation of oxygen free radicals in the presence of drugs was compared with their formation without drugs. The hyperlipidemic group was compared with control and hyperlipidemic plus drug treated groups $P < 0.05$ was considered to be significant.

Results

Primary screening of compounds for antioxidant and lipid lowering activities

Aerobic oxidation of LDL in the absence of metal ions caused formation of lipid peroxides, the TBARS (0.5 nmol MDA/mg protein), which was markedly increased by 98-fold in the presence of Cu^{2+}, as reported in Table 2. Addition of the test compounds listed in Table 1, at 5 and 10 μmol/mL in the above reaction mixture, protected Cu^{2+} mediated oxidation of LDL-lipids in concentration-dependent manner but to varying extents. Amongst them all, seven compounds, namely **5b**, **5d**, **6e**, **8a**, **8b**, **10b** and **11a**, were found to be the most active. The data in Table 3 shows that administration of triton WR 1339 caused marked increase in the serum levels of TC, PL and Tg in rats. The cholesterol-lowering activity of compounds possessing potent antioxidant activity has also been reported simultaneously in Table 1. Two compounds, **5d** and **10b**, showing significant lipid lowering and antioxidant activities together, were selected for detailed in vitro and in vivo studies. The known drugs probucol and guggulipid were included simultaneously as control. The scavenging potential of these compounds against the formation of O_2^- and $^{\cdot}OH$ radicals as well as inhibitory effect against oxidation of LDL is reported in Table 2. On the other hand, the lipid-lowering effect of the compounds on the levels of serum TC, PL and Tg in triton-fed hyperlipidemic rats, at two different doses of 50 and 100 mg/kg b.wt is reported in Table 3.

Effect of compounds on lipid metabolism in cholesterol induced hyperlipidemia in rats

The data in Table 4 shows that feeding of cholesterol increased the animal serum levels of TC, PL and Tg by 69, 65 and 65%, respectively. This was accompanied with marked increase in the levels of lipid and apoprotein constituting β-lipoproteins (72–165%) and these effects were more pronounced for TC in VLDL and LDL (165 and 160%), respectively. Treatment with compounds **5d**, **10b**, probucol and guggulipid at the dose

Table 2. Effect of compounds on generation of oxygen free radicals in vitro

Test compounds	Generation of superoxide anions[a] (2 μmol/mL)	Generation of hydroxyl radicals[b] (2 μmol/mL)	Lipid peroxidation in LDL induced by Cu^{2+} (5 μmol/mL)[c]
None	61.49±4.40	10.66±0.28	47.59±2.12
Compd **5d**	37.23±1.78	4.78±0.51	18.26±2.10
Compd **10b**	37.76±2.50	5.24±0.48	12.21±1.25
Probucol	38.32±1.45	6.49±1.01	18.55±1.50
Guggulipid[d]	59.54±6.81^{NS}	9.50±1.00^{NS}	46.59±5.36^{NS}

[a]nmol Formazon formed/min.
[b]nmol MDA/h.
[c]nmol MDA/mg protein.
[d]Guggulipid was studied at 500 μg/mL in the in vitro experiment. Values are mean ±sd of four separate observations; $P < 0.001$; NS = not significant as compared with experiment without drugs. LDL oxidized in absence of Cu^{2+} contains 0.5 nmol MDA/mol protein.

Table 3. Lipid lowering activity of compound **5d** and **10b** in triton induced hyperlipidemic rats[a,b]

		Triton and test compound treatment (% decrease)							
		Compound **5d**		Compound **10b**		Probucol		Guggulipid	
Experiment schedule	Triton only (% increase)	50 mg/kg	100 mg/kg	50 mg/kg	100 mg/kg	50 mg/kg	100 mg/kg	50 mg/kg	100 mg/kg
TC	4.9-fold***	13*	39***	4^{NS}	22**	13*	29**	24*	40***
PL	4.3-fold***	12*	30***	9^{NS}	17*	15*	29**	23*	35***
Tg	1.9-fold***	13*	34***	10^{NS}	18*	12*	25**	18*	28***

[a]The lipid lowering activity and its significance was deduced by comparing the levels of ±sd of six hyperlipidemic rats in both, with drug and without drug treated groups.
[b]$P^{*} < 0.5$; $^{**} < 0.01$; $^{***} < 0.001$; NS = not significant.

Table 4. Effect of compounds **5d** and **10b** on serum lipoprotein lipids in cholesterol fed hyperlipidemic rats[a]

Biochemical parameters	Cholesterol only (% increase)	Cholesterol and test compound treatment (% reversal)			
		Compd **5d** (50 mg/kg p.o.)	Compd **10b** (50 mg/kg p.o.)	Probucol (50 mg/kg p.o.)	Guggulipid (50 mg/kg p.o.)
Serum TC	67	60	40	47	35
PL	65	80	32	66	74
Tg	65	53	18*	66	64
Lipid peroxide	70	44	33	67	57
VLDL-TC	71	71	47	70	57
PL	165	55	51	55	55
Tg	71	42	20*	55	57
apoprotein	162	44	10^{NS}	54	65
Lipid peroxide	58	30	20*	42	32
LDL-TC	160	46	31	62	46
PL	62	61	43	51	49
Tg	107	51	36	59	55
Apoprotein	102	60	15	63	68
Lipid peroxide	64	19	35	27	26

[a]The percent change in the levels of lipid and apoproteins and its significance was deduced by comparing the values in the cholesterol fed group and in the control and cholesterol plus drug treated groups ±sd of six animals in both; $P < 0.001$ except * < 0.05; NS = not significant.

Table 5. Effect of compounds **5d** and **10b** on lipid metabolism in cholesterol induced hyperlipidemic rats[a]

Biochemical parameters	Cholesterol only (% change)	Cholesterol and test compound treatment (% reversal)			
		Compound **5d** (50 mg/kg)	Compound **10b** (50 mg/kg)	Probucol (50 mg/kg)	Guggulipid (50 mg/kg)
Plasma/Serum					
LCAT	−32**	52	23*	19*	50
HDL-TC	−28*	72	36	12^{NS}	100
PL	-17^{NS}	75	68	34	77
Tg	−27*	67	61	20*	79
Apoprotein	−21*	63	16^{NS}	—	46
Liver					
Lipoprotein					
Lipases	−41	63	11^{NS}	93	80
SOD	−29*	60	54	78	81
Lipid peroxide	+86	49	11^{NS}	67	75
Cholesterol biosynthesis	−32**	33**	8^{NS}	46	50
TC	+79	39	9^{NS}	44	48
PL	+49	64	42	64	65
Tg	+42	44	15	42	29**
Faecal cholic acid	−45	28*	9^{NS}	29*	36
Deoxycholic acid	−50	50	15*	45	45

[a]The percent change in the levels of lipid and apoproteins and its significance was deduced by comparing the values in cholesterol fed group and in the control and cholesterol plus drug treated groups ±sd of six animals in both; $P < 0.001$ except * < 0.05; ** < 0.01; NS = not significant.

of 50 mg/kg significantly reduced these levels of lipids and apoproteins in hyperlipidemic animals. At the same time-treatment with drugs also lowered the increased levels of lipid peroxides in serum, VLDL and LDL (70, 58 and 64%) of cholesterol fed rats. As reported in Table 5, cholesterol feeding caused the inhibition of plasma LCAT activity (32%) and decreased HDL lipids and apoprotein (17–28%). Treatment with drugs except probucol caused the reactivation of enzyme and a partial recovery of HDL. In the hyperlipidemic situation, due to feed back regulation, the hepatic cholesterol biosynthesis was suppressed by 24% as observed by the decreased incorporation of [1-C^{14}] sodium acetate and this effect was reinforced by their treatment with drugs except compound **10b**. Administration of cholesterol suppressed hepatic LPL and SOD activities (41 and 29%) followed by the increase in the levels of TC, PL, Tg and lipid peroxides by 80, 50, 42 and 86%, respectively. Treatment with drugs stimulated these enzymes and down regulated the levels of lipid and lipid peroxides in hyperlipidemic rats. The faecal excretion of cholic acid and deoxycolic acid, which, decreased by 45 and 50%, respectively in hyperlipidemia, was also shown to be recovered in cholesterol and drug fed animals.

Hepatic microsomal lipid peroxidation

It was observed that the hepatic microsomes isolated from cholesterol fed animals were more prone to peroxidation of their lipids induced by both enzymic (59%) and nonenzymic (80%) systems, as shown in Table 6. Drug treatment made them less susceptible against challenge induced oxidative degradation of their lipids in both types of systems.

Table 6. Effect of compounds on hepatic microsomal lipid peroxidation in cholesterol induced hyperlipidemic rats in vitro[a,b]

Drugs	None (without peroxidant added)	NADPH- induced system (enzymic peroxidation)	Fe^{2+}-ascorbate induced system (Non enzymic peroxidation)
Control	2.00±0.07	2.86±0.23	2.28±0.08
Cholesterol fed	3.04±0.13	4.54±0.23	4.12±0.21
Cholesterol + compd **5d** fed	2.38±0.25	2.95±0.06	3.48±0.24
Cholesterol + compd **10b** fed	2.83±0.23^{NS}	3.50±0.30	3.84±0.12*
Cholesterol + probucol fed	2.62±0.08	3.42±0.08	3.33±0.43**
Cholesterol + guggulipid fed	2.27±0.07	2.86±0.20	2.68±0.25

[a]Values expressed as nmol MDA/mg protein are mean ±sd of six rats; $P < 0.001$ except * < 0.05, ** < 0.01, NS = not significant.
[b]Cholesterol fed group was compared with control and cholesterol plus drug treated.

Table 7. Effect of compounds **5d** and **10b** on isoproterenol induced ischemia in rats[a]

Biochemical parameters	Isoproterenol (% changes)	Isoproterenol and test compound treatment (% reversal)			
		Compound **5d** (50 mg/kg)	Compound **10b** (50 mg/kg)	Probucol (50 mg/kg)	Guggulipid (50 mg/kg)
Blood					
CPK	+90	93	55	100	78
Alkaline phosphatase	+54	54	37**	59	45
GOT	+53	61	51	53	47
GPT	+59	38**	22*	29*	38**
Heart					
Ca-ATPase	−33**	70	8^{NS}	26	70
Phospholipase	+152	46	—	50	40**
Phospholipid	−44	75	29*	42	72
Xanthine-oxidase	+60	48	33*	37**	27*
Lipid peroxides	+69	55	26	86	22*
SOD	−59	63	7^{NS}	43	60
Glycogen	−45	69	11^{NS}	43	40

[a]The percent change in biochemical parameters and its significance was deduced by comparing the values in ischemic group with control and ischemic plus drug treated groups ±sd of six animals; $P < 0.001$ except * < 0.05, ** < 0.01, NS = not significant.

Effect of compounds on cardiac ischemia

Isoproterenol induced ischemia appeared with increased levels of serum enzymes namely CPK, Alkaline phosphatase, GOT, GPT by 90, 36, 53 and 56%, respectively, in rats. Treatment with compound **5d**, **10b**, probucol and guggulipid at the dose of 50 mg/kg significantly suppressed the activities of these blood enzymes, as shown in Table 7. In an ischemic heart, although suppressed activities of Ca-ATPase (33%) and SOD (59%) were observed with depletion of glycogen (45%) and PL (44%), there were significant increases in phospholipase (151%) and xanthine oxidase (60%) activities followed by formation of TBARS (70%). Treatment with compound **5d**, probucol and guggulipid significantly reversed these biochemical parameters in hearts of ischemic and drug fed rats. In contrast, compound **10b** was observed to be less effective.

Discussion

As the major aim of the present study was to synthesize compounds possessing antioxidant as well as hypolipidemic activities together, all the compounds were first screened for in vitro antioxidant activity. For this we have used Cu^{2+}-induced LDL oxidation as a model of nonenzymic stimulation of the peroxidation reaction. The percentage prevention of this oxidation by the present series of test compounds was the measure of activity and indeed few of them (**5d**, **6e** and **10b**) were found to be more active than probucol.[39] The analysis of the structure–activity relationship indicated that, in comparison to unsubstituted amino group at position 3, the amino ethyl amino group elicit better biological response. Increasing or decreasing the carbon atom in this chain was not found to be effective, with the exception of compounds **10b** and **11a**. On the other hand, replacing the *N*, *N*-diethyl group with some heterocyclic system also did not prove to be effective. The halogen substituted phenyl group was observed to be more suitable in comparison to alkyl substituted phenyl group for antioxidant activity. In contrast, the unsubstituted phenyl group with exception of compounds **8a** and **11a** did not influenced the biological activity. All the compounds that were found to be potent antioxidants were screened for cholesterol lowering activity in triton induced hyperlipidemia in a rat model. After analyzing the data of both the activities, compounds **5d** and **10b** were selected for detailed studies.

Superoxide anions and H_2O_2 interacts in the presence of iron salts to generate $^{\cdot}OH$, which is mainly responsible for decomposition of peroxidized polyunsaturated fatty acids into lipid peroxidation products in the body.[40] Antioxidant activity of compound **5d** and **10b** was further confirmed by their actions, as scavenger of $O_2^{\cdot-}$ and $^{\cdot}OH$ formed in vitro as reported in Table 2. The antioxidant potential of compounds **5d** and **10b** was comparable to probucol however guggulipid did not show any activity

in in vitro system. As these compounds show antioxidant activity both against the Cu^{2+} mediated oxidation of LDL and Fe^{2+} mediated generation of ·OH, it may be quite likely that these compounds acts as chelators of Cu^{2+} and Fe^{2+}. Triton induced hyperlipidemia in rat is acute model for primary screening of lipid lowering activity of drugs. Triton WR-1339 acts as surfactant and suppresses the action of lipases to block the uptake of lipoproteins from circulation by extrahepatic tissues, thereby resulting in an increase in the level of blood lipids.[41–43] Since experiments with 50 mg/kg of test compounds showed slight lipid lowering action, the subsequent experiments were performed with 100 mg/kg dose of compounds. Compound **5d**, probucol and guggulipid exhibit better lipid lowering action than compound **10b**. The present investigation with cholesterol fed hyperlipidemic animals shows that compounds **5d**, **10b** and guggulipid could increase the level of HDL by increasing the activity of LCAT, which plays a key role in the regulation of lipoprotein metabolism.[44] The lipid lowering action of probucol to catalyze the hyperlipidemic VLDL and LDL may be through some different mechanism than compounds **5d**, **10b** and guggulipid. Suppression of hepatic cholesterol biosynthesis and increase of lipolytic activity in the liver of drug treated hyperlipidemic rats may be responsible for a down regulation of lipids simultaneously with their faster catabolism resulting in a decrease of β-lipoproteins. Here too, compound **5d**, probucol and guggulipid were more effective than compound **10b**. The stimulation of LDL catabolism by test drugs in hyperlipidemic animals may be due to a significant decrease in the levels of serum and liver lipids. These compounds may also enhance the synthesis of LDL apoprotein (Apo B) as well as receptor protein, to accelerate the turn over of cholesterol.[45] The observed decrease in the levels of TBARS in liver and blood lipoproteins in treated animals by these compounds is also in agreement with their antioxidant activity in vitro. Lipid lowering activity may also be linked with faecal bile acid excretion, which in turn may stimulate the conversion of cholesterol in to bile acid in liver.[46]

We have also observed that the compounds exerted beneficial effect on experimental ischemia. Increased CPK activity, depletion of heart glycogen and PL were significantly reversed by compound **5d** and guggulipid in isoproterenol treated rats. The decrease in heart phospholipid may be explained due to increase phospholipase activity[47] and these parameters were partially reversed by the treatment with compounds. It was suggested that activation of phospholipases is mediated through lipid peroxidation with significant decrease in ATP levels during isoproterenol induced myocardial necrosis.[48] The test drugs compound **5d** and guggulipid significantly suppressed the enzyme activity of xanthine oxidase and decrease the level of TBARS by stimulating their protections by SOD and Ca-ATPase.

Conclusion

The 3-substituted amino-3-aryl-6-hydroxy-hex-2-ene-1-one derivatives described herein represents a new class of hypolipidemic and antioxidant agents. Preliminary results indicates that of all the synthesized compounds, 3-[2-(*N*, *N*′-diethylamino)ethylamino]-1-(4-chlorophenyl)-6-hydroxy-hex-2-ene-1-one (**5d**) is the most active compound. The antioxidant activity of these compounds could be due to the chelation with the Fe^{2+} or Cu^{2+} since they were found to be active only in the non-enzymic systems. The lipid lowering action of this compound may be due to activation of LCAT, liver lipolytic activity, and increased faecal bile acid excretion as well as inhibition of hepatic cholesterol biosynthesis. Also, from the structure–activity point of view, it is quite evident that presence of an amino ethyl amino chain elicit better biological response. However, it will be interesting to study the effect of increase or decrease in carbon chain of these molecules and also replacing the hydroxyl moiety with some other pharmacophores. The most promising compound **5d** is being taken up for further detailed evaluation.

Experimental

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. ^{1}H NMR 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). Mass spectrometry was carried out on a Jeol JMS-D-300 spectrometer at 70 eV. Elemental analyses were performed by a Carlo Erba 1108 microanalyzer. Silica gel (60-120 mesh) and basic aluminium oxide (100 mesh, pH 9.5) were used for column chromatography.

General procedure for 1-aryl-6-bromo-1, 3-hexanediones (2a–e)

To a cold stirred solution of appropriate compounds from **1a–e** (4.8 mmol) in dry dichloromethane (20 mL) was added dropwise a solution of phosphorous tribromide (0.46 mL, 4.8 mmol) in 5 mL dry dichloromethane over a period of 20 min. The stirring was continued for 45 min to 1 h at 0–5 °C. The reaction mixture was decomposed with ice-cold water and extracted with chloroform (2×30 mL). The organic layers were combined, washed with brine, dried over sodium sulphate and evaporated to obtain a residue. This residue upon column chromatography over silica gel using hexane: ethyl acetate (99:1, v/v) as eluent furnished the bromo derivatives **2a–e**. Further elution with hexane:ethyl acetate (90:10, v/v) yields the minor derivatives **3a–e**. The compounds **2a–e** were recrystallized from ether: petroleum ether mixture.

1-Phenyl-6-bromo-1, 3-hexanedione (2a). (55%, 39–41 °C): IR (neat) 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.25 (m, 2H, CH_2), 2.64 (t, 2H, *J* = 7 Hz, CH_2), 3.50 (t, 2H, *J* = 6 Hz, CH_2), 6.20 (s, 1H, =CH), 7.47 (m, 3H, Ar-H), 7.88 (m, 2H, Ar-H); Mass (EI) *m*/*z* 268(M^+). Anal. calcd of $C_{12}H_{13}BrO_2$ C, 53.53, H, 4.83. Found C, 53.72, H, 4.63%.

1-(4-Bromophenyl)-6-bromo-1, 3-hexanedione (2b). (52%, 55–56 °C): IR (KBr) 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ

2.24 (m, 2H, CH_2), 2.42 (t, 2H, $J=7$ Hz, CH_2), 3.49 (t, 2H, $J=6$ Hz, CH_2), 6.16 (s, 1H, =CH), 7.56, 7.61 (d, 2H, $J=9$ Hz, Ar-H), 7.72, 7.76 (d, 2H, $J=9$ Hz, Ar-H); mass (EI) m/z 346(M^+). Anal. calcd for $C_{12}H_{12}Br_2O_2$ C, 41.41, H, 3.44. Found C, 41.26, H, 3.24%.

1-(4-Methylphenyl)-6-bromo-1, 3-hexanedione (2c). (62%, 59–61 °C): IR (KBr) 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (m, 2H, CH_2), 2.41 (s, 3H, Ar4-Me), 2.62 (t, 2H, $J=7$ Hz, CH_2), 3.49 (t, 2H, $J=6$ Hz, CH_2), 6.17 (s, 1H, =CH), 7.23, 7.27 (d, 2H, $J=8$ Hz, Ar-H), 7.76, 7.80 (d, 2H, $J=8$ Hz, Ar-H); mass (EI) m/z 282(M^+). Anal. calcd for $C_{13}H_{15}BrO_2$ C, 55.14, H, 5.33. Found C, 55.32, H, 5.61%.

1-(4-Chlorophenyl-6-bromo-1, 3-hexanedione (2d). (58%, 58 °C): IR (KBr) 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (m, 2H, CH_2), 2.64 (t, 2H, $J=7$ Hz, CH_2), 3.49 (t, 2H, $J=6$ Hz, CH_2), 6.16 (s, 1H, =CH), 7.41, 7.45 (d, 2H, $J=8$ Hz, Ar-H), 7.80, 7.84 (d, 2H, $J=8$ Hz, Ar-H); mass (EI) m/z 302(M^+). Anal. calcd for $C_{12}H_{13}BrClO_2$ C, 47.47, H, 3.98. Found C, 47.67, H, 4.12%.

1-(4-Fluorophenyl-6-bromo-1, 3-hexanedione (2e). (65%, 65 °C): IR (KBr) 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (m, 2H, CH_2), 2.63 (t, 2H, $J=7$ Hz, CH_2), 3.49 (t, 2H, $J=6$ Hz, CH_2), 6.15 (s, 1H, =CH), 7.13 (m, 2H, Ar-H), 7.89 (m, 2H, Ar-H); mass (EI) m/z 286(M^+). Anal. calcd for $C_{12}H_{13}BrFO_2$ C, 54.68, H, 4.17. Found C, 54.28, H, 4.01%.

1-Aryl-2-(fuan-2-yl)-1-oxo-2-ethylidenes (3a–e). These compounds were prepared as reported previously in the literature.[17]

General method for 3-substituted amino-1-aryl-6-hydroxy-hex-2-ene-1-ones (4–12a–e)

Method A. To a solution of appropriate compound from **2a–e** (3.7 mmol) in 20 mL methanol in a steel bomb were added appropriate primary amines (3.7 mmol) (methanolic ammonia for **4a–e**). The sealed tube was placed in an oil bath maintained between 95 and 110 °C for 1.5–3.0 h. The reaction mixture was allowed to cool and the excess solvent was evaporated under vacuo. The residue thus obtained was either directly subjected to column chromatography over basic aluminium oxide or was extracted with chloroform and the residue obtained after usual work up was subjected to column chromatography over basic aluminium oxide. The elution with chloroform:methanol (99:1, v/v) furnished the desired amines as solids or oils.

Method B. 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 to 25 min, solid separates out, to which was added dropwise a solution of suitable amine (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 8–20 h. On completion 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 chromatography over basic aluminium oxide using chloroform:methanol (99:1, v/v) as eluent yield the amino derivatives.

3-Amino-6-hydroxy-1-phenyl-hex-2-ene-1-one (4a). (65%, 83–84 °C): IR (KBr) 3350, 3200, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (m, 2H, CH_2), 2.31 (t, 2H, $J=7$ Hz, CH_2), 3.62 (t, 2H, $J=6$ Hz, CH_2), 5.69 (s, 1H, =CH), 6.00 (brs, 1H, NH_2), 7.32 (m, 3H, Ar-H), 7.78 (m, 2H, Ar-H), 10.32 (brs, 1H, NH_2); mass (EI) m/z 205 (M^+). (Anal. calcd for $C_{12}H_{15}NO_2$ C, 70.24, H, 7.31, N, 6.82. Found C, 70.44, H, 7.34, N, 7.02%.

3-Amino-1- (4-bromophenyl)-6-hydroxy-hex-2-ene-1-one (4b). (87%, 123–125 °C): IR (KBr) 3370, 3220, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (m, 2H, CH_2), 2.40 (t, 2H, $J=7$ Hz, CH_2), 3.72 (t, 2H, $J=6$ Hz, CH_2), 5.65 (s, 1H, =CH), 5.91 (brs, 1H, NH_2), 7.42, 7.51 (d, 2H, $J=9$ Hz, Ar-H), 7.64, 7.72 (d, 2H, $J=9$ Hz, Ar-H), 10.28(brs, 1H, NH_2); mass (EI) m/z 283 (M^+). Anal. calcd for $C_{12}H_{14}BrNO_2$ C, 50.71, H, 4.96, N, 4.93. Found C, 50.41, H, 5.14, N, 5.02%.

3-Amino-6-hydroxy-1-(4-methylphenyl)-hex-2-ene-1-one (4c). (83%, 125–126 °C): IR (KBr) 3355, 3200, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (m, 2H, CH_2), 2.40 (t, 2H, $J=7$ Hz, CH_2), 3.74 (t, 2H, $J=6$ Hz, CH_2), 5.52 (brs, 1H, NH_2), 5.75 (s, 1H, =CH), 7.20, 7.23 (d, 2H, $J=9$ Hz, Ar-H), 7.77, 7.80 (d, 2H, $J=9$ Hz, Ar-H), 10.21(brs, 1H, NH_2); mass (EI) m/z 219 (M^+). Anal. calcd for $C_{13}H_{17}NO_2$ C, 71.20, H, 7.81, N, 6.38. Found C, 70.94, H, 7.45, N, 5.93%.

3-Amino-1-(4-chlorophenyl)-6-hydroxy-hex-2-ene-1-one (4d). (85%, 119–120 °C): IR (KBr) 3265, 3190, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 2H, CH_2), 2.41 (t, 2H, $J=7$ Hz, CH_2), 3.75 (t, 2H, $J=6$ Hz, CH_2), 4.91 (brs, 1H, NH_2), 5.70 (s, 1H, =CH), 7.36, 7.38 (d, 2H, $J=9$ Hz, Ar-H), 7.79, 7.82 (d, 2H, $J=9$ Hz, Ar-H), 8.95(brs, 1H, NH_2); mass (EI) m/z 239 (M^+). Anal. calcd for $C_{12}H_{14}ClNO_2$ C, 60.12, H, 5.88, N, 5.84. Found C, 60.26, H, 5.93, N, 5.78%.

3-Amino-1-(4-fluorophenyl)-6-hydroxy-hex-2-ene-1-one (4e). (86%, 123–124 °C): IR (KBr) 3352, 3190, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (m, 2H, CH_2), 2.23 (t, 2H, $J=7$ Hz, CH_2), 3.43 (t, 2H, $J=6$ Hz, CH_2), 4.91 (brs, 1H, NH_2), 5.66 (s, 1H, =CH), 7.71 (m, 2H, Ar-H), 7.75 (d, 1H, Ar-H), 7.83 (m, 2H, Ar-H), 9.96 (brs, 1H, NH_2); mass (EI) m/z 223 (M^+). Anal. calcd for $C_{12}H_{14}FNO_2$ C, 64.55, H, 6.32, N, 6.27. Found C, 64.60, H, 6.53, N, 5.98%.

3-[2-(*N*,*N*′-Diethylamino)ethylamino]-6-hydroxy-1-phenyl-hex-2-ene-1-one (5a). (53%, oil): IR (Neat) 3360, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 6H, $J=7$ Hz, 2×CH_3), 1.98 (m, 2H, CH_2), 2.59 (m, 8H, 4×CH_2), 3.45 (q, 2H, $J=6$ Hz, CH_2), 4.10 (t, 2H, $J=6$ Hz, CH_2), 5.61 (s, 1H, =CH), 7.35 (m, 3H, Ar-H), 7.80 (m, 2H, Ar-H), 11.47(brs, 1H, NH); mass (EI) m/z 304 (M^+). Anal. calcd for $C_{18}H_{28}N_2O_2$ C, 71.01, H, 9.26, N, 9.20. Found C, 70.72, H, 9.06, N, 9.08%.

3-[2-(*N*,*N*′-Diethylamino)ethylamino]-1-(4-bromophenyl)-6-hydroxy-hex-2-ene-1-one (5b). (58%, oil): IR (neat) 3375, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 6H, $J=7$ Hz, 2×CH_3), 1.88 (m, 2H, CH_2), 2.48 (t, 2H, $J=6$ Hz, CH_2), 2.59 (t, 4H, 2×CH_2), 2.70 (t, 2H, $J=6$ Hz, CH_2), 3.46 (q, 2H, $J=6$ Hz, CH_2), 3.74 (t, 2H, $J=6$ Hz, CH_2), 5.63 (s, 1H,=CH), 7.50, 7.53 (d, 2H, $J=9$ Hz, Ar-H), 7.70, 7.73 (d, 2H, $J=9$ Hz, Ar-H), 11.50 (brs, 1H, NH); mass (EI) *m*/*z* 268 (M^+-114). Anal. calcd for $C_{18}H_{27}BrN_2O_2$ C, 56.40, H, 7.09, N, 7.30. Found C, 56.64, H, 7.20, N, 7.77%.

3-[2-(*N*,*N*′-Diethylamino)ethylamino]-6-hydroxy-1-(4-methylphenyl)-hex-2-ene-1-one (5c). (50%, oil): IR (neat) 3386, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 6H, $J=7$ Hz, 2×CH_3), 1.91 (m, 2H, CH_2), 2.48 (s, 3H, Ar4-Me), 2.48 (t, 2H, $J=6$ Hz, CH_2), 2.59 (t, 4H, 2×CH_2), 2.66 (t, 2H, $J=6$ Hz, CH_2), 3.48 (q, 2H, $J=6$ Hz, CH_2), 3.76 (t, 2H, $J=6$ Hz, CH_2), 5.70 (s, 1H,=CH), 7.21, 7.24 (d, 2H, $J=9$ Hz, Ar-H), 7.77, 7.80 (d, 2H, $J=9$ Hz, Ar-H), 11.50 (brs, 1H, NH); mass (EI) *m*/*z* 318 (M^+). Anal. calcd for $C_{19}H_{30}BrN_2O_2$ C, 71.66, H, 9.49, N, 8.79. Found C, 71.45, H, 9.25, N, 8.40%.

3-[2-(*N*,*N*′-Diethylamino)ethylamino]-1-(4-chlorophenyl)-6-hydroxy-hex-2-ene-1-one (5d). (64%, oil): IR (neat) 3386, 1596 cm^{-1}; ^2H NMR ($CDCl_3$) δ 1.06 (t, 6H, $J=7$ Hz, 2×CH_3), 1.88 (m, 2H, CH_2), 2.48 (t, 2H, $J=6$ Hz, CH_2), 2.58 (t, 4H, 2×CH_2), 2.67 (t, 2H, $J=6$ Hz, CH_2), 3.45 (q, 2H, $J=6$ Hz, CH_2), 3.76 (t, 2H, $J=6$ Hz, CH_2), 5.60 (s, 1H,=CH), 7.33, 7.36 (d, 2H, $J=9$ Hz, Ar-H), 7.77, 7.80 (d, 2H, $J=9$ Hz, Ar-H), 11.50 (brs, 1H, NH); ^{13}C NMR 11.54 (CH_3), 28.74 (CH_2), 30.90 (CH_2), 41.68 (CH_2), 47.37 (CH_2), 61.26 (CH_2), 90.88 (CH_2), 128.26, 128.87 (2×CH), 136.31 (C), 139.02 (C), 168.57 (C), 186.28 (C) ppm; mass (EI) *m*/*z* 338 (M^+). Anal. calcd for $C_{18}H_{27}ClN_2O_2$ C, 63.79, H, 8.02, N, 8.26. Found C, 63.55, H, 8.19, N, 7.97%.

3-[2-(*N*,*N*′-Diethylamino)ethylamino]-1-(4-fluorophenyl)-6-hydroxy-hex-2-ene-1-one (5e). (67%, oil): IR (neat) 3369, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, 6H, $J=7$ Hz, 2×CH_3), 1.89 (m, 2H, CH_2), 2.49 (t, 2H, $J=6$ Hz, CH_2), 2.62 (t, 4H, 2×CH_2), 2.71 (t, 2H, $J=6$ Hz, CH_2), 3.50 (q, 2H, $J=6$ Hz, CH_2), 3.75 (t, 2H, $J=6$ Hz, CH_2), 5.63 (s, 1H, =CH), 7.07 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H), 11.46 (brs, 1H, NH); mass (EI) *m*/*z* 322 (M^+). Anal. calcd for $C_{18}H_{27}FN_2O_2$ C, 71.01, H, 9.26, N, 9.20. Found C, 70.92, H, 9.06, N, 9.08%.

1-Phenyl-3-[2-(pyrrolidin-1-yl)ethylamino]-6-hydroxy-hex-2-ene-1-one (6a). (44%, oil): IR (neat) 3358, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.26 (brs, 4H, CH_2), 2.53 (m, 4H, 2×CH_2), 3.47 (m, 2H, CH_2), 3.72 (t, 2H, $J=6$ Hz, CH_2), 5.68 (s, 1H,=CH), 7.40 (m, 3H, Ar-H), 7.84 (m, 2H, Ar-H), 11.57 (brs, 1H, NH); mass (EI) *m*/*z* 304 (M^+). Anal. calcd for $C_{18}H_{26}N_2O_2$ C, 71.01, H, 9.20, N, 9.20. Found C, 70.75, H, 9.05, N, 9.07%.

1-(4-Bromophenyl)-3-[2-(pyrrolidin-1-yl)ethylamino]-6-hydroxy-hex-2-ene-1-one (6b). (41%, 117–118 °C): IR (KBr) 3360, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 4H, 2×CH_2), 1.99 (m, 2H, CH_2), 2.58 (t, 2H, $J=6$ Hz, CH_2), 2.98 (t, 4H, 2×CH_2), 3.05 (t, 2H, $J=6$ Hz, CH_2), 3.74 (t, 2H, $J=6$ Hz, CH_2), 3.80 (q, 2H, $J=8$ Hz, CH_2), 5.70 (s, 1H, =CH), 7.52, 7.55 (d, 2H, $J=9$ Hz, Ar-H), 7.69, 7.72 (d, 2H, $J=9$ Hz, Ar-H), 11.59 (brs, 1H, NH); mass (EI) *m*/*z* 266 (M^+-114). Anal. calcd for $C_{18}H_{25}BrN_2O_2$ C, 71.01, H, 9.26, N, 9.20. Found C, 70.72, H, 9.06, N, 9.08%.

1-(4-Methylphenyl)-3-[(-2pyrrolidin-1-yl)ethylamino]-6-hydroxy-hex-2-ene-1-one (6c). (43%, oil): IR (Neat) 3396, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 4H, 2×CH_2), 2.01 (m, 2H, CH_2), 2.32 (m, 11H, 4×CH_2 and Ar4-Me), 3.44 (q, 2H, $J=6$ Hz, CH_2), 3.72 (t, 2H, $J=6$ Hz, CH_2), 5.69 (s, 1H,=CH), 7.19, 7.22 (d, 2H, $J=9$ Hz, Ar-H), 7.74, 7.77 (d, 2H, $J=9$ Hz, Ar-H), 11.51 (brs, 1H, NH); mass (EI) *m*/*z* 316 (M^+).(Anal. calcd for $C_{18}H_{28}N_2O_2$ C, 72.11, H, 8.91, N, 8.85. Found C, 72.23, H, 8.64, N, 8.68%.

1-(4-Chlorophenyl)-3-[2-(pyrrolidin-1-yl) ethylamino]-6-hydroxy-hex-2-ene-1-one (6d). (45%, 87–88 °C): IR (KBr) 3388, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 6H, 3×CH_2), 2.49 (t, 2H, $J=6$ Hz, CH_2), 2.72 (t, 4H, $J=6$ Hz, 2×CH_2), 2.79 (t, 2H, $J=9$ Hz, CH_2), 3.54 (q, 2H, $J=8$ Hz, CH_2), 3.73 (t, 2H, $J=6$ Hz, CH_2), 5.65 (s, 1H,=CH), 7.34, 7.37 (d, 2H, $J=9$ Hz, Ar-H), 7.69, 7.72 (d, 2H, $J=9$ Hz, Ar-H), 11.55 (brs, 1H, NH); mass (EI) *m*/*z* 338 ($M^+ + 2$). Anal. calcd for $C_{18}H_{25}ClN_2O_2$ C, 67.47, H, 7.48, N, 8.31. Found C, 67,95, H, 7.51, N, 7.96%.

1-(4-Flourophenyl)-3-[2-(pyrrolidin-1-yl) ethylamino]-6-hydroxy-hex-2-ene-1-one (6e). (41%, oil): IR (neat) 3365, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (m, 6H, 3×CH_2), 2.46 (m, 4H, 2×CH_2), 2.59 (t, 2H, $J=6$ Hz, 2×CH_2), 2.79 (t, 2H, $J=9$ Hz, CH_2), 3.54 (q, 2H, $J=8$ Hz, CH_2), 3.70 (t, 2H, $J=6$ Hz, CH_2), 5.65 (s, 1H, =CH), 7.34, 7.37 (d, 2H, $J=9$ Hz, Ar-H), 7.69, 7.72 (d, 2H, $J=9$ Hz, Ar-H), 11.56 (brs, 1H, NH); mass (EI) *m*/*z* 320 (M^+). Anal. calcd for $C_{18}H_{25}FN_2O_2$ C, 67.50, H, 7.86, N, 8.74. Found C, 67.35, H, 7.56, N, 8.56%.

3-[2-(Morpholin-4-yl) ethylamino]-1-phenyl-6-hydroxy-hex-2-ene-1-one (7a). (42%, 62–63 °C): IR (KBr) 3188, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.48 (t, 2H, $J=6$ Hz, CH_2), 2.62 (m, 4H, 2×CH_2), 2.64 (t, 2H, $J=6$ Hz, CH_2), 3.50 (q, 2H, $J=6$ Hz, CH_2), 3.75 (m, 6H, 3×CH_2), 5.70 (s, 1H,=CH), 7.39 (m, 3H, Ar-H), 7.84 (m, 2H, Ar-H), 11.48 (brs, 1H, NH); mass (EI) *m*/*z* 318(M^+). Anal. calcd for $C_{18}H_{26}N_2O_3$ C, 67.89, H, 8.23, N, 8.80. Found C, 67.54, H, 8.14, N, 8.60%).

1-(4-Bromophenyl)-3-[2-(morpholin-4-yl)ethylamino]-6-hydroxy-hex-2-ene-1-one (7b). (49%, 118–120 °C): IR (KBr) 3176, 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.46 (t, 2H, $J=6$ Hz, CH_2), 2.53 (m, 4H, 2×CH_2), 2.63 (t, 2H, $J=6$ Hz, CH_2), 3.49 (q, 2H, $J=6$ Hz, CH_2), 3.75 (m, 6H, 3×CH_2), 5.63 (s, 1H, =CH), 7.50, 7.53 (d, 2H, $J=9$ Hz, Ar-H), 7.70, 7.73 (d, 2H, $J=9$ Hz, Ar-H), 11.48 (brs, 1H, NH); mass (EI) *m*/*z* 397(M^+). Anal. calcd for $C_{18}H_{25}BrN_2O_3$ C, 54.41, H, 6.34, N, 7.04. Found C, 54.65, H, 6.47, N, 7.26%.

1-(4-Methylphenyl)-3-[(2-morpholin-4-yl) ethylamino)]-6-hydroxy-hex-2-ene-1-one (7c). (46%, 69–70 °C): IR

(KBr) 3180, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.37 (s, 3H, Ar4-Me), 2.46 (t, 2H, $J=6$ Hz, CH_2), 2.53 (m, 4H, 2×CH_2), 2.63 (t, 2H, $J=6$ Hz, CH_2), 3.47 (q, 2H, $J=6$ Hz, CH_2), 3.75 (m, 6H, 3×CH_2), 5.68 (s, 1H,=CH), 7.23, 7.26 (d, 2H, $J=9$ Hz, Ar-H), 7.74, 7.77 (d, 2H, $J=9$ Hz, Ar-H), 11.43 (brs, 1H, NH); mass (EI) m/z 332 (M^+). (Anal. calcd for $C_{19}H_{28}N_2O_3$ C, 68.84, H, 8.48, N, 8.42. Found C, 68.89, H, 8.67, N, 8.72%.

1-(4-Chlorophenyl)-3-[2-(morpholin-4-yl) ethylamino]-6-hydroxy-hex-2-ene-1-one (7d). (46%, 100–101 °C): IR (KBr) 3188, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.47 (t, 2H, $J=6$ Hz, CH_2), 2.53 (m, 4H, 2×CH_2), 2.63 (t, 2H, $J=6$ Hz, CH_2), 3.48 (q, 2H, $J=6$ Hz, CH_2), 3.75 (m, 6H, 3×CH_2), 5.64 (s, 1H,=CH), 7.34, 7.37 (d, 2H, $J=9$ Hz, Ar-H), 7.77, 7.80 (d, 2H, $J=9$ Hz, Ar-H), 11.54 (brs, 1H, NH); mass (EI) m/z 352 (M^+). Anal. calcd for $C_{18}H_{25}ClN_2O_3$ C, 61.27, H, 7.14, N, 7.93. Found C, 61.64, H, 7.14, N, 8.39%.

1-(4-Fluorophenyl)-3-[2-(morpholin-4-yl)ethylamino]-6-hydroxy-hex-2-ene-1-one (7e). (35%, 118–112 °C): IR (KBr) 3406, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.50 (t, 2H, $J=6$ Hz, CH_2), 2.63 (m, 4H, 2×CH_2), 2.63 (t, 2H, $J=6$ Hz, CH_2), 3.49 (q, 2H, $J=6$ Hz, CH_2), 3.74 (m, 6H, 3×CH_2), 5.64 (s, 1H,=CH), 7.06 (m, 2H, Ar-H), 7.86 (m, 2H, Ar-H), 11.44 (brs, 1H, NH); mass (EI) m/z 338 (M^+). Anal. calcd for $C_{18}H_{25}FN_2O_3$ C, 64.26, H, 7.49, N, 8.32. Found C, 64.08, H, 7.43, N, 8.15%.

3-[2-(Piperazin-1-yl) ethylamino]-1-phenyl-6-hydroxy-hex-2-ene-1-one (8a). (47%, oil): IR (neat) 3340, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (m, 2H, CH_2), 2.46 (m, 6H, 3×CH_2), 2.60(t, 2H, $J=6$ Hz, CH_2), 2.93 (t, 4H, $J=6$ Hz, 2×CH_2), 3.48 (q, 2H, $J=6$ Hz, CH_2), 3.70 (t, 2H, $J=6$ Hz, CH_2), 5.69 (s, 1H, = CH), 7.40 (m, 3H, Ar-H), 7.83 (m, 2H, Ar-H), 11.46 (brs, 1H, NH); mass (EI) m/z 188 (M^+-129). Anal. calcd for $C_{18}H_{27}N_3O_2$ C, 68.10, H, 8.57, N, 13.23. Found C, 68.61, H, 8.37, N, 13.63%.

1-(4-Bromophenyl)-3-[2-(piperazin-1-yl) ethylamino]-6-hydroxy-hex-2-ene-1-one (8b). (63%, 126–128 °C): IR (KBr) 3371, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (m, 2H, CH_2), 2.48 (m, 6H, 3×CH_2), 2.63 (t, 2H, $J=6$ Hz, CH_2), 2.93 (t, 4H, $J=6$ Hz, 2×CH_2), 3.50 (q, 2H, $J=6$ Hz, CH_2), 3.75 (t, 2H, $J=6$ Hz, CH_2), 5.64 (s, 1H,=CH), 7.48, 7.51 (d, 2H, $J=9$ Hz, Ar-H), 7.70, 7.73 (d, 2H, $J=9$ Hz, Ar-H), 11.49 (brs, 1H, NH); mass (EI) m/z 266 (M^+-129). Anal. calcd for $C_{18}H_{26}BrN_3O_2$ C, 54.49, H, 6.60, N, 10.59. Found C, 54.27, H, 6.62, N, 10.35%.

1-(4-Methylphenyl)-3-[2-(piperazin-1-yl) ethylamino]-6-hydroxy-hex-2-ene-1-one (8c). (60%, 160–161 °C): IR (KBr) 3344, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 2H, CH_2), 2.37 (s, 3H, Ar4-Me), 2.46 (m, 6H, 3×CH_2), 2.61 (t, 2H, $J=6$ Hz, CH_2), 2.91 (t, 4H, $J=6$ Hz, 2×CH_2), 3.47 (q, 2H, $J=6$ Hz, CH_2), 3.56 (t, 2H, $J=6$ Hz, CH_2), 5.67 (s, 1H,=CH), 7.17, 7.20 (d, 2H, $J=9$ Hz, Ar-H), 7.73, 7.77 (d, 2H, $J=9$ Hz, Ar-H), 11.42 (brs, 1H, NH; mass (EI) m/z 202 (M^+-129). Anal. calcd for $C_{19}H_{29}N_3O_2$ C, 68.84, H, 8.81, N, 12.67. Found C, 68.67, H, 9.05, N, 12.88%.

1-(4-Chlorophenyl)-3-[2-(piperazin-1-yl)ethylamino]-6-hydroxy-hex-2-ene-1-one (8d). (70%, 178–180 °C): IR (KBr) 3380, 1593 cm^{-1}; ^1H NMR (D_2O) δ 1.69 (m, 2H, CH_2), 2.33 (t, 2H, $J=6$ Hz, CH_2), 2.64 (m, 6H, 3×CH_2), 3.16 (t, 4H, $J=6$ Hz, 2×CH_2), 3.45 (q, 2H, $J=6$ Hz, CH_2), 3.54 (t, 2H, $J=6$ Hz, CH_2), 5.57 (s, 1H,=CH), 7.28, 7.31 (d, 2H, $J=9$ Hz, Ar-H), 7.55, 7.58 (d, 2H, $J=9$ Hz, Ar-H), 11.49 (brs, 1H, NH; mass (EI) m/z 222 (M^+-129). Anal. calcd for $C_{18}H_{26}ClN_3O_2$ C, 61.44, H, 7.44, N, 11.94. Found C, 61.27, H, 7.62, N, 12.15%.

1-(4-Flourophenyl)-3-[2-(piperazin-1-yl) ethylamino]-6-hydroxy-hex-2-ene-1-one (8e). (65%, 195–196 °C): IR (KBr) 3392, 1585 cm^{-1}; ^1H NMR (D_2O) δ 1.72 (m, 2H, CH_2), 2.33 (t, 2H, $J=6$ Hz, CH_2), 2.66 (m, 6H, 3×CH_2), 3.18 (t, 4H, $J=6$ Hz, 2×CH_2), 3.44 (q, 2H, $J=6$ Hz, CH_2), 3.56 (t, 2H, $J=6$ Hz, CH_2), 5.62 (s, 1H,=CH), 7.06 (m, 2H, Ar-H), 7.68 (m, 2H, Ar-H); mass (EI) m/z 206 (M^+-129). Anal. calcd for $C_{18}H_{26}FN_3O_2$ C, 64.45, H, 7.81, N, 12.52. Found C, 64.27, H, 7.62, N, 12.35%.

3-[(Piperidin-4-yl) methylamino]-1-phenyl-6-hydroxy-hex-2-ene-1-one (9a). (58%, 138–139 °C): IR (KBr) 3323, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (m, 4H, 2×CH_2), 1.78 (m, 2H, CH_2), 1.89(t, 2H, $J=6$ Hz, CH_2), 2.49(t, 2H, $J=6$ Hz, CH_2), 2.69 (m, 2H, CH_2), 3.18 (t, 4H, $J=6$ Hz, 2×CH_2), 3.78 (t, 2H, $J=6$ Hz, CH_2), 5.72 (s, 1H, = CH), 7.45 (m, 3H, Ar-H), 7.88 (m, 2H, Ar-H), 11.67 (brs, 1H, NH); mass (EI) m/z 302 (M^+). Anal. calcd for $C_{18}H_{26}N_2O_2.1/2\ H_2O$ C, 69.45, H, 8.36, N, 9.00. Found C, 69.20, H, 8.76, N, 9.40%.

1-(4-Bromophenyl)-3-[(piperidin-4-yl) methylamino]-6-hydroxy-hex-2-ene-1-one (9b). (72%, 187–188 °C): IR (KBr) 3344, 1600 cm^{-1}; ^1H NMR (D_2O) δ 1.29 (m, 2H, 1H each of 2×CH_2), 1.53 (m, 2H, 1H each of 2×CH_2), 1.75 (m, 3H, CH and CH_2), 2.18 (t, 2H, $J=7$ Hz, CH_2), 2.79 (m, 2H, 1H each of 2×CH_2), 3.15 (m, 2H, 1H each of 2×CH_2), 3.27 (m, 2H, CH_2), 3.41 (t, 2H, $J=6$ Hz, CH_2), 5.40 (s, 1H,=CH), 7.28, 7.30 (d, 2H, $J=9$ Hz, Ar-H), 7.32, 7.35 (d, 2H, $J=9$ Hz, Ar-H); mass (EI) m/z 267 (M^+-113). Anal. calcd for $C_{18}H_{25}Br\ N_2O_2$ C, 56.69, H, 6.61, N, 7.34. Found C, 56.37, H, 6.62, N, 7.35%.

1-(4-Methylphenyl)-3-[(piperidin-4-yl) methylamino]-6-hydroxy-hex-2-ene-1-one (9c). (79%, 183–184 °C): IR (KBr) 3320, 1598 cm^{-1}; ^1H NMR (D_2O) δ 1.29 (m, 2H, 1H each of 2×CH_2), 1.65 (m, 2H, 1H each of 2×CH_2), 1.93 (m, 3H, CH and CH_2), 2.24 (s, 3H, Ar4-Me), 2.27 (t, 2H, $J=7$ Hz, CH_2), 2.88 (m, 2H, 1H each of 2×CH_2), 3.20 (m, 2H, 1H each of 2×CH_2), 3.25 (m, 2H, CH_2), 3.74 (t, 2H, $J=6$ Hz, CH_2), 5.68 (s, 1H,=CH), 7.40, 7.44 (d, 2H, $J=8$ Hz, Ar-H), 7.80, 7.84 (d, 2H, $J=8$ Hz, Ar-H); mass (EI) m/z 316 (M^+). Anal. calcd for $C_{19}H_{28}\ N_2O_2$ C, 72.11, H, 8.91, N, 8.85. Found C, 72.39, H, 8.62, N, 9.07%.

1-(4-Chlorophenyl)-3-[(piperidin-4-yl) methylamino]-6-hydroxy-hex-2-ene-1-one (9d). (74%, 122–123 °C): IR (KBr) 3380, 1598 cm^{-1}; ^1H NMR (D_2O) δ 1.25 (m, 2H,

1H each of 2×CH_2), 1.56 (m, 2H, 1H each of 2×CH_2), 1.76 (m, 3H, CH and CH_2), 2.19 (t, 2H, J = 7 Hz, CH_2), 2.75 (m, 2H, 1H each of 2×CH_2), 3.17 (m, 4H, 1H each of 2×CH_2 and CH_2), 3.38 (t, 2H, J = 6 Hz, CH_2), 5.51 (s, 1H, = CH), 7.17, 7.19 (d, 2H, J = 9 Hz, Ar-H), 7.43, 7.45 (d, 2H, J = 9 Hz, Ar-H); mass (EI) m/z 223(M^+-113). Anal. calcd for $C_{18}H_{25}ClN_2O_2$ C, 64.18, H, 7.48, N, 8.31. Found C, 63.93, H, 7.62, N, 8.35%.

1-(4-Fluorophenyl)-3-[(piperidin-4-yl)methylamino]-6-hydroxy-hex-2-ene-1-one (9e). (74%, 65–68 °C): IR (KBr) 3398, 1585 cm^{-1}; ^1H NMR (D_2O) δ 1.32 (m, 2H, 1H each of 2×CH_2), 1.65 (m, 2H, 1H each of 2×CH_2), 1.81 (m, 3H, CH and CH_2), 2.29 (t, 2H, J = 7 Hz, CH_2), 2.82 (m, 2H, 1H each of 2×CH_2), 3.25 (m, 4H, 1H each of 2×CH_2 and CH_2), 3.48 (t, 2H, J = 6 Hz, CH_2), 5.61 (s, 1H,=CH), 7.01 (m, 2H, Ar-H), 7.64 (m, 2H, Ar-H); mass (EI) m/z 320 (M^+). Anal. calcd for $C_{18}H_{25}FN_2O_2$ C, 67.47, H, 7.86, N, 8.74. Found C, 67.19, H, 7.99, N, 8.56%.

3-(Phenylmethylamino)-1-phenyl-6-hydroxy-hex-2-ene-1-one (10a). (66%, oil): IR (KBr) 3402, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 2H, CH_2), 2.47 (t, 2H, J = 6 Hz, CH_2), 3.70 (t, 2H, J = 6 Hz, CH_2), 4.56, 4.59 (d, 2H, J = 6 Hz, CH_2), 5.77 (s, 1H,=CH), 7.41 (m, 8H, Ar-H), 7.85 (m, 2H, Ar-H), 12.07 (t, 1H, J = 6 Hz, NH); mass (EI) m/z 295 (M^+). Anal. calcd for $C_{19}H_{21}NO_2$ C, 77.26, H, 7.16, N, 4.74. Found C, 77.46, H, 7.23, N, 4.60%.

1-(4-Bromophenyl)-3-(phenylmethylamino)-6-hydroxy-hex-2-ene-1-one (10b). (43%, 71–72 °C): IR (neat) 3386, 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 2H, CH_2), 2.49 (t, 2H, J = 6 Hz, CH_2), 3.73 (t, 2H, J = 6 Hz, CH_2), 4.60, 4.62 (d, 2H, J = 6 Hz, CH_2), 5.74 (s, 1H,=CH), 7.35 (m, 5H, Ar-H), 7.53, 7.56 (d, 2H, J = 9 Hz, Ar-H), 7.73, 7.76 (d, 2H, J = 9 Hz, Ar-H), 11.86 (brs, 1H, NH); mass (EI) m/z 374 (M^+ + 1). Anal. calcd for $C_{19}H_{20}Br\,NO_2$ C, 60.96, H, 5.34, N, 3.74. Found C, 60.78, H, 5.23, N, 3.38%.

1-(4-Methylphenyl)-3-(phenylmethylamino)-6-hydroxy-hex-2-ene-1-one (10c). (48%, oil): IR (Neat) 3394, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (m, 2H, CH_2), 2.39 (s, 3H, Ar4-Me), 2.43 (t, 2H, J = 6 Hz, CH_2), 3.69 (t, 2H, J = 6 Hz, CH_2), 4.55, 4.57 (d, 2H, J = 6 Hz, CH_2), 5.77 (s, 1H,=CH), 7.18, 7.21 (d, 2H, J = 9 Hz, Ar-H), 7.30 (m, 5H, Ar-H), 7.78, 7.81 (d, 2H, J = 9 Hz, Ar-H), 11.78 (brs, 1H, NH); mass (EI) m/z 309 (M^+). Anal. calcd for $C_{20}H_{23}NO_2$ C, 77.63, H, 7.49, N, 4.52. Found C, 77.76, H, 7.32, N, 4.32%.

1-(4-Chlorophenyl)-3-(phenylmethylamino)-6-hydroxy-hex-2-ene-1-one (10d). (49%, 222–223 °C): IR (KBr) 3423, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 2H, CH_2), 2.46 (t, 2H, J = 6 Hz, CH_2), 3.69 (t, 2H, J = 6 Hz, CH_2), 4.56, 4.58 (d, 2H, J = 6 Hz, CH_2), 5.71 (s, 1H, = CH), 7.36 (m, 7H, Ar-H), 7.68, 7.71 (d, 2H, J = 9 Hz, Ar-H), 11.81 (brs, 1H, NH); mass (EI) m/z 329 (M^+). Anal. calcd for $C_{19}H_{20}ClNO_2$ C, 69.19, H, 6.11, N, 4.24. Found C, 69.00, H, 5.85, N, 4.05%.

1-(4-Fluorophenyl)-3-(phenylmethylamino)-6-hydroxy-hex-2-ene-1-one (10e). (51%, 77–78 °C): IR (KBr) 3392, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (m, 2H, CH_2), 2.48 (t, 2H, J = 6 Hz, CH_2), 3.71 (t, 2H, J = 6 Hz, CH_2), 4.58, 4.60 (d, 2H, J = 6 Hz, CH_2), 5.72 (s, 1H,=CH), 7.08 (m, 2H, Ar-H), 7.36 (m, 5H, Ar-H), 7.89 (m, 2H, Ar-H), 11.79 (brs, 1H, NH); mass (EI) m/z 313 (M^+). Anal. calcd for $C_{19}H_{20}FNO_2$ C, 72.82, H, 6.43, N, 4.47. Found C, 72.48, H, 6.60, N, 4.60%.

1-Phenyl 3-[3-(pyrrolidin-2-one-1yl)propylamino]-6-hydroxy-hex-2-ene-1-one (11a). (45%, oil): IR (neat) 3382, 1668, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (m, 6H, 3×CH_2), 2.06 (m, 2H, CH_2), 2.34 (m, 2H, CH_2), 2.45 (t, 2H, J = 6 Hz, CH_2), 3.43 (m, 2H, 2×CH_2), 3.72 (t, 2H, J = 6 Hz, CH_2), 5.69 (s, 1H,=CH), 7.38 (m, 3H, Ar-H), 7.83 (m, 2H, Ar-H), 11.45 (s, 1H, NH); mass (EI) m/z 191 (M^+ −141). Anal. calcd for $C_{19}H_{26}N_2O_3$ C, 68.64, H, 7.88, N, 8.42. Found C, 68.62, H, 7.61, N, 8.89%.

1-(4-Bromophenyl)-3-[3-(pyrrolidin-2-one-1yl)propylamino]-6-hydroxy-hex-2-ene-1-one (11b). (46%, 107–108 °C): IR (KBr) 3367, 1672, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (m, 4H, 2×CH_2), 2.05 (m, 2H, CH_2), 2.18 (m, 2H, CH_2), 2.38 (m, 2H, CH_2), 2.49 (t, 2H, J = 6 Hz, CH_2), 3.46 (m, 4H, 2×CH_2), 3.73 (t, 2H, J = 6 Hz, CH_2), 5.65 (s, 1H,=CH), 7.52, 7.55 (d, 2H, J = 9 Hz, Ar-H), 7.71, 7.74 (d, 2H, J = 9 Hz, Ar-H), 11.59 (s, 1H, NH); mass (EI) m/z 408 (M^+). Anal. calcd for $C_{19}H_{25}BrN_2O_3$ C, 55.75, H, 6.15, N, 6.84. Found C, 55.96, H, 6.46, N, 6.64%.

1-(4-Methylphenyl)-3-[3-(pyrrolidin-2-one-1-yl)propylamino]-6-hydroxy-hex-2-ene-1-one (11c). (26%, oil): IR (Neat) 3388, 1670, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (m, 4H, 2×CH_2), 2.36 (m, 9H, 3×CH_2 and Ar4-Me), 3.46 (m, 4H, 2×CH_2), 3.72 (t, 2H, J = 6 Hz, CH_2), 5.67 (s, 1H, = CH), 7.18, 7.21 (d, 2H, J = 9 Hz, Ar-H), 7.73, 7.75 (d, 2H, J = 9 Hz, Ar-H), 11.50 (s, 1H, NH); mass (EI) m/z 203 (M^+ −141). Anal. calcd for $C_{20}H_{28}N_2O_3$ C, 69.76, H, 8.14, N, 8.14. Found C, 67.57, H, 8.12, N, 8.39%.

1-(4-Chlorophenyl)-3-[3-(pyrrolidin-2-one-1-yl)propylamino]-6-hydroxy-hex-2-ene-1-one (11d). (63%, oil): IR (Neat) 3382, 1665, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 6H, 3×CH_2), 2.03 (m, 2H, CH_2), 2.34 (m, 2H, CH_2), 2.48 (t, 2H, J = 6 Hz, CH_2), 3.43 (m, 4H, 2×CH_2), 3.73 (t, 2H, J = 6 Hz, CH_2), 5.64 (s, 1H,=CH), 7.34, 7.37 (d, 2H, J = 9 Hz, Ar-H), 7.76, 7.79 (d, 2H, J = 9 Hz, Ar-H), 11.56 (s, 1H, NH); mass (EI) m/z 223(M^+ −141). Anal. calcd for $C_{19}H_{25}ClN_2O_3$ C, 62.54, H, 6.90, N, 7.67. Found C, 62.54, H, 6.97, N, 7.50%.

1-(4-Fluorophenyl)-3-[3-(pyrrolidin-2-one-1-yl)propylamino]-6-hydroxy-hex-2-ene-1-one (11e). (52%, oil): IR (neat) 3384, 1670, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (m, 6H, 3×CH_2), 2.03 (m, 2H, CH_2), 2.34 (m, 2H, CH_2), 2.49 (t, 2H, J = 6 Hz, CH_2), 3.45 (m, 4H, 2×CH_2), 3.74 (t, 2H, J = 6 Hz, CH_2), 5.64 (s, 1H,=CH), 7.07 (m, 2H, Ar-H), 7.83 (m, 2H, Ar-H), 11.51 (s, 1H, NH); mass (EI) m/z 348 (M^+). Anal. calcd for $C_{19}H_{25}FN_2O_3$ C65.49, H, 7.23, N, 8.03. Found C, 65.63, H, 7.56, N, 7.98%.

3-[3-(*N*,*N*′-Diethylamino)propylamino]-1-phenyl-6-hydroxy-hex-2-ene-1-one (12a). (67%, oil): IR (neat) 3363,

1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, 6H, $J=6$ Hz, $2\times CH_3$), 1.87 (m, 4H, $2\times CH_2$), 2.55 (m, 8H, $4\times CH_2$), 3.46 (q, 2H, $J=6$ Hz, CH_2), 3.72 (t, 2H, $J=6$ Hz, CH_2), 5.67 (s, 1H,=CH), 7.38 (m, 3H, Ar-H), 7.84 (m, 2H, Ar-H), 10.82 (brs, 1H, NH); mass (EI) m/z 318 (M^+). Anal. calcd for $C_{19}H_{30}N_2O_2$ C, 71.69, H, 9.43, N, 8.80. Found C, 71.42, H, 9.36, N, 8.52%.

1-(Bromophenyl)-3-[3-(*N*,*N*′-diethylamino)propylamino]-6-hydroxy-hex-2-ene-1-one (12b). (71%, oil): IR (neat) 3392, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 6H, $J=6$ Hz, $2\times CH_3$), 1.85 (m, 4H, $2\times CH_2$), 2.53 (m, 8H, $4\times CH_2$), 3.49 (q, 2H, $J=6$ Hz, CH_2), 3.69 (t, 2H, $J=6$ Hz, CH_2), 5.62 (s, 1H,=CH), 7.50, 7.53 (d, 2H, $J=9$ Hz, Ar-H), 7.71, 7.74 (d, 2H, $J=9$ Hz, Ar-H), 11.56 (brs, 1H, NH); mass (EI) m/z 396 (M^+). Anal. calcd for $C_{19}H_{29}BrN_2O_2$ C, 57.43, H, 7.35, N, 7.04. Found C, 57.56, H, 7.07, N, 6.45%.

3-[(3-*N*,*N*′-Diethylamino)propylamino]-1-(methylphenyl)-6-hydroxy-hex-2-ene-1-one (12c). (68%, oil): IR (Neat) 3363, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 6H, $J=6$ Hz, $2\times CH_3$), 1.85 (m, 4H, $2\times CH_2$), 2.38 (s, 3H, Ar4-Me), 2.52 (m, 8H, $4\times CH_2$), 3.46 (q, 2H, $J=6$ Hz, CH_2), 3.70 (t, 2H, $J=6$ Hz, CH_2), 5.67 (s, 1H,=CH), 7.18, 7.21 (d, 2H, $J=9$ Hz, Ar-H), 7.74, 7.77 (d, 2H, $J=9$ Hz, Ar-H), 11.50 (s, 1H, NH); mass (EI) m/z 332 (M^+). Anal. calcd for $C_{20}H_{32}N_2O_2$ C, 72.25, H, 9.69, N, 8.42. Found C, 72.46, H, 9.75, N, 8.63%.

1-(Chlorophenyl)-3-[3-(*N*,*N*′-diethylamino)propylamino]-6-hydroxy-hex-2-ene-1-one (12d). (56%, oil): IR (Neat) 3392, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 6H, $J=6$ Hz, $2\times CH_3$), 1.85 (m, 4H, $2\times CH_2$), 2.52 (m, 8H, $4\times CH_2$), 3.47 (q, 2H, $J=6$ Hz, CH_2), 3.69 (t, 2H, $J=6$ Hz, CH_2), 5.62 (s, 1H,=CH), 7.34, 7.37 (d, 2H, $J=9$ Hz, Ar-H), 7.77, 7.80 (d, 2H, $J=9$ Hz, Ar-H), 11.55 (brs, 1H, NH); mass (EI) m/z 352 (M^+). Anal. calcd for $C_{19}H_{29}ClN_2O_2$ C, 64.68, H, 8.23, N, 7.94. Found C, 64.82, H, 8.62, N, 7.82%.

1-(Fluorophenyl)-3-[3-(*N*,*N*′-diethylamino)propylamino]-6-hydroxy-hex-2-ene-1-one (12e). (31%, oil): IR (Neat) 3379, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, 6H, $J=6$ Hz, $2\times CH_3$), 1.87, 1.93 (2m, 4H, $2\times CH_2$), 2.53 (t, 2H, $J=6$ Hz, CH_2), 2.77 (m, 6H, $3\times CH_2$), 3.57 (q, 2H, $J=6$ Hz, CH_2), 3.72 (t, 2H, $J=6$ Hz, CH_2), 5.65 (s, 1H,=CH), 7.06 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H), 11.54 (brs, 1H, NH); mass (EI) m/z 336 (M^+).Anal. calcd for $C_{19}H_{29}FN_2O_2$ C, 67.87, H, 8.63, N, 8.33. Found C, 67.75, H, 8.60, N, 7.90%.

1-Aryl-3-(*N*-substituted amino)-1,8-dicarbonyl-7-oxa-nona-dec-2-enes (13–16). To a stirred solution of appropriate compound from **4c**, **4e**, **10b** and **12a** (4.4 mmol) in 20 mL of dry dichloromethane was added triethylamine (0.63 mL, 6.2 mmol) and 4-dimethyl-aminopyridine (0.54 g, 4.4 mmol). After 20 min a solution of lauryl chloride (1.37 mL, 6.2 mmol) in 10 mL of dry dichloromethane was added dropwise over a period of 15 min under stirring. The reaction was continued for 45 min to 1 h. Thereafter the reaction mixture was washed with water and extracted with chloroform (2×30 mL). The organic layers were combined, washed with brine, dried over sodium sulphate and evaporated to obtain a residue. This residue upon chromatography over basic aluminium oxide using chloroform: methanol (99.5:0.5, v/v) as eluent furnished the pure acetates.

3-Amino-1-(4-methylphenyl)-1,8-dicarbonyl-7-oxa-nona-dec-2-ene (13). (50%, oil): IR (neat) 1730, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $J=6$ Hz, CH_3), 1.26 (brs, 18H, $9\times CH_2$), 1.63 (t, 2H, $J=6$ Hz, CH_2), 1.95 (m, 2H, CH_2), 2.32 (m, 2H, CH_2), 2.39 (s, 3H, Ar4-CH_3), 4.17 (t, 2H, $J=6$ Hz, CH_2), 5.26 (brs, 1H, NH_2), 5.74 (s, 1H,=CH), 7.20, 7.23 (d, 2H, $J=9$ Hz, Ar-H), 7.79, 7.82 (d, 2H, $J=9$ Hz, Ar-H), 10.22 (brs, 1H, NH_2); mass (EI) m/z 400 (M^+). Anal. calcd for $C_{25}H_{38}NO_3$ C, 74.95, H, 9.56, N, 3.49. Found C, 74.46, H, 9.62, N, 3.26%.

3-Amino-1-(4-fluorophenyl)-1,8-dicarbonyl-7-oxa-nona-dec-2-ene (14). (51%, oil): IR (neat) 1728, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, $J=6$ Hz, CH_3), 1.25 (brs, 18H, $9\times CH_2$), 1.62 (t, 2H, $J=6$ Hz, CH_2), 1.98 (m, 2H, CH_2), 2.32 (m, 2H, CH_2), 4.16 (t, 2H, $J=6$ Hz, CH_2), 4.56 (brs, 1H, NH_2), 5.69 (s, 1H,=CH), 7.07 (m, 2H, Ar-H), 7.88 (m, 2H, Ar-H), 10.10 (brs, 1H, NH_2); mass (EI) m/z 405 (M^+). Anal. calcd for $C_{24}H_{36}FNO_3$ C, 71.07, H, 8.94, N, 3.45. Found C, 71.47, H, 8.72, N, 3.43%.

1-(4-Bromophenyl)-3-(phenylmethylamino)-1,8-dicarbonyl-7-oxa-nona-dec-2-ene (15). (49%, oil): IR (neat) 1728, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $J=6$ Hz, CH_3), 1.26 (brs, 22H, $11\times CH_2$), 1.92 (m, 5H, CH_2), 2.37 (m, 6H, $3\times CH_2$), 3.26 (m, 2H, CH_2), 4.19 (t, 2H, $J=6$ Hz, CH_2), 4.56 (brs, 1H, NH_2), 5.64 (s, 1H,=CH), 7.51, 7.54 (d, 2H, $J=9$ Hz, Ar-H), 7.70, 7.73 (d, 2H, $J=9$ Hz, Ar-H), 11.67 (s, 1H, NH); mass (EI) m/z 562 (M^+). Anal. calcd for $C_{30}H_{27}BrN_2O_3$ C, 63.93, H, 8.40, N, 4.96. Found C, 63.72, H, 8.32, N, 4.68%.

3-[(3-*N*,*N*′-Diethylamino)propylamino]-1,8-dicarbonyl-7-oxa-nona-dec-2-ene (16). (45%, oil): IR (neat) 1730, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $J=6$ Hz, CH_3), 1.03 (t, 6H, $J=6$ Hz, $2\times CH_3$), 1.26 (brs, 18H, $9\times CH_2$), 1.63 (t, 2H, $J=6$ Hz, CH_2), 1.97 (m, 2H, CH_2), 2.32 (t, 2H, $J=6$ Hz, $3\times CH_2$), 2.42 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 3.37 (q, 2H, $J=6$ Hz, CH_2), 4.17 (t, 2H, $J=6$ Hz, CH_2), 5.66 (s, 1H,=CH), 7.41 (m, 3H, Ar-H), 7.85 (m, 2H, Ar-H), 10.60 (s, 1H, NH); mass (EI) m/z 562 (M^+). Anal. calcd for $C_{31}H_{52}N_2O_3$ C, 74.35, H, 10.46, N, 5.59. Found C, 74.20, H, 10.26, N, 5.50%.

2,2-Difluoro-6-[(3-bromo)-4-aryl-1-oxania-boratobenzoates] (18a–b). To a solution of compound **2a–b** (3.7 mmol) in 20 mL of dry ether was added boron trifluoride etherate (1.05 mL, 7.4 mmol) dropwise over a period of 15 min. The resulting reaction mixture was stirred at room temperature for 45 min. The desired products separated out as solids, which were filtered and washed repeatedly with dry ether to obtain pure products.

2,2-Difluoro-6-[(3-bromo)-4-phenyl-1-oxania-boratobenzoate] (18a). (75%, 78–79 °C): ^1H NMR ($CDCl_3$) δ 2.33 (m, 2H, CH_2), 2.84 (t, 2H, $J=7$ Hz, CH_2), 3.48 (t, 2H,

$J=6$ Hz, CH_2), 6.68 (s, 1H, =CH), 7.57 (m, 3H, Ar-H), 8.05 (m, 2H, Ar-H); mass (EI) m/z 315 (M^+). Anal. calcd for $C_{12}H_{12}BBrF_2O_3$ C, 45.47, H, 3.81. Found C, 45.07, H, 3.62%.

2,2-Difluoro-6-[(3-bromo)-4-bromophenyl-1-oxania-boratobenzoate] (18b). (78%, 119–121 °C): ^{1}H NMR ($CDCl_3$) δ 2.33 (m, 2H, CH_2), 2.83 (t, 2H, $J=7$ Hz, CH_2), 3.54 (t, 2H, $J=6$ Hz, CH_2), 6.52 (s, 1H,=CH), 7.55, 7.65 (d, 2H, $J=9$ Hz, Ar-H), 7.79, 7.88 (d, 2H, $J=9$ Hz, Ar-H); mass (EI) m/z 394 (M^+). Anal. calcd for $C_{12}H_{11}$ $BBr_2F_2O_3$ C, 36.54, H, 2.79. Found C, 36.39, H, 2.73%.

3-[(3-*N,N′*-Diethylamino)propylamino]-1-aryl-6-bromo-hex-2-ene-1-ones (19a–b). To a stirred solution of compound **2a** or **b** (3.5 mmol) in dry dichloromethane (20 mL) was added borontrifluoride etherate (0.65 mL, 7.0 mmol). After 15 min, a solution of diethylaminopropyl amine (5.3 mmol) in dry dichloromethane (10 mL) was added dropwise and the reaction was allowed to continue at room temperature for 10 h. After completion, the reaction was extracted with chloroform (2×30 mL). Usual work of the organic layer was followed by column chromatography over basic alumina. Elution with chloroform:methanol (99.5:0.5, v/v) yields the pure products.

3-[(3-*N,N′*-Diethylamino)propylamino]-1-phenyl-6-bromo-hex-2-ene-1-one (19a). (52%, oil); IR (neat) 1600 (C=O); ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 2H, CH_2), 1.01 (t, 6H, $J=7$ Hz, 2×CH_3), 1.75 (m, 2H, CH_2), 2.49 (m, 10H, 5×CH_2), 3.50 (q, 2H, $J=7$ Hz, CH_2), 5.36 (s, 1H,=CH), 7.30 (m, 3H, Ar-H), 7.75 (m, 2H, Ar-H); mass (EI) m/z 301 (M^+-79). Anal. calcd for $C_{19}H_{29}BrN_2O_3$ C, 59.85, H, 7.66, N, 7.34. Found C, 59.62, H, 7.48, N, 7.02%.

3-[(3-*N,N′*-Diethylamino)propylamino]-1-(4-bromophenyl)-6-bromo-hex-2-ene-1-one (19b). (48%, oil); IR (neat) 1598 (C=O); ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 2H, CH_2), 1.01 (t, 6H, $J=9$ Hz, 2×CH_3), 1.81 (m, 2H, CH_2), 2.55 (m, 10H, 5×CH_2), 3.10 (q, 2H, $J=7$ Hz, CH_2), 5.30 (s, 1H, = CH), 7.37, 7.47 (d, 2H, $J=9$ Hz, Ar-H), 7.59, 7.69 (d, 2H, 2H, $J=9$ Hz, Ar-H); mass (EI) m/z 460 (M^+). Anal. calcd for $C_{19}H_{28}Br_2N_2O_3$ C, 49.58, H, 6.13, N, 6.08. Found C, 49.52, H, 5.82, N, 5.98%.

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