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Original paper

Substituted acrylophenones and related mannich bases as possible spermicides and inhibitors of HIV envelope glycoprotein–CD4 interaction☆

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Abstract

Several appropriately substituted 4-(dialkylamino-alkyl)-substituted-styryl-alkyl ketones or acetophenones were prepared and subjected to the Mannich reaction to yield compounds that would incorporate both α,β-unsaturated keto groups and a substituted aminomethyl function with or without another olefinic moiety at position 4. The spermicidal activity of the prepared compounds was evaluated. Several compounds **2d**, **4a** and **4e** were found to possess spermicidal activity at 0.005% concentration, while compounds **2a**, **2c**, **2f**, **3a** and **4b** were active at 0.01% concentration. Compounds **2a**, **2c**, **3a**, **4a** and **4e** also inhibited the interaction between recombinant HIV Env and CD4. Out of these, compound **2c** was found to be most active.

Keywords: Spermicides; HIV Env–CD4 interaction; Mannich bases; 2-Dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]prop-2-en-1-one and 4-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]penta-1,4-dien-3-one; 1-[4-(Dialkylaminoalkoxy)phenyl]-3-dialkylamino-propan-1-one; 5-Dialkylaminoalkyl-1-[(4-dialkylaminoalkoxy)phenyl]pent-1-en-3-one

1. Introduction

In a recent survey carried out on the acceptability of different methods of contraception, it was found that there is a growing trend towards the use of local contraceptive agents and devices, particularly, new spermicides possessing *anti*-human immuno-deficiency virus (HIV), anti-fungal and anti-bacterial activity for medicating condoms or in other barrier contraceptive preparations.

Several α,β-unsaturated ketones have a wide spectrum of biological activity, including anti-tumour activity that has been attributed to reactivity towards cellular thiols. A number of nuclear substituted styryl ketone-related Mannich bases and allyl alcohols were found to show anti-bacterial and anti-tumour activity [1,2]. Several Mannich bases of formyl and other substituted phenols [3,4], N-substituted α-amino alkyl acrylophenones and related compounds [5], substituted quinotoxin derivatives [6,7] exhibited spermicidal activity against human spermatozoa. Several styryl ketones and their Mannich bases, incorporating an α,β-unsaturated keto system, were prepared and tested for their spermicidal potential against human spermatozoa in our laboratory [8–11]. One of these compounds, 1-(4-methoxy-phenyl)-4-piperidyl-methyl-penta-1,4-dien-3-one [10,11], CDRI compound no. 87/132, also inhibited the binding of HIV envelope protein (HIV Env) with its receptor on mammalian cells, the CD4 molecule. Encouraged by these findings, it was considered of interest to prepare a

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series of appropriately substituted styryl alkyl ketones followed by their Mannich reaction to yield compounds that would incorporate both α,β-unsaturated keto groups and a substituted aminomethyl function with and without another olefinic moiety at position 4.

2. Chemistry

The hydroxy group of 4-acetyl-phenol or 1-(4-hydroxyphenyl)butan-1-en-3-one or 4-acetyl-2-isopropyl-5-methyl-phenol was amino-alkylated with disubstituted-aminoalkyl-halides in presence of a mild base like potassium carbonate and catalytic amount of sodium iodide to give 4-(dialkylaminoalkyloxy)acetophenone or 1-(4-(dialkylaminoalkyloxy)phenyl)butan-1-en-3-one or 4-(dialkylaminoalkyloxy)-5-isopropyl-2-methyl-acetophenone in 40–50% yield. Sodium salt of 4-acetyl-2-isopropyl-5-methyl-phenol was also reacted with epichlorohydrin in presence of sodium hydroxide and the epoxide so formed was opened with a secondary amine to get 4-[3-dialkylamino-2-hydroxy-propoxy]-5-isopropyl-2-methyl-acetophenone.

The 4-dialkylaminoalkoxy acetophenone or 1-[4-(dialkylaminoalkoxy)phenyl]buta-1-en-3-one or 4-[3-dialkylamino-2-hydroxy-propoxy]-5-isopropyl-2-methyl-acetophenone were subjected to reaction with a secondary amine in presence of excess of paraformaldehyde in glacial acetic acid under gentle refluxing to yield 2-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]prop-2-en-1-one or 4-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]penta-1,4-dien-3-one, or 2-dialkylaminomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-dialkylaminopropoxy)phenyl]prop-2-en-1-one, respectively.

When 4-dialkylaminoalkoxy acetophenone or 1-[4-(dialkylaminoalkoxy)phenyl]buta-1-en-3-one or 4-[3-dialkylamino-2-hydroxy-propoxy]-5-isopropyl-2-methyl-acetophenone were subjected to Mannich reaction in absolute ethanol or in propan-1-ol in presence of a few drops of concentrated hydrochloric acid under reflux, the major products formed were 1-[4-(dialkylaminoalkoxy)phenyl]-3-dialkylamino-propan-1-one or 5-dialkylaminoalkyl-1-[(4-dialkylaminoalkoxy)phenyl]pent-1-en-3-one or 3-(4-dialkylamino)-1-[5-isopropyl-2-methyl-4-(2-dialkylaminoethoxy)phenyl]propan-1-one, respectively along with 2-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]prop-2-en-1-one or 4-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]penta-1,4-dien-3-one, or 2-dialkylaminomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-dialkylaminopropoxy)phenyl]prop-2-en-1-one formed in trace amounts (Fig. 1a–c).

3. Biological screening

3.1. Spermicidal activity

The spermicidal activity was determined using the Sander–Cramer assay [12] using Krebs–Ringer bicarbonate buffer (pH 7.6). The minimum effective concentration (MEC) is reported in % (wt./vol.) of test material as determined with three individual human semen samples. The compounds were dissolved in physiological saline/DMSO at different concentrations. Semen and test compound solutions were mixed in the ratio of 1:5 (about 5 s), and immediately examined under a phase contrast microscope. The results were scored as positive if 100% of spermatozoa became immotile within 20 s, whereas even if only one or two spermatozoa showed sluggish motility, the test concentration of the compound was scored negative. The control slides were prepared by adding physiological saline instead of test solutions.

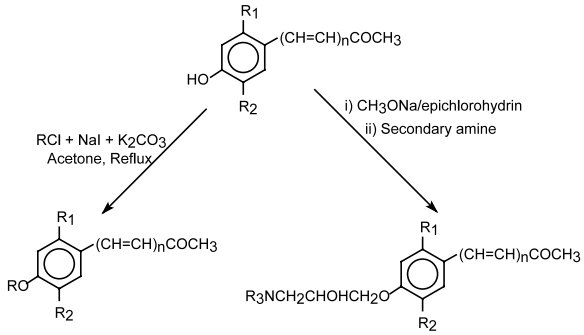
3.2. Inhibition of HIV-1 Env–CD4 interaction

A quantitative bioassay to measure the fusion of cells derived from cell lines HL2/3 and HLCD4-CAT in the presence of test compounds was carried out [13]. The HL2/3 line contains stably integrated copies of the HIV-1 clone HXB2/3gpt and expresses high levels of HIV-1 proteins (Gag, Env, Tat, Rev and Nef) but no infectious virus. Co-culture of HL2/3 cells with the CD4-expressing cell line HLCD4-CAT results in efficient cell fusion within 6–12 h and activates CAT gene expression in HLCD4-CAT. Fusion efficiency was quantitated by assaying CAT activation using a colorimetric enzyme immunoassay (Boehringer Mannheim, Germany). Fusion in the presence or absence of test compounds was measured with dextran sulphate as positive control for inhibition.

4. Results and discussion

1-(4-Methoxy-phenyl)-4-(piperidyl-methyl)penta-1,4-dien-3-one [10,11], CDRI compound no. 87/132, is a potent spermicide as well as a strong inhibitor of HIV–CD4 interaction. A series of its analogues was prepared by substituting methoxy group with dialkylamino-alkyl group to increase water solubility. The criterion for selection of the side chain were based on the observation that the side chain of nonoxynol-9 has nine carbon atoms at the *para* position of the phenyl ring. Therefore, side chains having eight or nine carbon atoms with a secondary amino group, to increase water solubility, were selected.

The compounds listed in Table 1 were prepared and tested for their spermicidal activity. Several compounds

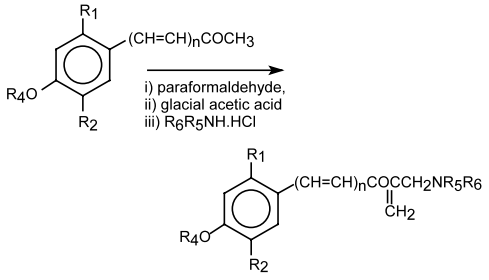


(1a – 1g) (1h – 1j)

Where:

$R_1 = R_2 = H$, n = 0, R = piperidyl propyl	**1a**
$R_1 = R_2 = H$, n = 0, R = piperidyl ethyl	**1b**
$R_1 = R_2 = H$, n = 0, R = pyrrolidyl ethyl	**1c**
$R_1 = R_2 = H$, n = 1, R = piperidyl propyl	**1d**
$R_1 = R_2 = H$, n = 1, R = pyrrolidyl ethyl	**1e**
$R_1 = R_2 = H$, n = 1, R = dimethylamino propyl	**1f**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R = piperidyl ethyl	**1g**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_3N = piperidyl	**1h**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_3N = morpholinyl	**1i**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_3N = pyrrolidyl	**1j**

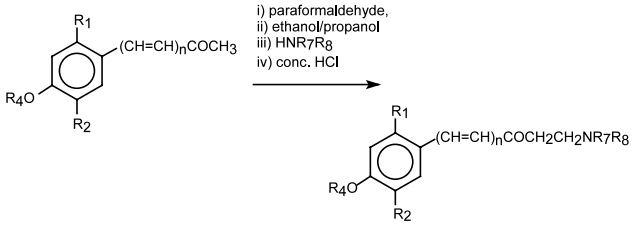
(a)



Where:

$R_1 = R_2 = H$, n = 0, R_4 = piperidyl propyl, NR_5R_6 = piperidyl	**2a**
$R_1 = R_2 = H$, n = 0, R_4 = piperidyl propyl, NR_5R_6 = morpholyl	**2b**
$R_1 = R_2 = H$, n = 0, R_4 = piperidyl propyl, NR_5R_6 = pyrrolidyl	**2c**
$R_1 = R_2 = H$, n = 0, R_4 = piperidyl ethyl, NR_5R_6 = piperidyl	**2d**
$R_1 = R_2 = H$, n = 0, R_4 = piperidyl ethyl, NR_5R_6 = morpholyl	**2e**
$R_1 = R_2 = H$, n = 0, R_4 = pyrrolidyl ethyl, NR_5R_6 = piperidyl	**2f**
$R_1 = R_2 = H$, n = 0, R_4 = pyrrolidyl ethyl, NR_5R_6 = morpholyl	**2g**
$R_1 = R_2 = H$, n = 0, R_4 = pyrrolidyl ethyl, NR_5R_6 = 4-methyl-piperazine	**2h**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_5R_6 = piperidyl	**3a**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_5R_6 = morpholyl	**3b**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_5R_6 = 4-methyl-piperazinyl	**3c**
$R_1 = R_2 = H$, n = 1, R_4 = pyrrolidyl ethyl, NR_5R_6 = piperidyl	**3d**
$R_1 = R_2 = H$, n = 1, R_4 = pyrrolidyl ethyl, NR_5R_6 = morpholyl	**3e**
$R_1 = R_2 = H$, n = 1, R_4 = pyrrolidyl ethyl, NR_5R_6 = 4-methyl-piperazine	**3f**
$R_1 = R_2 = H$, n = 1, R_4 = dimethyl propyl, NR_5R_6 = piperidyl	**3g**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-piperidyl-2-hydroxy-propyl, NR_5R_6 = piperidyl	**4a**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-piperidyl-2-hydroxy-propyl, NR_5R_6 = morpholyl	**4b**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-morpholyl-2-hydroxy-propyl, NR_5R_6 = piperidyl	**4c**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-morpholyl-2-hydroxy-propyl, NR_5R_6 = morpholyl	**4d**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-pyrrolidyl-2-hydroxy-propyl, NR_5R_6 = piperidyl	**4e**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-pyrrolidyl-2-hydroxy-propyl, NR_5R_6 = morpholyl	**4f**

(b)



Where:

$R_1 = R_2 = H$, n = 0, R_4 = piperidyl propyl, NR_7R_8 = pyrrolidyl	**5a**
$R_1 = R_2 = H$, n = 0, R_4 = piperidyl propyl, NR_7R_8 = morpholyl	**5b**
$R_1 = R_2 = H$, n = 0, R_4 = piperidyl propyl, NR_7R_8 = 4-methyl-piperazinyl	**5c**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_7R_8 = piperidyl	**6a**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_7R_8 = morpholyl	**6b**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_7R_8 = 4-methyl-piperazinyl	**6c**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_7R_8 = 3-methyl-piperidyl	**6d**
$R_1 = R_2 = H$, n = 1, R_4 = piperidyl propyl, NR_7R_8 = 4-methyl-piperidyl	**6e**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 3-piperidyl-2-hydroxy-propyl, NR_5R_6 = morpholyl	**7a**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 2-piperidyl-ethyl, NR_5R_6 = morpholyl	**7b**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 2-piperidyl-ethyl, NR_5R_6 = 4-methyl-piperazinyl	**7c**
$R_1 = CH_3$, R_2 = isopropyl, n = 0, R_4 = 2-piperidyl-ethyl, NR_5R_6 = 4-methyl-piperidyl	**7d**

(c)

Fig. 1. Synthesis of different compounds reported.

Table 1
Spermicidal efficacy of the compounds prepared against human spermatozoa

Compound	Spermicidal activity (% concentration)	Compound	Spermicidal activity (% concentration)
2a	0.01	**4c**	0.1
2b	1.0	**4d**	1.0
2c	0.01	**4e**	0.005
2d	0.005	**4f**	0.1
2e	1.0	**5a**	inactive
2f	0.01	**5b**	inactive
2g	0.1	**5c**	inactive
2h	0.1	**6a**	1.0
3a	0.01	**6b**	inactive
3b	0.1	**6c**	inactive
3c	0.05	**6d**	1.0
3d	0.1	**6e**	1.0
3e	inactive	**7a**	0.1
3f	inactive	**7b**	0.1
3g	0.1	**7c**	1.0
4a	0.005	**7d**	0.1
4b	0.01	–	–

showed 100% spermicidal activity at a concentration range 1.0–0.005%.

The amino group in the ether linkage in the side chain as well as in the amino methyl group played a very important role. Piperidine and pyrrolidine derivatives showed activity at higher dilution than morpholine or *N*-methyl-piperazine derivatives. If the amino group was morpholine, the compounds showed very marginal activity or were inactive at 1.0% concentration.

All the compounds belonging to the series 1-[4-(3-dialkylaminoalkoxy)phenyl]-3-dialkylamino-propan-1-one were devoid of spermicidal activity at 1.0% concentration.

When a CH=CH moiety was introduced between the phenyl ring and the $COCH_2$ group the 5-(4-dialkylamino)-1-[4-(dialkylaminoalkoxy)phenyl]pent-1-en-3-one, some compounds such as **6a**, **6d**, **6e** showed spermicidal activity at 1.0% concentration. Introduction of a methylene group in the compounds mentioned in Fig. 1, i.e. 4-(dialkylaminomethyl)-1-[4-(3-dialkylaminoalkoxy)phenyl]pent-1,4-dien-3-one, led to sharp increase in the spermicidal activity. One of these compounds i.e. **3a** was found to be active at 0.01% concentration.

When a CH=CH moiety was not present between the phenyl ring and the $COC{=}CH_2$ group e.g. the 1-[4-(3-dialkylamino-alkoxy)phenyl]-2-dialkylamino-methyl-propan-2-en-1-one some compounds i.e. **2a**, showed spermicidal activity at 0.005% concentration.

The compounds derived from thymol and having hydroxy group in the propyl side chain e.g. **4a**, **4e** showed activity at lower concentration than the corresponding compounds derived from 4-acetyl phenol without hydroxy group in the propyl side chain.

Two compounds, **4a** and **2d**, exhibiting high spermicidal activity were also checked for their effect on fusion of HL2/3 and HLCD4-CAT cells (Fig. 2). Both compounds showed dose-dependent inhibition of HIV-1 Env–CD4 interaction resulting in decreased CAT reporter gene expression.

5. Experimental

All the m.p.s were determined on a hot stage apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin–Elmer 881 spectrophotometer as KBr discs or neat. ^{1}H-NMR spectra were recorded on a Bruker DPX-200 MHz or Bruker Avance DRX-300 MHz FT NMR instrument using TMS as internal standard and $CDCl_3$ as a solvent unless stated

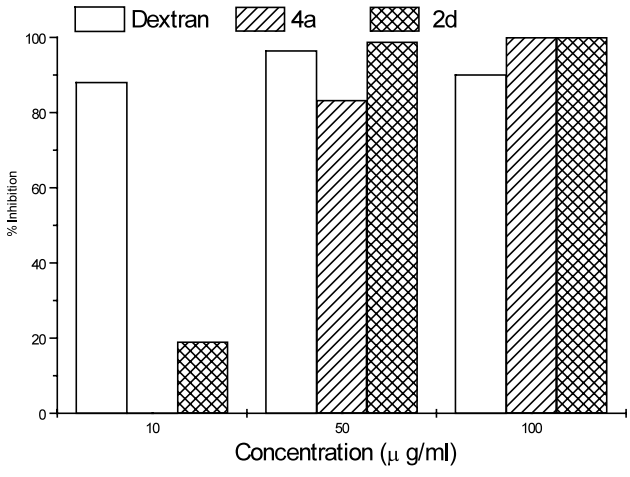


Fig. 2. Inhibition of HIV Env–CD4 interaction by different compounds.

otherwise. The mass spectra were recorded on JEOL-JMS-D-300 mass spectrometer and elemental analyses were carried out on Carlo–Erba 1108 analyser.

5.1. General procedure for O-dialkylamino-alkylation of 4-acetyl-phenols or 4-hydroxybenzylidineacetones or 4-acetyl-2-isopropyl-5-methyl-phenol

4-Acetyl-phenols or 4-hydroxybenzylidineacetones or 4-acetyl-2-isopropyl-5-methyl-phenol (0.1 mol) was treated with dialkylamino-alkyl-halide-hydrohalide (0.15 mol), K_2CO_3 (0.21 mol), NaI (0.05 mol) in 50 mL of C_3H_6O, the mixture was refluxed for 20 h [14], cooled, filtered, C_3H_6O was distilled off and the resultant oily liquid was purified on a column of neutral alumina using C_6H_6 and methanolic C_6H_6 as eluent. Removal of the solvent gave a viscous mass in 30–42% yield. The compounds synthesised by the above procedure are as follows.

5.1.1. 1-[4-(3-Piperidinopropoxy)phenyl]ethan-1-one (**1a**)

Yield: 41%. M.p. viscous mass. IR (cm^{-1}): ν 1674, 1600, 1573. EIMS: m/z 261 [M^+]. ^{1}H-NMR: δ 1.3–1.8 (m, 6H, CH_2), 1.9–2.3 (m, 5H, O–CH_2–CH_2, $COCH_3$), 2.4–2.5 (m, 6H, N–CH_2), 3.9–4.2 (t, 2H, O–CH_2), 6.7–7.0 (m, 2H, Ar–H), 7.7–8.0 (m, 2H, Ar–H). Anal. Found: C, 73.93; H, 9.18; N, 5.73. Calc. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36%.

5.1.2. 1-[4-(2-Piperidinoethoxy)phenyl]ethan-1-one (**1b**)

Yield: 40%. M.p. 58–60 °C. IR (cm^{-1}): ν 1674, 1604, 1510, 1264. EIMS: m/z 247 [M^+]. ^{1}H-NMR: δ 1.58–1.77 (m, 6H, CH_2), 2.48–2.55 (m, 7H, CH_2–N, $COCH_3$), 2.76–2.87 (t, 2H, N–CH_2CH_2O), 4.13–4.20 (t, 2H, O–CH_2), 6.91–7.00 (m, 2H, Ar–H), 7.90–7.94 (m, 2H, Ar–H). Anal. Found: C, 73.28; H, 8.89; N, 6.05. Calc. for $C_{15}H_{21}NO_2$: C, 72.89; H, 8.50; N, 5.66%.

5.1.3. 1-{4-[2-(Pyrrolidin-1-yl)ethoxy]phenyl}ethan-1-one (**1c**)

Yield: 31%. M.p. Oil. IR (cm^{-1}): ν 1674, 1600, 1508, 1260. EIMS: m/z 233 [M^+]. ^{1}H-NMR: δ 1.71–1.86 (m, 4H, CH_2), 2.45–2.66 (m, 7H, CH_2–N, $COCH_3$), 2.86–2.96 (d, 2H, N–CH_2CH_2O), 4.07–4.27 (t, 2H, O–CH_2), 6.92–6.93 (m, 2H, Ar–H), 7.84–7.85 (m, 2H, Ar–H). Anal. Found: C, 71.93; H, 7.97; N, 5.81. Calc. for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.00%.

5.1.4. 4-[4-(3-Piperidinopropoxy)phenyl]but-3-en-2-one (**1d**)

Yield: 45%. M.p. (Tartrate) 140–141 °C. IR (cm^{-1}): ν 1681, 1658, 1598, 1512, 1263. EIMS: m/z 287 [M^+]. ^{1}H-NMR: δ 1.62–1.97 (m, 8H, CH_2, O–CH_2–CH_2), 2.32–2.41 (m, 9H, N–CH_2, $COCH_3$), 4.08–4.18 (t, 2H, O–CH_2), 6.57–6.63 (d, 2H, CH=CH), 6.87–6.99 (m, 2H, Ar–H), 7.40–7.50 (m, 2H, Ar–H). Anal. Found: 75.63; H, 9.05; N, 5.25. Calc. for $C_{18}H_{25}NO_2$: C, 75.26; H, 8.71; N, 4.87%.

5.1.5. 4-{4-[2-(Pyrrolidin-1-yl)ethoxy]phenyl}but-3-en-2-one (**1e**)

Yield: 35%. M.p. 78–79 °C. IR (cm^{-1}): ν 1664, 1602, 1512, 1250. EIMS: m/z 259 [M^+]. ^{1}H-NMR: δ 1.71–1.82 (m, 4H, CH_2), 2.17 (s, 3H, CO–CH_3), 2.26–2.64 (m, 4H, CH_2–N), 2.89–2.95 (t, 2H, N–CH_2), 4.12–4.18 (t, 2H, O–CH_2), 6.56 (d, 1H, CH=CH), 6.64 (d, 1H, CH=CH), 6.82–6.86 (m, 2H, Ar–H), 7.43–7.46 (m, 3H, Ar–H). Anal. Found: C, 73.88; H, 7.76; N, 5.11. Calc. for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.10; N, 5.40%.

5.1.6. 4-[4-(3-Diethylaminopropoxy)phenyl]but-3-en-2-one (**1f**)

Yield: 32%. M.p. viscous. IR (cm^{-1}): ν 1656, 1598, 1512, 1249. EIMS: m/z 247 [M^+]. ^{1}H-NMR: δ 1.9–2.0 (m, 2H, O–CH_2–CH_2), 2.1–2 (m, 11H, N–CH_3, N–CH_2, $COCH_3$), 4.0–4.1 (t, 2H, O–CH_2), 6.5–6.6 (d, 2H, CH=CH), 6.8–7.0 (m, 2H, Ar–H), 7.4–7.8 (m, 2H, Ar–H). Anal. Found: C, 72.62; H, 8.22; N, 5.01. Calc. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50, N, 5.39%.

5.1.7. 1-[5-Isopropyl-2-methyl-4-(3-piperidinoethoxy)phenyl]ethan-1-one (**1g**)

Yield: 48%. M.p. viscous mass. IR (cm^{-1}): ν 1668, 1604, 1556, 1504. EIMS: m/z 302 [M^+]. ^{1}H-NMR: δ 1.20–1.24 (m, 6H, $CH(CH_3)_2$), 1.44–1.68 (m, 6H, CH_2), 2.45–2.55 (m, 10H, CH_2–N, Ar–CH_3, $COCH_3$), 2.78–2.84 (t, 2H, N–CH_2), 3.23–3.27 (d, 1H, CH), 4.12–4.18 (t, 2H, O–CH_2), 6.75 (s, 1H, Ar–H), 7.70 (s, 1H, Ar–H). Anal. Found: C, 75.86; H, 9.98; N, 4.98. Calc. for $C_{19}H_{29}NO_2$: C, 75.49; H, 9.60; N, 4.63%.

5.2. General procedure for synthesis of 1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-dialkylaminopropoxy)phenyl]ethan-1-one

4-Acetyl-2-isopropyl-5-methyl-phenol (0.1 mol) was added to methanolic CH_3ONa, prepared by dissolving 0.21 mol of Na in 100 mL of dry MeOH under stirring. The resulting mixture was cooled and treated with epichlorohydrin (0.1 mol). It was refluxed for 5 h. The resulting mass so obtained was added gradually to ice-cold water, stirred and extracted with $CHCl_3$ (3×25 mL). The combined $CHCl_3$ extract was washed with water; organic layer was dried, concentrated to get a viscous mass, which was purified by chromatography over silica gel using C_6H_6 as an eluent.

3-(4-Acetyl-2-isopropyl-5-methyl-phenoxy)-1,2-epoxy-propane (0.1 mol), as obtained above, in EtOH was treated with (0.21 mol) secondary amine like piperidine, morpholine or pyrrolidine. The mixture was heated

under reflux for 6 h. Bulk of the solvent was distilled off under reduced pressure. The viscous mass obtained was treated with water (50 mL) extracted with $CHCl_3$; the $CHCl_3$ layer washed with saline water, dried and concentrated to a viscous liquid, which was purified by column chromatography over neutral alumina.

*5.2.1. 1-{5-Isopropyl-2-methyl-4-[2-hydroxy-3-piperidinopropoxy}phenyl]ethane-1-one (**1h**)*

Yield: 42%. M.p. semi solid. IR (cm^{-1}): *v* 1670, 1600, 1504, 1356. EIMS: *m/z* 333 [M^+]. ^{1}H-NMR: δ 1.21–1.24 (d, 6H, CH–(CH_3)$_2$), 1.54–1.74 (m, 6H, CH_2), 2.53–2.55 (d, 6H, Ar–CH_3, Ar–COCH_3), 2.67–2.87 (m, 6H, N–CH_2), 3.21–3.24 (m, 1H, C*H*), 3.97–4.14 (m, 3H, O–CH_2, C*H*OH), 6.66–6.73 (s, 1H, Ar–H), 7.69–7.74 (s, 1H, Ar–H). Anal. Found: C, 71.75; H, 9.69; N, 4.55. Calc. for $C_{20}H_{31}NO_3$: C, 72.0; H, 9.30; N, 4.20%.

*5.2.2. 1-{5-Isopropyl-2-methyl-4-[2-hydroxy-3-morpholinopropoxy}phenyl]ethane-1-one (**1i**)*

Yield: 34%. M.p. viscous mass. IR (cm^{-1}): *v* 1670, 1606, 1504, 1252. EIMS: *m/z* 335 [M^+]. ^{1}H-NMR: δ 1.22–1.25 (d, 6H, CH–(CH_3)$_2$), 2.43–2.55 (d, 6H, Ar–CH_3, Ar–COCH_3), 3.05–3.28 (m, 7H, N–CH_2, C*H*), 3.97–4.36 (m, 6H, O–CH_2), 4.58 (m, 1H, C*H*OH), 6.66–6.73 (s, 1H, Ar–H), 7.59–7.78 (s, 1H, Ar–H). Anal. Found: C, 68.36; H, 8.96; N, 4.48. Calc. for $C_{19}H_{29}NO_4$: C, 68.05; H, 8.65; N, 4.17%.

*5.2.3. 1-{5-Isopropyl-2-methyl-4-[2-hydroxy-3-(pyrrolidin-1-yl)propoxy}phenyl]ethane-1-one (**1j**)*

Yield: 42%. M.p. viscous. IR (cm^{-1}): *v* 1670, 1606, 1504, 1353. EIMS: *m/z* 319 [M^+]. ^{1}H-NMR: δ 1.08–1.25 (d, 6H, (CH_3)$_2$CH), 2.01–2.42 (m, 4H, CH_2), 2.55–2.68 (d, 6H, Ar–CH_3, Ar–COCH_3), 2.72–2.98 (m, 7H, NCH_2, C*H*), 3.19–3.30 (m, 1H, C*H*OH), 3.90–4.00 (t, 2H, O–CH_2), 6.67 (s, 1H, Ar–H), 7.72 (s, 1H, Ar–H). Anal. Found: C, 71.86; H, 9.47; N, 4.75. Calc. for $C_{19}H_{29}NO_3$: C, 71.47; H, 9.09; N, 4.38%.

5.3. General procedure for synthesis of 2-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]prop-2-en-1-one and 4-dialkylaminomethyl-1-[4-(dialkylaminoalkoxy)phenyl]penta-1,4-dien-3-one

Substituted 4-(dialkylaminoalkoxy)acetophenones or 1-[substituted-4-(dialkylamino-alkoxy)phenyl]buta-1-en-3-one (0.1 mmol), paraformaldehyde (0.3 mmol), secondary amine hydrochloride (0.12 mmol) in glacial AcOH were heated under gentle reflux for 5–6 h. Bulk of the solvent was distilled off under reduced pressure and the residue taken in water, neutralised up to pH 7 with $NaHCO_3$. The solution was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residual viscous mass was purified by chromatography over deactivated neutral alumina. The compounds synthesised by the above procedure are as follows.

*5.3.1. 2-Piperidinomethyl-1-[4-(3-piperidinopropoxy)phenyl]prop-2-en-1-one (**2a**)*

Yield: 35%. M.p. (Tartrate) 134–135 °C. IR (cm^{-1}): *v* 1651, 1571, 1508, 1255. EIMS: *m/z* 369 [M^+]. ^{1}H-NMR: δ 1.3–1.7 (m, 12H, CH_2), 1.8–2.2 (m, 2H, O–CH_2–CH_2), 2.3–2.6 (m, 12H, N–CH_2), 3.9–4.1 (t, 2H, O–CH_2), 5.5–5.6 (s, 1H, =CH_2), 5.8–5.9 (s, 1H, =CH_2), 6.7–7.0 (m, 2H, Ar–H), 7.7–7.9 (m, 2H, Ar–H). Anal. Found: C, 75.08; H, 9.49; N, 7.82. Calc. for $C_{23}H_{34}N_2O_2$: C, 74.79; H, 9.21; N, 7.58%.

*5.3.2. 2-Morpholinomethyl-1-[4-(3-piperidinopropoxy)phenyl]prop-2-en-1-one (**2b**)*

Yield: 37%. M.p. (Tartrate) 110–111 °C. IR (cm^{-1}): *v* 1651, 1573, 1510, 1257. EIMS: *m/z* 373 [M^+]. ^{1}H-NMR: δ 1.5–1.6 (m, 6H, CH_2), 1.9–2.0 (m, 2H, O–CH_2CH_2), 2.4–2.5 (m, 12H, NCH_2), 3.6–3.7 (m, 4H, OCH_2), 4.04–4.08 (t, 2H, O–CH_2), 5.63 (s, 1H, =CH_2), 5.89 (s, 1H, =CH_2), 6.8–6.9 (m, 2H, Ar–H), 7.7–7.9 (m, 2H, Ar–H). Anal. Found: C, 70.43; H, 8.22; N, 7.23. Calc. for $C_{22}H_{32}N_2O_3$: C, 70.77; H, 8.57; N, 7.50%.

*5.3.3. 2-Pyrrolidinomethyl-1-[4-(3-piperidinopropoxy)phenyl]prop-2-en-1-one (**2c**)*

Yield: 30%. M.p. (Tartrate) 124–125 °C. IR (cm^{-1}): *v* 1651, 1598, 1508, 1255. EIMS: *m/z* 357 [M^+]. ^{1}H-NMR: δ 1.5–1.6 (m, 10H, CH_2), 1.7–2.0 (m, 2H, O–CH_2–CH_2), 2.4–2.5 (m, 12H, N–CH_2), 4.03–4.09 (t, 2H, O–CH_2), 5.73 (s, 1H, =CH_2), 6.05 (s, 1H, =CH_2), 6.90–6.94 (m, 2H, Ar–H), 7.7–7.8 (m, 2H, Ar–H). Anal. Found: C, 74.50; H, 9.32; N, 8.23. Calc. for $C_{22}H_{32}N_2O_2$: C, 74.15; H, 8.98; N, 7.86%.

*5.3.4. 2-Piperidinomethyl-1-[4-(2-piperidinoethoxy)phenyl]prop-2-en-1-one (**2d**)*

Yield: 22%. M.p. (Tartrate) 126–127 °C. IR (cm^{-1}): *v* 1648, 1600, 1520, 1308. EIMS: *m/z* 356 [M^+] ^{1}H-NMR: δ 1.27–1.41 (m, 12H, CH_2), 2.56–2.66 (m, 12H, N–CH_2), 3.97–4.09 (t, 2H, O–CH_2), 5.40 (s, 1H, =CH_2), 5.83 (s, 1H, =CH_2), 6.88–6.92 (m, 2H, Ar–H), 7.71–7.73 (m, 2H, Ar–H). Anal. Found: C, 73.78; H, 8.61; N, 7.48. Calc. for $C_{22}H_{32}N_2O_2$: C, 74.15; H, 8.98; N, 7.86%.

*5.3.5. 2-Morpholinomethyl-1-[4-(2-piperidinoethoxy)phenyl]prop-2-en-1-one (**2e**)*

Yield: 20%. M.p. (Tartrate) 132–133 °C. IR (cm^{-1}): *v* 2940, 1662, 1602, 1522, 1218. EIMS: *m/z* 358 [M^+]. ^{1}H-NMR: δ 1.45–1.47 (m, 6H, CH_2), 2.51–2.83 (m, 12H, NCH_2), 3.38–3.70 (m, 4H, O–CH_2), 4.14–4.20 (t, 2H, O–CH_2), 5.91 (s, 1H, =CH_2), 6.05 (s, 1H, =CH_2), 6.91–6.95 (m, 2H, Ar–H), 7.79–7.83 (m, 2H, Ar–H).

Anal. Found: C, 70.63; H, 8.62; N, 8.06. Calc. for $C_{21}H_{30}N_2O_3$: C, 70.39; H, 8.37; N, 7.82%.

*5.3.6. 2-Piperidinomethyl-1-[4-(2-pyrrolidinoethoxy)phenyl]prop-2-en-1-one (**2f**)*

Yield: 35%. M.p. (Tartrate) 110–111 °C. IR (cm^{-1}): *v* 1654, 1600, 1506, 1256. EIMS: *m/z* 342 [M^+]. ^{1}H-NMR: δ 1.25–1.62 (m, 10H, CH_2), 2.42–2.576 (m, 8H, CH_2–N), 3.00–3.05 (t, 2H, N–CH_2), 3.32–3.44 (t, 2H, N–CH_2), 4.22–4.28 (t, 2H, O–CH_2), 5.67 (s, 1H, =CH_2), 6.09 (s, 1H, =CH_2), 6.93–6.97 (m, 2H, Ar–H), 7.84–7.85 (m, 2H, Ar–H). Anal. Found: C, 73.92; H, 9.11; N, 8.52. Calc. for $C_{21}H_{30}N_2O_2$: C, 73.68; H, 8.77; N, 8.18%.

*5.3.7. 2-Morpholinomethyl-1-[4-(2-pyrolidinoethoxy)phenyl]prop-2-en-1-one (**2g**)*

Yield: 39%. M.p. (Tartrate) 118–120 °C. IR (cm^{-1}): *v* 1624, 1600, 1232. EIMS: *m/z* 344 [M^+]. ^{1}H-NMR: δ 1.71–1.91 (m, 4H, CH_2), 2.48–2.83 (m, 8H, CH_2–N), 3.05–3.28 (m, 4H, N–CH_2), 3.65–3.69 (t, 4H, O–CH_2), 4.26–4.32 (t, 2H, O–CH_2), 5.65 (s, 1H, =CH_2), 5.71 (s, 1H, =CH_2), 6.92–6.97 (m, 2H, Ar–H), 7.79–7.83 (m, 2H, Ar–H). Anal. Found: C, 69.47; H, 8.41; N, 8.38. Calc. for $C_{20}H_{28}N_2O_3$: C, 69.76; H, 8.13; N, 8.13%.

*5.3.8. 2-[4-Methylpiperazin-1-yl]-1-[4-(2-pyrolidinoethoxy)phenyl]prop-2-en-1-one (**2h**)*

Yield: 35%. M.p. viscous mass. IR (cm^{-1}): *v* 1636, 1604, 1508, 1248. EIMS: *m/z* 357 [M^+]. ^{1}H-NMR: δ 1.66–1.75 (m, 4H, CH_2), 2.57–2.89 (m, 19H, NCH_2, N–CH_3), 4.14–4.23 (t, 2H, O–CH_2), 5.56 (s, 1H, =CH_2), 5.65 (s, 1H, =CH_2), 7.01–7.06 (m, 2H, Ar–H), 7.79–7.83 (m, 2H, Ar–H). Anal. Found: C, 70.95; H, 9.02; N, 11.52. Calc. for $C_{21}H_{31}N_3O_2$: C, 70.58; H, 8.68; N, 11.76%.

*5.3.9. 4-Piperidinomethyl-1-[4-(3-piperidinopropoxy)phenyl]penta-1,4-dien-3-one (**3a**)*

Yield: 36%. M.p. (Tartrate) 160–161 °C. IR (cm^{-1}): *v* 1652, 1593, 1512, 1251. EIMS: *m/z* 396 [M^+]. ^{1}H-NMR: δ 1.6–1.8 (m, 12H, CH_2), 1.9–2.1 (t, 2H, O–CH_2–CH_2), 2.4–2.7 (m, 12H, N–CH_2), 3.9–4.2 (t, 2H, OCH_2), 5.90 (s, 1H, =CH_2), 6.20 (s, 1H, =CH_2), 6.9–7.0 (d, 2H, C*H*=C*H*), 7.1–7.2 (m, 2H, Ar–H), 7.5–7.7 (m, 2H, Ar–H). Anal. Found: C, 75.38; H, 8.72; N, 6.69. Calc. for $C_{25}H_{36}N_2O_2$: C, 75.75; H, 9.09; N, 7.07%.

*5.3.10. 4-Morpholinomethyl-1-[4-(3-piperidinopropoxy)phenyl]penta-1,4-dien-3-one (**3b**)*

Yield: 49%. M.p. (Tartrate) 160–161 °C. IR (cm^{-1}): *v* 1652, 1593, 1512, 1251. EIMS: *m/z* 399 [M^+]. ^{1}H-NMR: δ 1.6–1.8 (m, 6H, CH_2), 1.9–2.1 (t, 2H, O–CH_2–CH_2–CH_2), 2.4–2.8 (m, 12H, N–CH_2), 3.6–3.8 (m, 4H, CH_2–O), 4.0–4.1 (t, 2H, O–CH_2), 5.80 (s, 1H, =CH_2), 6.15 (s, 1H, =CH_2), 6.8–7.0 (d, 2H, C*H*=C*H*), 7.1–7.2 (m, 2H, Ar–H), 7.5–7.7 (m, 2H, Ar–H). Anal. Found: C, 72.08; H, 8.25; N, 7.42. Calc. for $C_{24}H_{34}N_2O_2$: C, 72.36; H, 8.54; N, 7.03%.

*5.3.11. 4-(4-Methylpiperazin-1-yl)methyl-1-[4-(3-piperidinopropoxy)phenyl]penta-1,4-dien-3-one (**3c**)*

Yield: 28%. M.p. (Tartrate) 140–141 °C. IR (cm^{-1}): *v* 1590, 1512, 1216. EIMS: *m/z* 411 [M^+]. ^{1}H-NMR: δ 1.25–1.78 (m, 8H, CH_2), 2.23 (s, 3H, N–CH_3), 2.42–2.75 (m, 16H, N–CH_2), 4.05–4.11 (t, 2H, O–CH_2), 5.89 (s, 1H, =CH_2), 6.02 (s, 1H, =CH_2), 6.87–6.92 (d, 1H, CH=C*H*), 7.07–7.15 (d, 1H, C*H*=CH), 7.35–7.49 (m, 2H, Ar–H), 7.54–7.59 (m, 2H, Ar–H). Anal. Found: C, 73.27; H, 8.79; N, 9.84. Calc. for $C_{25}H_{37}N_3O_2$: C, 72.99; H, 9.00; N, 10.21%.

*5.3.12. 4-Piperidinomethyl-1-[4-(2-pyrrolidinoethoxy)phenyl]penta-1,4-dien-3-one (**3d**)*

Yield: 15%. M.p. (Tartrate) 130–131 °C. IR (cm^{-1}): *v* 1646, 1600, 1514, 1248. EIMS: *m/z* 368 [M^+]. ^{1}H-NMR: δ 1.41–1.62 (m, 10H, CH_2), 2.39–2.63 (m, 8H, CH_2N), 2.89–2.94 (t, 2H, NCH_2), 3.28–3.43 (t, 2H, N–CH_2), 4.11–4.19 (t, 2H, OCH_2), 5.90 (s, 1H, =CH_2), 6.11 (s, 1H, =CH_2), 6.90–6.95 (d, 1H, CH=C*H*), 7.00–7.04 (d, 1H, C*H*=CH), 7.50–7.54 (m, 2H, Ar–H), 7.58–7.61 (m, 2H, Ar–H). Anal. Found: C, 74.63; H, 8.31; N, 7.21. Calc. for $C_{23}H_{32}N_2O_2$: C, 75.0; H, 8.69; N, 7.60%.

*5.3.13. 4-Morpholinomethyl-1-[4-(2-pyrrolidinoethoxy)phenyl]penta-1,4-dien-3-one (**3e**)*

Yield: 11%. M.p. (Tartrate) 116–117 °C. IR (cm^{-1}): *v* 1664, 1502, 1246. EIMS: *m/z* 370 [M^+]. ^{1}H-NMR: δ 1.87 (bs, 4H, CH_2), 2.43–2.85 (m, 8H, N–CH_2), 2.98–3.04 (t, 2H, N–CH_2), 3.62–3.72 (m, 4H, O–CH_2), 4.19–4.24 (t, 2H, O–CH_2), 5.92 (s, 1H, =CH_2), 6.13 (s, 1H, =CH_2), 6.67–6.75 (d, 2H, C*H*=C*H*), 6.91–6.95 (m, 2H, Ar–H), 7.50–7.55 (m, 2H, Ar–H). Anal. Found: C, 71.75; H, 7.98; N, 7.76. Calc. for $C_{22}H_{30}N_2O_3$: C, 71.35; H, 8.10; N, 7.56%.

*5.3.14. 4-(4-Methylpiperazin-1-yl)methyl-1-[4-(2-pyrrolidinoethoxy)phenyl]penta-1,4-dien-3-one (**3f**)*

Yield: 17% M.p. (Tartrate) 180–181 °C. IR 1664, 1590, 1530, 1226. EIMS: *m/z* 383 [M^+]. ^{1}H-NMR: δ 1.66–1.69 (m, 4H, CH_2), 2.50–2.84 (m, 19H, N–CH_2, N–CH_3), 4.10–4.16 (t, 2H, O–CH_2), 6.05 (s, 1H, =CH_2), 6.28 (s, 1H, =CH_2), 6.94 (d, 1H, CH=C*H*), 6.99 (d, 1H, C*H*=CH), 7.60–7.63 (d, 2H, Ar–H), 7.65–7.69 (m, 2H, Ar–H). Anal. Found: C, 71.75; H, 8.29; N, 10.60. Calc. for $C_{23}H_{33}N_3O_2$: C, 72.06; H, 8.61; N, 10.96%.

*5.3.15. 4-Piperidinomethyl-1-[4-(3-dimethylaminopropoxy)phenyl]penta-1,4-dien-3-one (**3g**)*

Yield: 34%. M.p. (Tartrate) 120–121 °C. IR (cm^{-1}): *v* 1656, 1596, 1512, 1255. EIMS: *m/z* 356 [M^+]. ^{1}H-NMR: δ 1.2–1.7 (m, 6H, CH_2), 2.0–2.1 (m, 2H, O–$CH_2CH_2CH_2$), 2.3–2.6 (m, 14H, NCH_2), 4.0–4.2 (t, 2H, O–CH_2), 6.0 (s, 1H, =CH_2), 6.2 (s, 1H, =CH_2), 6.9–7.0 (d, 2H, CH=CH), 7.1–7.2 (m, 2H, Ar–H), 7.5–7.6 (m, 2H, Ar–H). Anal. Found: C, 73.78; H, 8.63; N, 7.49. Calc. for $C_{22}H_{32}N_2O_2$: C, 74.15; H, 8.98; N, 7.86%.

*5.3.16. 2-Piperidinomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-piperidinopropoxy)phenyl]prop-2-en-1-one (**4a**)*

Yield: 33%. M.p. (Tartrate) 164–166 °C. IR (cm^{-1}): *v* 1739, 1612, 1502, 1251. EIMS: *m/z* 441 [M^+]. ^{1}H-NMR: δ 1.0–1.3 (d, 6H, $(CH_3)_2CH$), 1.4–2.2 (m, 12H, CH_2), 2.3–2.4 (s, 3H, Ar–CH_3), 2.5–3.3 (m, 13H, N–CH_2, CH), 3.9–4.4 (m, 3H, O–CH_2, CHOH), 5.9–6.0 (s, 1H, =CH_2), 6.1–6.2 (s, 1H, =CH_2), 6.6–6.7 (m, 1H, Ar–H), 7.2–7.3 (m, 1H, Ar–H). Anal. Found: C, 73.15; H, 9.18; N, 5.98. Calc. for $C_{27}H_{42}N_2O_3$: C, 73.46; H, 9.52; N, 6.34%.

*5.3.17. 2-Morpholinomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-piperidinopropoxy)phenyl]prop-2-en-1-one (**4b**)*

Yield: 27.0%. M.p. (Tartrate) 186–188 °C. IR (cm^{-1}): *v* 1736, 1602, 1254. EIMS: *m/z* 444 [M^+]. ^{1}H-NMR: δ 1.19 (bs, 6H, $(CH_3)_2CH$), 1.82–1.92 (m, 6H, CH_2), 2.3 (s, 3H, Ar–CH_3), 3.09–3.63 (m, 13H, N–CH_2, CH), 4.01–4.19 (m, 7H, O–CH_2, CHOH), 6.31 (s, 1H, =CH_2), 6.68 (s, 1H, =CH_2), 6.94 (s, 1H, Ar–H), 7.31 (s, 1H, Ar–H). Anal. Found: C, 70.58; H, 9.31; N, 6.68. $C_{26}H_{40}N_2O_4$: C, 70.27; H, 9.00; N, 6.30%.

*5.3.18. 2-Piperidinomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-morpholinopropoxy)phenyl]prop-2-en-1-one (**4c**)*

Yield: 39%. M.p. (Tartrate) 138–139 °C. IR (cm^{-1}): *v* 2944, 1740, 1512, 1242. EIMS: *m/z* 444 [M^+]. ^{1}H-NMR: δ 1.15–1.20 (m, 6H, $(CH_3)_2CH$), 1.25–1.57 (m, 6H, CH_2), 2.00–2.08 (s, 3H, Ar–CH_3), 2.37–2.67 (m, 13H, N–CH_2, CH), 3.69–3.74 (m, 4H, O–CH_2), 4.05–4.16 (m, 3H, O–CH_2, CHOH), 5.79 (s, 1H, =CH_2), 5.95 (s, 1H, =CH_2), 7.06 (d, 1H, Ar–H), 7.45 (d, 1H, Ar–H). Anal. Found: C, 69.89; H, 8.65; N, 5.99. Calc. for $C_{26}H_{40}N_2O_4$: C, 70.27; H, 9.00; N, 6.30%.

*5.3.19. 2-Morpholinomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-morpholinopropoxy)phenyl]prop-2-en-1-one (**4d**)*

Yield: 43%. M.p. (Tartrate) 179–182 °C. IR (cm^{-1}): *v* 1740, 1610, 1516, 1216. EIMS: *m/z* 446 [M^+]. ^{1}H-NMR: δ 1.16–1.25 (m, 6H, $(CH_3)_2CH$), 2.08 (s, 3H, Ar–CH_3), 2.28–2.68 (m, 13H, N–CH_2, CH), 3.70–3.75 (m, 8H, O–CH_2), 4.03–4.16 (m, 3H, O–CH_2, CHOH), 5.68 (s, 1H, =CH_2), 5.96 (s, 1H, =CH_2), 6.66 (d, 1H, Ar–H), 7.21 (d, 1H, Ar–H). Anal. Found: C, 67.63; H, 8.90; N, 6.62. Calc. for $C_{25}H_{38}N_2O_5$: C, 67.26; H, 8.52; N, 6.27%.

*5.3.20. 2-Piperidinomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-pyrrolidinopropoxy)phenyl]prop-2-en-1-one (**4e**)*

Yield: 15%. M.p. (Tartrate) 118–120 °C. IR (cm^{-1}): *v* 1743, 1606, 1220, 1112. EIMS: *m/z* 428 [M^+]. ^{1}H-NMR: δ 1.1–1.3 (m, 6H, $(CH_3)_2CH$), 1.4–2.0 (m, 10H, CH_2), 2.1–2.3 (s, 3H, Ar–CH_3), 2.4–3.3 (m, 13H, N–CH_2, CH), 3.9–4.3 (m, 3H, O–CH_2, CHOH), 6.0 (s, 1H, =CH_2), 6.1 (s, 1H, =CH_2), 6.7 (d, 1H, Ar–H), 7.3 (d, 1H, Ar–H). Anal. Found: C, 73.24; H, 9.70; N, 6.91. Calc. for $C_{26}H_{40}N_2O_3$: C, 72.89; H, 9.34; N, 6.54%.

*5.3.21. 2-Morpholinomethyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-pyrrolidinopropoxy)phenyl]prop-2-en-1-one (**4f**)*

Yield: 18%. M.p. (Tartrate) 170–174 °C. IR (cm^{-1}): *v* 1744, 1682, 1532, 1220. EIMS: *m/z* 430 [M^+]. ^{1}H-NMR: δ 1.14–1.25 (m, 6H, $(CH_3)_2$), 1.70–1.77, (m, 4H, CH_2), 2.08 (s, 3H, Ar–CH_3), 2.33–2.69 (m, 12H, N–CH_2), 3.22–3.34 (m, 1H, CH), 3.68–3.72 (m, 4H, O–CH_2), 4.12–4.20 (m, 3H, O–CH_2, CHOH), 5.93 (s, 1H, =CH_2), 6.20 (s, 1H, =CH_2), 6.68–6.72 (d, 1H, Ar–H), 7.20–7.26 (d, 1H, Ar–H). Anal. Found: C, 70.07; H, 9.15; N, 6.85. Calc. for $C_{25}H_{38}N_2O_4$: C, 69.76; H, 8.83; N, 6.51%.

5.4. General procedure for the synthesis of 1-[4-(dialkylaminoalkoxy)phenyl]-3-dialkylamino-propan-1-one or 5-dialkylaminoalkyl-1-[(4-dialkylaminoalkoxy)phenyl]pent-1-en-3-one

Substituted 4-dialkylamino-alkoxy acetophenone or substituted 1-(4-dialkylamino-alkoxy-phenyl)buta-1-en-3-one (0.1 mol), paraformaldehyde (0.2 mol), and secondary amine hydrochloride (0.2 mol) in absolute EtOH or in propan-1-ol (20 mL) were heated to reflux temperature. Concentrated HCl was added until pH 3 was reached. The mixture was heated under reflux for 9 h. The solvent was then removed in vacuum, residue dissolved in water (50 mL), 5% aq. solution of $NaHCO_3$ was added to bring the pH upto 7.5. The solution was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residual viscous mass was purified by chromatography over deactivated neutral alumina using C_6H_6/C_6H_6–MeOH mixture as the eluent. The following compounds were synthesised by the above procedure.

*5.4.1. 1-[4-(3-Piperidinopropoxy)phenyl]3-pyrrolidin-1-ylpropan-1-one (**5a**)*

Yield: 17%. M.p. (Tartrate) 110–111 °C. IR (cm^{-1}): *v* 1743, 1668, 1604, 1514. EIMS: *m/z* 345 ([M^+]+1). ^{1}H-NMR: δ 1.4–1.9 (m, 10H, CH_2), 2.0–2.1 (m, 4H, COCH_2, O–CH_2–CH_2), 2.2–2.6 (m, 12H, N–CH_2), 4.0–4.2 (t, 2H, O–CH_2), 6.9–7.0 (d, 2H, Ar–H), 7.9–8.0 (d, 2H, Ar–H). Anal. Found: C, 73.45; H, 9.66; N, 7.88. Calc. for $C_{21}H_{32}N_2O_2$: C, 73.25; H, 9.30; N, 8.13%.

*5.4.2. 1-[4-(3-Piperidinopropoxy)phenyl]3-morpholin-1-ylpropan-1-one (**5b**)*

Yield: 18%. M.p. (Tartrate) 153–154 °C. IR (cm^{-1}): *v* 1728, 1672, 1600, 1512. EIMS: *m/z* 361 ([M^+]+1). ^{1}H-NMR: δ 1.4–1.7 (m, 6H, CH_2), 1.9–2.1 (m, 4H, COCH_2, O–CH_2–CH_2), 2.2–2.6 (m, 12H, N–CH_2), 3.6–3.8 (m, 4H, CH_2–O), 4.0–4.1 (t, 2H, O–CH_2), 6.9–7.0 (d, 2H, Ar–H), 7.9–8.0 (d, 2H, Ar–H). Anal. Found: C, 70.31; H, 9.27; N, 8.16. Calc. for $C_{21}H_{32}N_2O_3$: C, 70.0; H, 8.88; N, 7.77%.

*5.4.3. 1-[4-(3-Piperidinopropoxy)phenyl]3-(4-methylpiperazin-1-yl)propan-1-one (**5c**)*

Yield: 14%. M.p. (Tartrate) 98–99 °C. IR (cm^{-1}): *v* 1672, 1600, 1512. EIMS: *m/z* 373 [M^+]. ^{1}H-NMR: δ 1.4–1.5 (m, 6H, CH_2), 1.9–2.0 (d, 2H, O–CH_2–CH_2), 2.28 (s, 3H, N–CH_3), 2.4–2.5 (m, 14H, N–CH_2), 2.83–2.87 (d, 2H, CH_2–N), 3.0–3.1 (d, 2H, CH_2–O), 4.0–4.1 (t, 2H, O–CH_2), 6.9–6.94 (d, 2H, Ar–H), 7.90–7.94 (d, 2H, Ar–H). Anal. Found: C, 71.15; H, 9.0; N, 11.66. Calc. for $C_{22}H_{35}N_3O_2$: C, 70.77; H, 9.38; N, 11.26%.

*5.4.4. 5-(Piperidyl)-1-[4-(3-piperidinopropoxy)phenyl]pent-1-en-3-one (**6a**)*

Yield: 16%. M.p. (Tartrate) 120–122. IR (cm^{-1}): *v* 1654, 1596, 1512. EIMS: *m/z* 384 [M^+]. ^{1}H-NMR: δ 1.5–1.7 (m, 12H, CH_2), 1.95–1.98 (d, 2H, O–CH_2–CH_2), 2.3–2.5 (m, 12H, N–CH_2), 2.7–2.8 (d, 2H, CO–CH_2), 4.0–4.06 (t, 2H, O–CH_2), 6.54–6.57 (s, 1H, Ar–C*H*=CH), 6.62–6.65 (s, 2H, Ar–H), 7.3–7.4 (m, 3H, Ar–H, CH=C*H*–CO). Anal. Found: C, 74.61; H, 9.76; N, 7.62. Calc. for $C_{24}H_{36}N_2O_2$: C, 75.0; H, 9.37; N, 7.29%.

*5.4.5. 5-(Morpholinyl)-1-[4-(3-piperidinopropoxy)phenyl]pent-1-en-3-one (**6b**)*

Yield: 14%. M.p. (Tartrate) 123–124 °C. IR (cm^{-1}): *v* 1652, 1596, 1512, 1172. EIMS: *m/z* 386 [M^+]. ^{1}H-NMR: δ 1.4–1.5 (m, 6H, CH_2), 1.95–1.98 (d, 2H, O–CH_2–CH_2), 2.3–2.5 (m, 10H, N–CH_2), 2.7–2.8 (m, 4H, N–CH_2–CO), 3.6–3.7 (t, 4H, O–CH_2), 4.01–4.07 (t, 2H, O–CH_2), 6.5–6.6 (s, 1H, Ar–C*H*=CH), 6.8–7.0 (s, 2H, Ar–H), 7.46–7.49 (m, 3H, Ar–H, CH=C*H*–CO). Anal. Found: C, 71.12; H, 8.42; N, 6.87. Calc. for $C_{23}H_{34}N_2O_3$: C, 71.50; H, 8.80; N, 7.25%.

*5.4.6. 5-(4-Methylpiperazin-1-yl)-1-[4-(3-piperidylpropoxy)phenyl]pent-1-en-3-one (**6c**)*

Yield: 15%. M.p. (Tartrate) 124–125 °C. IR (cm^{-1}): *v* 1652, 1596, 1512, 1170. EIMS: *m/z* 399 [M^+]. ^{1}H-NMR: δ 1.43–1.59 (m, 6H, CH_2), 1.94–1.97 (t, 2H, O–CH_2–CH_2), 2.28 (s, 3H, N–CH_3), 2.3–2.5 (m, 14H, N–CH_2), 2.7–2.8 (m, 4H, N–CH_2, CO–CH_2), 4.01–4.07 (t, 2H, O–CH_2), 6.5–6.6 (s, 1H, Ar–CH=C*H*), 6.6–6.7 (d, 2H, Ar–H), 7.41–7.48 (m, 3H, Ar–H, C*H*=CH–CO). Anal. Found: C, 72.54; H, 9.62; N, 10.84. Calc. for $C_{24}H_{37}N_3O_2$: C, 72.18; H, 9.27; N, 10.52%.

*5.4.7. 5-(3-Methyl-piperidyl)-1-[4-(3-piperidinopropoxy)phenyl]pent-1-en-3-one (**6d**)*

Yield: 15%. M.p. (Tartrate) 182–183 °C. IR (cm^{-1}): *v* 1598, 1512, 1217, 1172, 1039. EIMS: *m/z* 398 [M^+]. ^{1}H-NMR: δ 0.85–0.88 (d, 3H, CH–CH_3), 1.43–1.59 (m, 10H, CH_2), 1.94–1.97 (d, 2H, O–CH_2–CH_2), 2.35–2.50 (m, 10H, CH_2N, COCH_2), 2.72–2.86 (m, 5H, N–CH_2, C*H*–CH_3), 4.01–4.07 (t, 2H, O–CH_2), 6.58–6.62 (s, 2H, Ar–C*H*=CH, Ar–H), 7.45–7.49 (m, 3H, Ar–H, CH=C*H*–CO). Anal. Found: C, 75.71; H, 9.92; N, 7.27. Calc. for $C_{25}H_{38}N_2O_2$: C, 75.37; H, 9.54; N, 7.03%.

*5.4.8. 5-(4-Methylpiperidyl)-1-[4-(3-piperidino-propoxy)phenyl]pent-1-en-3-one (**6e**)*

Yield: 18%. M.p. (Tartrate) 108–109 °C. IR (cm^{-1}): *v* 1741, 1654, 1596, 1217, 1170. EIMS: *m/z* 398 [M^+]. ^{1}H-NMR: δ 0.90–0.93 (d, 3H, CH–CH_3), 1.44–1.59 (m, 10H, CH_2), 1.94–1.98 (d, 2H, O–CH_2–CH_2), 2.35–2.51 (m, 8H, N–CH_2), 2.77–2.92 (m, 5H, N–CH_2, C*H*–CH_3), 4.0–4.07 (t, 2H, O–CH_2), 6.80 (s, 1H, Ar–C*H*=CH), 6.84–6.91 (m, 2H, Ar–H), 7.44–7.49 (m, 3H, Ar–H, CH=C*H*–CO). Anal. Found: C, 75.10; H, 9.81; N, 6.66. Calc. for $C_{25}H_{38}N_2O_2$: C, 75.37; H, 9.54; N, 7.03%.

*5.4.9. 3-Morpholinyl-1-[5-isopropyl-2-methyl-4-(2-hydroxy-3-piperidino-propoxy)phenyl]propan-1-one (**7a**)*

Yield: 12.0%. M.p. (Tartrate) 112–115 °C. IR (cm^{-1}): *v* 1670, 1608, 1554, 1512, 1363. EIMS: *m/z* 432 [M^+]. ^{1}H-NMR: δ 1.21–1.25 (m, 6H, CH(CH_3)$_2$), 1.52–1.68 (m, 16H, CH_2), 2.36–2.82 (m, 17H, CH_2, N–COCH_2, Ar–CH_3), 3.09 (m, 1H, C*H*), 3.68–3.73 (m, 5H, O–CH_2, C*H*–OH), 4.02–4.06 (t, 2H, O–CH_2), 6.67 (s, 1H, Ar–H), 7.56 (s, 1H, Ar–H). Anal. Found: C, 69.83; H, 9.08; N, 6.62. Calc. for $C_{25}H_{40}N_2O_4$: C, 69.44; H, 9.25; N, 6.48%.

*5.4.10. 3-(Morpholinyl)-1-[5-isopropyl-2-methyl-4-(2-piperidinoethoxy)phenyl]propan-1-one (**7b**)*

Yield: 21%. M.p. (Tartrate) 180 °C. IR (cm^{-1}): *v* 1670, 1606, 1556, 1502, 1359, 1309, 1064. Mass: *m/z* 402 [M^+]. ^{1}H-NMR: δ 1.16–1.23 (m, 6H, CH(CH_3)$_2$), 1.48–1.50 (m, 6H, CH_2), 2.03 (s, 3H, Ar–CH_3), 2.47–2.60 (m, 12H, CH_2–N, COCH_2), 2.78–2.83 (d, 2H, N–CH_2), 3.05–3.09 (m, 1H, C*H*), 3.68–3.73 (m, 4H, O–

CH_2), 4.03–4.09 (t, 2H, O–CH_2), 6.75 (s, 1H, Ar–*H*), 7.56 (s, 1H, Ar–H). Anal. Found: C, 72.01; H, 9.82; N, 7.33. Calc. for $C_{24}H_{38}N_2O_3$: C, 71.64; H, 9.45; N, 6.96%.

*5.4.11. 3-(4-Methylpiperazin-1-yl)-1-[5-isopropyl-2-methyl-4-(2-piperidinoethoxy)phenyl]propan-1-one (**7c**)*

Yield: 19%. M.p. (Tartrate) 90 °C. IR (cm^{-1}): *v* 1672, 1606, 1556, 1502, 1353, 1309, 1251. Mass: *m/z* 415 [M^+]. ^{1}H-NMR: 1.23–1.25 (m, 6H, CH(CH_3)$_2$), 1.46–1.93 (m, 6H, CH_2), 2.17 (s, 3H, Ar–CH_3), 2.31 (s, 3H, N–CH_3), 2.46–2.63 (m, 14H, CH_2–N, COCH_2), 2.78–2.88 (d, 4H, N–CH_2), 3.26 (m, 1H, C*H*), 4.14–4.20 (t, 2H, O–CH_2), 6.56 (s, 1H, Ar–H), 7.56 (s, 1H, Ar–H). Anal. Found: C, 72.59; H, 10.26; N, 10.56. Calc. for $C_{25}H_{41}N_3O_2$: C, 72.28; H, 9.97; N, 10.12%.

*5.4.12. 3-(4-Methylpiperidyl)-1-[5-isopropyl-2-methyl-4-(2-piperidinoethoxy)phenyl]propan-1-one (**7d**)*

Yield: 17%. M.p. (Tartrate) 128–130 °C. IR (cm^{-1}): *v* 1668, 1604, 1556, 1504, 1307, 1215. Mass: *m/z* 414 [M^+]. ^{1}H-NMR: δ 1.20–1.24 (m, 6H, CH(CH_3)$_2$), 1.45–1.67 (m, 16H, CH_2, Ar–CH_3, CH–CH_3), 2.43–2.55 (m, 12H, CH_2–N, COCH_2), 2.80–2.86 (t, 2H, N–CH_2) 3.23–3.30 (m, 1H, C*H*), 4.13–4.19 (t, 2H, O–CH_2), 6.76 (s, 1H, Ar–H), 7.70 (s, 1H, Ar–H). Anal. Found: C, 75.75; H, 9.74; N, 6.54. Calc. for $C_{26}H_{42}N_2O_2$: C, 75.36; H, 10.14; N, 6.78%.

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