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In Search of New Chemical Entities with Spermicidal and Anti-HIV Activities†

Seema Srivastava,[a] Lakshmi Kant Bajpai,[a] Sanjay Batra,[a] Amiya P. Bhaduri,[a,*] J. P. Maikhuri,[b] Gopal Gupta[b] and J. D. Dhar[b]

[a]*Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226001, India*
[b]*Endocrinology Division, Central Drug Research Institute, Lucknow 226001, India*

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Abstract—Several compounds belonging to 2-isoxazolines (**4,5a–c**), isoxazoles (**3,6a–c**) and 1-amino-1-cycloalkyl-2-substituted phenyl ethanes (**16–18,a–e**) have been synthesised and found to possess spermicidal activity. Out of these a couple of compounds (**5a** and **6a**) exhibit anti-HIV activity.

The barrier method of contraception which had taken a backseat after the advent of oral pills is once again drawing attention as a response towards the prevention of AIDS and other sexually transmitted diseases. It is being envisaged that a chemical entity possessing spermicidal and anti-HIV activities would be of considerable utility for medicating condoms or for developing a new generation of vaginal contraceptives.

Previous knowledge has indicated that interfering with the sperm membrane bilayer structure or causing lipid peroxidation through reactive oxygen species leads to loss of motility and leakage of cellular components of sperm. However, to prevent such events sperm contains superoxide dismutase and other enzyme systems such as glutathione reductase which provide a defence system against lipid peroxidation.[1] Conceptually, if a compound is capable of interfering with the sperm bilayer or the defence mechanism against superoxides, it may prove lethal to the HIV virus and other bacteria of concern. However, the envisaged bioreactions must be viewed in the milieu of male ejaculate in the vagina and therefore the need arose to search for new chemcial entities capable of exhibiting spermicidal and anti-HIV activities. During the present study this search has been made in a manner to differentiate it from the earlier studies. Two distinct strategies for designing new chemical entities have been employed in the present study. The first one relates to the designing of compounds which in the milieu of male ejaculate will undergo reactions to generate intermediate prone to the cleavage of polarised sigma bond and the second one is concerned with the designing of molecules which will interfere with the ion channel of sperm membrane. It was envisaged that such compounds would generate in situ reactive intermediate for knocking out the in-built defence mechanism of male ejaculate towards oxidative damage. On the basis of these two conceptual components of design, the syntheses of 5-α-substituted acetyl-2-isoxazolines, 5-α-substituted acetyl-isoxazoles and 1-amino-1-cycloalkyl-2-substituted phenyl ethanes were undertaken. For the economics of the study it was conceived that all the synthesised compounds would be subjected to spermicidal tests and the couple of compounds exhibiting best spermicidal activity would be subjected to anti-HIV screening. The results of this study are presented here.

Chemistry

The syntheses of compounds belonging to 2-isoxazoline and isoxazole class are given in Scheme 1. The *N*-bromosuccimide (NBS) mediated transformation of 2-isoxazolines to their corresponding isoxazole derivatives was reported[2] to involve initial bromination of 2-isoxozoline ring followed by in situ dehydrobromination

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* Corresponding author. Tel.: +91-0522-224273; fax: +91-0522-223405.
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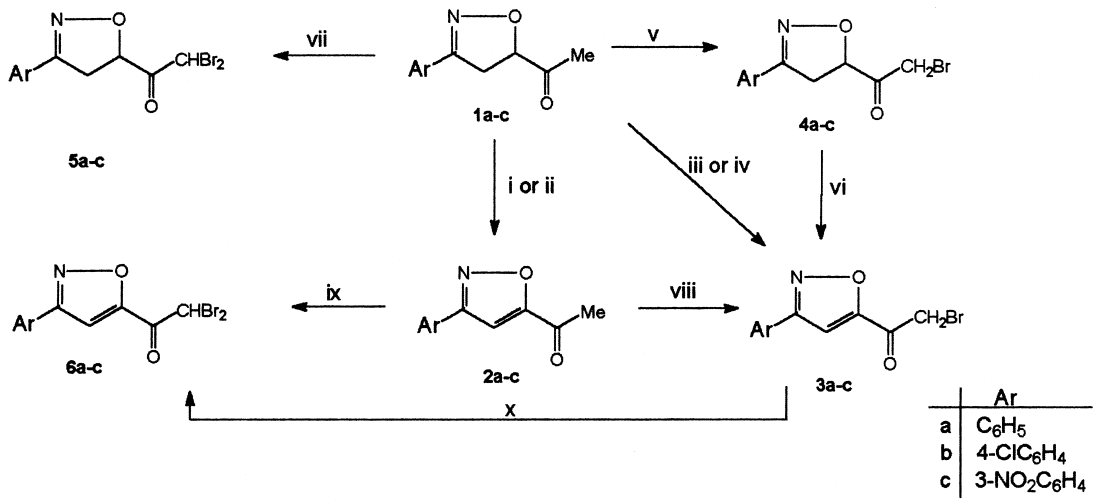


Scheme 1. Synthesis of 2-isoxazolines and isoxazole derivatives. Reagents and conditions: (i) NBS (2 mols), AlBN, CCl_4, N_2 ↑, 1 h; (ii) Br_2 (1 mol), DCM, overnight; (iii) NBS (5 mols), AlBN, CCl_4, N_2↑, 1 h; (iv) Br_2 (3 mols), light, DCM, 3 h; (v) Br_2 (3 mols) light, DCM, 1.5 h; (vi) Br_2 (1 mol), DCM, 2 h; (vii) Br_2 (4 mols), light, DCM:MeOH, 6 h; (viii) Br_2 (2 mols), DCM, 3 h; (ix) Br_2 (2 mols), DCM, 6 h; (x) Br_2 (1 mol) DCM, 3 h. (DCM = dichloromethane.).

in the presence of strong base. However, as no intermediate bromo derivative was isolated by these workers coupled with the report[3] that stability of 2-isoxozolines possessing acetyl group at position 5 was extremely poor under basic conditions there was a need to study the bromination of 5-acetyl-2-isoxazolines and their ability to undergo transformations to 5-acetyl-isoxazoles. Reactions of compounds **1(a–c)** with 2 mols of NBS in the presence of catalytic amount of α,α-azobisisobutyronitrile (AIBN) in carbon tetrachloride under nitrogen atmosphere yielded 5-acetyl-3-substituted phenyl-isoxazoles **2(a–c)** in excellent yields. The use of excess of NBS (ca. 5 mols) during the reaction led to the formation of brominated products **3(a–c)**. The need for excess of bromine suggested that the less favoured site of bromination is the acetyl group. In the light of these results, reactions of 5-acetyl-3-substituted phenyl-2-isoxazolines **1(a–c)** and 5-acetyl-3-substituted phenyl-isoxazoles **2(a–c)** with bromine were also studied. Reaction of compounds **1(a–c)** with 1 mol of bromine in dichloromethane afforded compounds **2(a–c)** but if the same reaction were carried out with 3 mols of bromine, a mixture of products (**4–6,a–c**) were obtained. Compared to these results, if compounds **1(a–c)** were reacted with 3 mols of bromine in the presence of light, they exclusively furnished the monobrominated derivatives **4(a–c)**. Instead of 3 mols, if 4 mols of bromine were used in the reaction of compounds **1(a–c)** in dichloromethane: methanol (10:2, v/v) mixture under light, the dibromo derivatives **5(a–c)** were exclusively obtained in good yields. Also the reaction of compounds **4(a–c)** with 1 mol of bromine under similar conditions led to the formation of compounds **5(a–c)**.

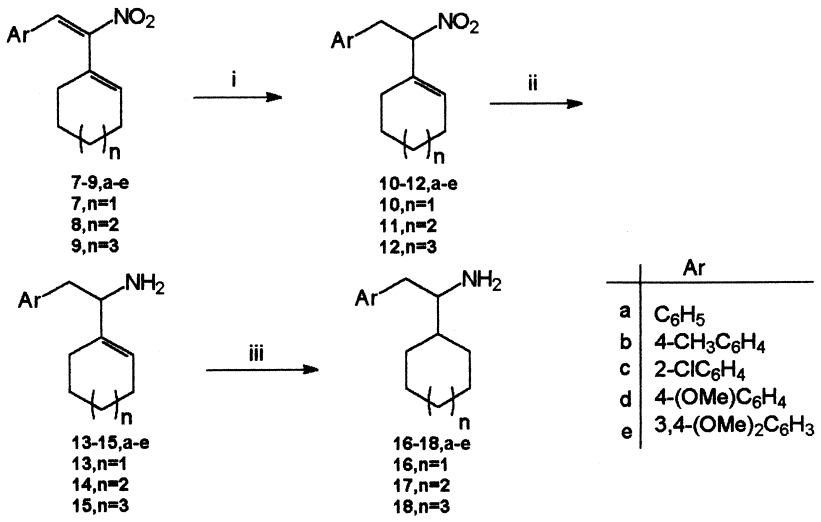
The bromination of 5-acetyl-2-phenyl-isoxazoles **2a** in the presence of bromine in carbon tetrachloride containing catalytic amount of acetic acid has been reported[4,5] to yield monobrominated derivative **3a** in 6 h. During this reaction, a small amount of α,α-dibromo derivative **6a** was also isolated. However, when we carried out the bromination of compounds **2(a–c)** with 2 mols of bromine in dichloromethane, the formation of monobrominated products **3(a–c)** within 3 h of reaction time was observed. Increase in the duration of reaction time to 6 h furnished exclusively the dibrominated products **6(a–c)**. It was also observed that the reaction of compounds **3(a–c)** with one mol of bromine led to the formation of dibromo products **6(a–c)** in quantitative yields. It is worth mentioning here that compounds **5(a–c)** on silica gel dehydrogenate to give compounds **4(a–c)**.

The strategy for the synthesis of 1-amino-1-cycloalkyl-2-substituted phenyl ethanes is outlined in Scheme 2. The regioselective sodium borohydride reductions of (1-cycloalken-1-yl)-1-nitro-2-substituted phenyl ethenes **7–9(a–e)**[6] furnished the corresponding ethanes **10–12(a–c)** which were subsequently hydrogenated in the presence of Raney–Nickel to obtain the unsaturated amines **13–15(a–e)**. These unsaturated amines were hydrogenated in turn in the presence of palladium–carbon to obtain the saturated amines **16–18(a–e)**. These amines were isolated from the reaction mixture as their corresponding oxalate salts.

Biological Assay

Spermicidal activity

The spermicidal activity was determined using Sander–Crammer's assay[7] using Kreb–Ringer bicarbonate buffer (pH 7.6). The minimum effective concentration (MEC) is reported in g% (weight/vol.) of test material as determined with three individual human semen samples. Only samples with $>50\times10^6$ sperms/mL and >50% motility were used in the tests. About 0.2 mL of human semen was treated with 1.0 mL of diluted



Scheme 2. Synthesis of 1-amino-1-cycloalkyl-2-substituted phenyl ethanes. Reagents and conditions: (i) $NaBH_4$, MeOH, 30 min; (ii) Raney–Ni/H_2, MeOH, 4.5 kg/cm^3, 3–4 h; (iii) 10% Pd-C/H_2, MeOH, 4.5 kg/cm^3, 24 h.

spermicide preparation. Compounds **16–18(a–e)** were dissolved in normal saline while compounds **2–6(a–c)** were initially dissolved in a few drops of DMSO and then these solutions were progressively diluted with saline until the weakest dilution completely immobilized the sperms in 20 s. This concentration is referred to as minimum effective concentration (MEC).

HIV inhibitory activity

Two compounds **5a** and **6a** were also evaluated in vitro for HIV-inhibitory activity, using HIV-1 glycoprotein mediated cell to cell fusion bioassay. This method involved use of human lymphoid cell line (TF 228.1.16) as effector cells, which stably expresses HIV-1 glycoprotein, and sup T^1 cells stably expressing CD4 as target cells. The cells were maintained in suspension culture at 37°C for 3 h using RPMI-1640 medium supplemented with 10% heat-activated fetal bovine serum. TF 228 cells (10^5) were mixed with sup T^1 cells in equal numbers in wells and appropriate dilutions of test compounds were added to each well. Fusion was determined by the presence of multinucleated cells (Syntia) and the inhibitory effect of compounds assessed either by the reduction or absence of syntia.

Results and Discussion

All the 2-isoxazolines (**4,5a–c**) and isoxazoles (**2,3,6a–c**) and 1-amino-1-cycloalkyl-2-substituted phenyl ethanes (**16–18,a–c**) were screened for spermicidal activity and the results have been summarized in Table 1.

In compounds representing 2-isoxazolines and isoxazole derivatives it was observed that except for the inactive compounds **2a** and **5b,** other compounds with substituents on the phenyl ring exhibited activity of lower order. However, in compounds **16–18(a–e)**, though the substitution on the phenyl ring contributed very little towards the spermicidal efficacy of the test compounds, the other substructural components, i.e. the cycloalkyl group, did influence the biological activity. The maximum spermicidal activity was exhibited by compounds possessing the cycloheptyl group.

The two compounds **5a** and **6a** evaluated for the anti-HIV activity indicate the reduction of syntia by more than 95% at a concentration of 25 μg/mL.

It can be concluded from the present study that substituted 2-isoxazolines and isoxazoles may serve as new leads for generating compounds which may be helpful in preventing the sexual transmission of AIDS by exhibiting the spermicidal and anti-HIV activity simultaneously.

Experimental

All the melting points were determined on a hot stage apparatus and are uncorrected. IR spectra 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

Table 1. Spermicidal screening data of compounds

Compd. no.	MEC[a]	Compd. no.	MEC	Compd. no.	MEC
2a	Not active	**5b**	Not active	**17a**	0.5
2b	0.5	**5c**	0.1	**17b**	0.01
2c	0.1	**6a**	0.05	**17c**	0.025
3a	0.01	**6b**	0.1	**17d**	0.01
3b	0.1	**6c**	0.1	**17e**	1.0
3c	0.1	**16a**	0.5	**18a**	0.01
4a	0.1	**16b**	0.5	**18b**	Not active
4b	0.1	**16c**	0.1	**18c**	0.1
4c	0.01	**16d**	0.5	**18d**	0.1
5a	0.005	**16e**	1.0	**18e**	1.0

[a] MEC, minimum effective concentration in g% (w/vol).

standard and $CDCl_3$ as solvent until unless stated otherwise. The mass spectra were recorded on Jeol-JMS-D-300 mass spectrometer and chemical analyses were carried out on Carlo Erba 1108 analyzer.

General procedure for 5-acetyl-3-substituted phenyl isoxazoles (2a–c)

To a stirred solution of compound **1(a–c)** (4.2 mmol) in dry CCl_4 was added AIBN (catalytic amount) at 50°C under a N_2 atmosphere. After 10 min NBS (8.5 mmol) was added in portions to the reaction mixture and the temperature was raised to 65°C. After the addition was complete, the mixture was stirred for 1 h. Thereafter the separated solid was filtered and the filtrate was extracted with chloroform (2×30 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and evaporated to obtain pure products in 87–90% yields. These were recrystallized from hexane.

2a. M.P. 106–108°C; IR (cm^{-1}) 1697, 1604; EIMS *m/z* 188 ($M^+ + 1$); ^1H NMR δ 2.66 (s, 3H, CH_3), 7.21 (s, 1H, =CH), 7.49 (m, 3H, Ar–H), 7.83 (m, 2H, Ar–H); (Found: C, 70.22; H, 4.66; N, 7.82. $C_{11}H_9NO_2$ requires C, 70.57; H, 4.84; N, 7.48%).

2b. M.P. 134–136°C; IR (cm^{-1}) 1700, 1608; EIMS *m/z* 221 (M^+); ^1H NMR δ 2.66 (s, 3H, CH_3), 7.18 (s, 1H, =CH), 7.45–7.49 (d, 2H, *J* = 8 Hz, Ar–H), 7.76, 7.80 (d, 2H, *J* = 8 Hz, Ar–H); (Found: C, 59.42; H, 3.78, N, 6.61. $C_{11}H_8ClNO_2$ requires C, 59.61, H, 3.63, N, 6.32%).

2c. M.P. 126–127°C; IR (cm^{-1}) 1700, 1602; EIMS *m/z* 332 (M^+); ^1H NMR δ 2.70 (s, 3H,CH_3), 7.47 (s, 1H, = CH), 7.76 (m, 3H, Ar–H), 8.20, 8.24 (d, 1H, *J* = 8 Hz, Ar–H), 8.34, 8.37 (d, 1H, *J* = 8 Hz, Ar–H), 8.68 (s, 1H, Ar–H). (Found: C, 56.85; H, 3.08; N, 12.05. $C_{11}H_8N_2O_4$ requires C, 56.90, H, 3.47, N, 12.06%).

General procedure for 5-(2-bromoacetyl)-3-substituted phenyl isoxazoles (3a–c)

To a stirred solution of compounds **2(a–c)** (5.3 mmol) in dry dichloromethane (20 mL) was added a solution of bromine (0.84 mL, 15.3 mmol) in dry dichloromethane (5 mL) over a period of 20 min at 0°C. The stirring was continued at a temperature between 0 and 5°C for 3 h. The reaction mixture was quenched with ice cold water (50 mL) and extracted with chloroform (2×40 mL). The organic layers were combined and washed with saturated sodium thiosulphate solution. Usual work up of organic layer furnished a residue which on trituration with hexane gave solid products in 65–67% yields.

3a. M.P. 116–117°C; IR (cm^{-1}) 1716, 1600; EIMS *m/z* 267 (M^+); ^1H NMR δ 4.48 (s, 2H, CH_2–Br), 7.36 (s, 1H, =CH), 7.51 (m, 3H, Ar–H), 7.84 (m, 2H, Ar–H); (Found: C, 49.89, H, 2.86, N, 5.16. $C_{11}H_8BrNO_2$ requires C, 49.65, H, 3.02, N, 5.26%).

3b. M.P. 149–150°C; IR (cm^{-1}) 1710, 1604; EIMS *m/z* 300 ($M^+ + 1$); ^1H NMR: δ 4.49 (s, 2H, CH_2–Br), 7.20 (s, 1H, =CH), 7.45, 7.49 (d, 2H, *J* = 8 Hz, Ar–H), 7.78, 7.82 (d, 2H, *J* = 8 Hz, Ar–H), (Found: C, 44.22; H, 2.48; N, 4.81. $C_{11}H_7BrClNO_2$ requires C, 43.96; H, 2.34; N, 4.66%).

3c. M.P. 112–113°C; IR (cm^{-1}) 1706, 1590; EIMS *m/z* 310 (M^+); ^1H NMR δ 4.49 (s, 2H, CH_2–Br), 7.45 (s, 1H, =CH), 7.73 (t, 1H, *J* = 8 Hz, Ar–H), 8.20, 8.24 (d, 2H, *J* = 8 Hz, Ar–H), 8.35, 8.39 (d, 1H, *J* = 8 Hz, Ar–H), 8.70 (s, 1H, Ar–H). (Found: C, 42.67, H, 1.99, N, 8.97. $C_{11}H_7BrN_2O_4$ requires C, 42.47, H, 2.20, N, 9.00%).

General procedure for 5-(2-bromoacetyl)-3-substituted phenyl isoxazolines (4a–c)

To a stirred ice cool solution of compound **1a–c** (5.2 mmol) in dry dichloromethane (20 mL) was added dropwise a solution of bromine (0.84 mL, 15.3 mmol) in dry dichloromethane (5 mL) under the exposure of tungsten lamp (Philips, 500 w). The reaction was allowed to proceed for 1.5 h at 0–5°C. Thereafter the reaction mixture was decomposed with ice cold water (50 mL) and extracted with chloroform (2×40 mL). The organic layers were combined and washed with saturated sodium thiosulphate solution. Usual workup of organic layer furnished a residue which on chromatography over silica gel (60–120 mesh) using hexane: ethylacetate (90:10, v/v) as eluent yielded the products which were recrystallized from hexane in 55–57% yields.

4a. M.P. 90–91°C; IR (cm^{-1}) 1742, 1604; EIMS *m/z* 267 (M^+); ^1H NMR δ 3.66 (dq, 2H, *J* = 10, 6 Hz, CH_2–CH), 4.36 (q, 2H, *J* = 13, 14 Hz, CH_2–Br), 5.35 (q, 1H, *J* = 6 Hz, CH_2–CH), 7.46 (m, 3H, Ar–H), 7.67 (m, 2H, Ar–H); (Found: C, 49.27; H, 3.63; N, 4.96. $C_{11}H_{10}$ $BrNO_2$ requires C, 49.43; H, 3.74; N, 5.24%).

4b. M.P. 88°C; IR (cm^{-1}) 1737, 1600; EIMS *m/z* 301 (M^+); ^1H NMR δ 3.58 (dq, 2H, *J* = 10, 6Hz, CH_2–CH), 4.37 (q, 2H, *J* = 14,16 Hz, CH_2–Br), 5.39 (q, 1H, *J* = 6 Hz, CH_2–CH), 7.39 (d, 2H, *J* = 8 Hz, Ar–H), 7.60, 7.64 (d, 2H, *J* = 8 Hz, Ar–H). (Found: C, 44.08, H, 2.86, N, 4.60. $C_{11}H_9BrClNO_2$ requires C, 43.5, H, 2.99, N, 4.65%).

4c. M.P. 123–124°C; IR (cm^{-1}) 1732, 1614; EIMS *m/z* 312 (M^+); ^1H NMR 3.77 (dq, 2H, *J* = 10, 6 Hz, CH_2–CH), 4.30 (q, 2H, *J* = 14, 16 Hz, CH_2–Br), 5.47 (q, 1H, *J* = 6 Hz, CH_2–CH), 7.64 (t, 1H, *J* = 8 Hz, Ar–H), 8.20, 8.24 (d, 1H, *J* = 8 Hz, Ar–H), 8.29, 8.33 (d, 1H, *J* = 8 Hz, Ar–H), 8.47 (s, 1H, Ar–H). (Found: C, 42.61, H, 2.96, N, 9.09. $C_{11}H_9BrN_2O_4$ requires C, 42.30, H, 2.88, N, 8.97%).

General procedure for 5-(2,2-dibromoacetyl)-3-substituted phenyl isoxazolines (5a–c)

To a stirred ice cool (0–5°C) solution of compounds **1(a–c)** (5.2 mmol) in dry dichloromethane: methanol mixture (20 mL) (10:2, v/v) was added dropwise a solution of bromine (1.12 mL, 21.1 mmol) in dichloromethane (5 mL) under the exposure of tungsten lamp (Philips, 500 w) over a period of 20 min. The reaction

mixture was stirred for 6 h at room temperature. Then it was decomposed with ice cold water (50 mL) and extracted with chloroform (2×40 mL). The organic layers were pooled and washed with sodium thiosulphate solution. Usual work up of organic layers furnished residues which were column chromatographed over silica gel using hexane:ethyl acetate (95:5, v/v) to obtain the pure products in 67–72% yields.

5a. M.P. 90–91°C; IR (cm^{-1}) 1724, 1602; EIMS *m/z* 345 (M^+); ^1H NMR δ 3.73 (m, 2H,-CH_2–CH), 5.63 (q, 1H, *J* = 6 Hz,-CH_2–CH), 6.55 (s, 1H, CH-Br_2), 7.44 (m, 3H, Ar–H), 7.66 (m, 2H, Ar–H); (Found: C, 38.59, H, 2.95, N, 4.43. $C_{11}H_9Br_2NO_2$ requires C, 38.26, H, 2.61, N, 4.05%).

5b. M.P. 121–122°C; IR (cm^{-1}) 1728, 1596; EIMS *m/z* 379 (M^+); ^1H NMR δ 3.69 (m, 2H,-CH_2–CH), 5.64 (q, 1H, *J* = 6 Hz,-CH_2–CH), 6.52 (s, 1H, CH–Br_2), 7.38, 7.42 (d, 2H, *J* = 8 Hz, Ar–H), 7.59,7.63 (d, 2H, *J* = 8 Hz, Ar–H); (Found: C, 34.49, H, 1.88, N, 3.93. $C_{11}H_8Br_2ClNO_2$ requires C, 34.63, H, 2.11, N, 3.67%).

5c. M.P. 118–119°C; IR (cm^{-1}) 1740, 1604; EIMS *m/z* 391 (M^+); ^1H NMR δ 3.72 (m, 2H,-CH_2–CH), 5.67(q, 1H, *J* = 6 Hz,-CH_2–CH), 6.50 (s, 1H, CH–Br_2), 7.64 (t, 1H, *J* = 8 Hz, Ar–H), 8.04, 8.08 (d, 1H, *J* = 8 Hz, Ar–H), 8.22, 8.26 (d, 1H, *J* = 8 Hz, Ar–H), 8.47 (s, 1H, Ar–H); (Found: C, 33.85, H, 2.44, N, 7.22. $C_{11}H_8Br_2N_2O_4$ requires C, 33.77, H, 2.04, N, 7.16%).

General procedure for 5-(2,2-dibromoacetyl)-3-substituted phenyl isoxazoles (6a–c)

To a stirred solution of compounds **2(a–c)** (5.3 mmol) in dry dichloromethane (20 mL) was added dropwise a solution of bromine (0.546 mL, 10.6 mmol) in dry dichloromethane at a temperature of 0–5°C. The reaction was continued for 6 h and then decomposed with ice cool water (50 mL). The reaction mixture was extracted with chloroform (2×40 ml). The organic layers were combined and washed with saturated sodium thiosulphate solution. Usual work up of organic layer furnished a residue which on trituration with hexane gave the solid products in 88–95% yields.

6a. M.P. 135–138°C; IR (cm^{-1}) 1710, 1598; EIMS: *m/z* 343 (M^+); ^1H NMR: δ 6.63 (m, 1H, =CH), 7.51 (m, 4H, CH–Br_2 and Ar–H), 7.85 (m, 2H, Ar–H); (Found C, 38.49, H, 2.35, N, 3.94. $C_{11}H_7Br_2NO_2$ requires C, 38.29, H, 2.04, N, 4.06%).

6b. M.P. 146–147°C; IR (cm^{-1}) 1706, 1596; EIMS *m/z* 377 (M^+); ^1H NMR δ 6.61 (s, 1H, =CH), 7.47, 7.51 (d, 3H, *J* = 8 Hz, CH–Br_2 merged with Ar–H), 7.77, 7.82 (d, 2H, *J* = 8 Hz, Ar–H). (Found C, 33.05, H, 1.44, N, 7.22. $C_{11}H_6Br_2ClNO_2 1H_2O$ requires C, 33.41, H, 1.51, N, 7.08%).

6c. M.P. 130–131°C; IR (cm^{-1}) 1702, 1606; EIMS *m/z* 388 (M^+); ^1H NMR: δ 6.61 (s, 1H,-CH), 7.59 (s, 1H, CH–Br_2), 7.73 (t, 1H, *J* = 8 Hz, Ar–H), 8.22, 8.25 (d, 1H, *J* = 8 Hz, Ar–H), 8.36, 8.41 (d, 1H, *J* = 8 Hz, Ar–H), 8.79 (s, 1H, Ar–H). (Found C, 33.62, H, 1.42, N, 7.58. $C_{11}H_6Br_2N_2O_4$ requires C, 33.87, H, 1.55, N, 7.18%).

General procedure for 1-(cycloalken-1-yl)-1-nitro-2-substituted phenyl ethanes (10–12,a–e)

To a stirred ice cool solution of the appropriate compound from **7–9(a–e)** (7 mmol) in methanol (50 mL) was added sodium borohydride (1.33 g, 35 mmol) in portions over a period of 20 min. The stirring was continued at room temperature for another 30 min. Thereafter, the excess of methanol was removed under vacuo and the residue so obtained was diluted with water (80 mL) and extracted with ethylacetate (3×40 mL). Usual work up of organic layer furnished an oil which was purified over silica gel column using hexane:ethylacetate (99.5:0.5, v/v) as eluent to furnish compounds **10–12(a–e)** in 45–55% yields.

10a. M.P. oil; EIMS *m/z* 185 (M^+-NO_2); ^1H NMR δ 1.86 (m, 8H, 4×CH_2), 3.08 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.52 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 5.09 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.90 (brs, 1H, CH=C), 7.20 (m, 5H, Ar–H) (Found: C, 72.38, H, 7.61, N, 5.71. $C_{14}H_{17}NO_2.1/2\ H_2O$ requires C, 72.70, H, 7.40, N, 6.05%).

10b. M.P. oil; EIMS *m/z* 245 (M^+); ^1H NMR δ 1.75 (m, 8H, 4×CH_2), 2.31 (s, 3H, Ar–CH_3), 2.94 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.32 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 4.91 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.76 (brs, 1H, CH=C), 6.82 (d, 2H, *J* = 9 Hz, Ar–H), 7.02 (d, 2H, *J* = 9 Hz, Ar–H) (Found: C, 73.48, H, 7.56, N, 5.68. $C_{15}H_{19}NO_2$ requires C, 73.44, H, 7.80, N, 5.70%).

10c. M.P. oil; EIMS *m/z* 265 (M^+); ^1H NMR δ 1.90 (m, 8H, 4×CH_2), 3.21 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.59 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 5.26 (dd, 2H, *J* = 14, 6 Hz, CH–NO_2), 5.90 (brs, 1H, CH=C), 7.16 (m, 4H, Ar–H) (Found: C, 63.01, H, 6.18, N, 5.54. $C_{14}H_{16}ClNO_2$ requires C, 63.27, H, 6.07 N, 5.27%)

10d. M.P. 54°C; EIMS *m/z* 261 (M^+); ^1H NMR δ 1.80 (m, 8H, 4×CH_2), 2.92 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.24 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.72 (s, 3H, Ar–OCH_3), 4.86 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.80 (brs, 1H, CH=C), 6.62 (d, 2H, *J* = 9 Hz, Ar–H), 6.92 (d, 2H, *J* = 9 Hz, Ar–H) (Found: C, 68.81, H, 7.54, N, 5.20. $C_{15}H_{19}ClNO_3$ requires C, 68.94, H, 7.32 N, 5.36%).

10e. M.P. 80–81°C; EIMS *m/z* 291 (M^+); ^1H NMR δ 1.84 (m, 8H, 4×CH_2), 2.99 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.48 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.82 (brs, 6H, 2×Ar–OCH_3), 5.02 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.92 (brs, 1H, CH=C), 6.70 (m, 3H, Ar–H) (Found: C, 65.90, H, 7.25, N, 4.82. $C_{16}H_{21}NO_4$ requires C, 65.95, H, 7.26, N, 4.80%).

11a. M.P. oil; EIMS *m/z* 245 (M^+); ^1H NMR δ 1.64 (m, 6H, 3×CH_2), 2.24 (m, 4H, 2×CH_2), 3.26 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.54 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 5.23 (dd, 1H, *J* = 14, 6.6 Hz, CH–NO_2), 6.04 (t, 1H, *J* = 6 Hz, CH=C), 7.28 (m, 5H, Ar–H) (Found: C,

73.21, H, 7.71, N, 5.56. $C_{15}H_{19}NO_2$ requires C, 73.44, H, 7.80, N, 5.70%).

11b. M.P. oil; EIMS *m/z* 259 (M^+); ^{1}H NMR δ 1.60 (m, 6H, 3×CH_2), 2.24 (m, 4H, 2×CH_2), 2.32 (s, 3H, Ar–CH_3), 3.04 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.42 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 5.04 (dd, 1H, *J* = 14, 6Hz, CH–NO_2), 6.04 (t, 1H, *J* = 6 Hz, CH=C), 7.04 (d, 2H, *J* = 9 Hz, Ar–H), 7.10 (d, 2H, *J* = 9 Hz, Ar–H), (Found: C, 74.33, H, 8.47, N, 5.36. $C_{16}H_{21}NO_2$ requires C, 74.13, H, 8.10, N, 5.40%).

11c. M.P. oil; EIMS *m/z* 279 (M^+); ^{1}H NMR δ 1.86 (m, 6H, 3×CH_2), 2.24 (m, 4H, 2×CH_2), 3.24 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.48 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 5.18 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.90 (t, 1H, *J* = 6.6 Hz, CH=C), 7.14 (m, 4H, Ar–H), (Found: C, 64.03, H, 6.51, N, 5.23. $C_{15}H_{18}ClNO_2$ requires C, 64.39, H, 6.48, N, 5.00%).

11d. M.P. oil; EIMS *m/z* 275 (M^+); ^{1}H NMR δ 1.85 (m, 6H, 3×CH_2), 3.04 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.42 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.70 (s, 3H, Ar–OCH_3), 5.00 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.95 (t, 1H, *J* = 6.6 Hz, CH=C), 6.76 (d, 2H, *J* = 9 Hz, Ar–H), 7.02 (d, 2H, *J* = 9 Hz, Ar–H), (Found: C, 69.78, H, 7.82, N, 4.64. $C_{16}H_{21}NO_3$ requires C, 69.81, H, 7.63, N, 5.09%).

11e. M.P. oil; EIMS *m/z* 305 (M^+); ^{1}H NMR δ 1.85 (m, 6H, 3×CH_2), 2.22 (m, 4H, 2×CH_2), 3.08 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.56 (dd, 1H, *J* = 14, 6 Hz, CH_2–Ar), 3.78 (brs, 6H, 2×Ar–OCH_3), 5.12 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 6.02 (t, 1H, *J* = 6 Hz, CH=C), 6.78 (m, 3H, Ar–H) (Found: C, 66.49, H, 7.61, N, 4.56. $C_{17}H_{23}NO_4$ requires C, 66.86, H, 7.59, N, 4.58%).

12a. M.P. oil; EIMS *m/z* 259 (M^+); ^{1}H NMR δ 1.54 (m, 8H, 4×CH_2), 2.24 (m, 4H, 2×CH_2), 3.10 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.50 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 5.08 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 6.02 (t, 1H, *J* = 8 Hz, CH=C), 7.30 (m, 5H, Ar–H) (Found: C, 74.28, H, 8.22, N, 5.59. $C_{16}H_{21}NO_2$ requires C, 74.13, H, 8.10, N, 5.40%).

12b. M.P. oil; EIMS *m/z* 273 (M^+); ^{1}H NMR δ 1.50 (m, 8H, 4×CH_2), 2.28 (m, 4H, 2×CH_2), 2.34 (s, 3H, Ar–CH_2), 3.08 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.49 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 5.16 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.98 (t, 1H, *J* = 6 Hz, CH=C), 7.08 (d, 2H, *J* = 9 Hz, Ar–H), 7.14 (d, 2H, *J* = 9 H, Ar–H), (Found: C, 74.33, H, 8.23, N, 4.85. $C_{17}H_{23}NO_2$ requires C, 74.72, H, 8.42, N, 5.12%).

12c. M.P. oil; EIMS *m/z* 293 (M^+); ^{1}H NMR δ 1.56 (m, 8H, 4×CH_2), 2.30 (m, 4H, 2×CH_2), 3.04 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.46 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 5.14 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 6.02 (t, 1H, *J* = 8 Hz, CH=C), 7.20 (m, 4 H, Ar–H) (Found: C, 65.52, H, 6.71, N, 4.58. $C_{16}H_{20}ClNO_2$ requires C, 65.41, H, 6.86, N, 4.76%).

12d. M.P. oil; EIMS *m/z* 289 (M^+); ^{1}H NMR δ 1.90 (m, 12H, 6×CH_2), 2.98 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.42 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.71 (s, 3H, Ar–OCH_3), 5.02 (dd, 1H, *J* = 14, 6 Hz, CH–NO_2), 5.88 (t, 1H, *J* = 8 Hz, CH=C), 6.74 (d, 2H, *J* = 9 Hz, Ar–H), 7.02 (d, 2H, *J* = 9 Hz, Ar–H) (Found: C, 70.24, H, 7.86, N, 4.53. $C_{17}H_{23}NO_3$ requires C, 70.56, H, 8.01, N, 4.53%).

12e. M.P. oil; EIMS *m/z* 319 (M^+); ^{1}H NMR δ 1.54 (m, 8H, 4×CH_2), 2.26 (m, 4H, 2×CH_2), 2.98 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.39 (dd, 1H, *J* = 14, 6 Hz, Ar–CH_2), 3.78 (s, 6H, 2×Ar–OCH_3), 5.18 (t, 1H, *J* = 8 Hz, CH=C), 6.76 (m, 3H, Ar–H) (Found: C, 67.48, H, 7.76, N, 4.32. $C_{18}H_{25}NO_4$ requires C, 67.68, H, 7.89, N, 4.38%).

General procedure for 1-amino-1-(cycloalken-1-yl)-2-substituted phenyl ethanes (13–15,a–e)

A mixture of appropriate compound from **10**–**12(a–e)** (7 mmol) and Raney–Ni (300 mg, wet) in methanol (30 mL) was subjected to hydrogenation at 4.5 kg/cm^3 for 3–4 h. Thereafter, the catalyst was filtered over Celite and the filtrate was concentrated to furnish compounds **13**–**15(a–e)**, which were subjected to the next step without further purification.

General procedure for 1-amino-1-cycloalkyl-2-substituted phenyl ethanes (16–18,a–e)

A mixture of appropriate compound from **13**–**15(a–e)** (crude from the above step) and 10% Pd-C (150 mg) in methanol (30 mL) was subjected to hydrogenation at 4.5 kg/cm^3 for 24 h. The reaction mixture was then filtered over a bed of Celite and the excess solvent was removed under vacuo to obtain amines **16**–**18(a–e)** as oils or solids in 85–90% yields. The pure amines were obtained as their corresponding oxalate salts.

General procedure for oxalate salts of amines 16–18(a–e)

To a solution of appropriate amine derivative from **16**–**18(a–e)** (2 mmol) in dry methanol (8 mL) was added a solution of oxalic acid dihydrate (2 mmol) in dry methanol (8 mL) slowly. The mixture was stirred at room temperature for 20 min. Thereafter, dry ether (60 mL) was added to the reaction mixture and it was left in refrigerator for 8–10 h. The separated solid was filtered, washed with dry ether and dried over P_2O_5 in a dessicator.

16a. M.P. oil; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 203 (M^+); ^{1}H NMR δ 1.91 (m, 5H, 2×CH_2 and CH), 1.71 (m, 6H, 3×CH_2), 2.96 (m, 1H, CH_2–Ar), 3.34 (m, 1H, CH_2–Ar), 3.46 (m, 1H, CH–NH_2), 7.28 (m, 5H, Ar–H), 8.34 (brs, 2H, NH_2) (Found: C, 82.41, H, 10.04, N, 7.05. $C_{14}H_{21}N$ requires C, 82.71, H, 10.04, N, 6.89%).

16b. M.P. oil IR (cm^{-1}) 3386 (N–H); EIMS *m/z* 217 (M^+); ^{1}H NMR (DMSO-d_6) δ 0.98 (m, 5H, 2×CH_2 and CH), 1.52 (m, 6H, 3×CH_2), 2.09 (s, 3H, Ar–CH_3), 2.54 (m, 1H, CH_2–Ar), 2.84 (m, 1H, CH_2–Ar), 3.14 (m, 1H, CH–NH_2), 6.44 (d, 2H, *J* = 9 Hz, Ar–H), 7.04 (d, 2H, *J* = 9 Hz, Ar–H) (Found: C, 82.98, H, 10.51, N, 6.58. $C_{15}H_{23}N$ requires C, 82.90, H, 10.66, N, 6.45%).

16c. M.P. 192°C; IR (cm^{-1}) 3392 (N-H); EIMS *m/z* 237 (M^+); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 1.18 (m, 5H, 2×CH_2 and CH), 1.78 (m, 6H, 3×CH_2), 2.59 (m, 1H, CH_2–Ar), 3.08 (m, 1H, CH_2–Ar), 3.34 (m, 1H, CH–NH_2), 7.24 (m, 4H, Ar–H), 8.21 (brs, 2H, NH_2) (Found: C, 68.42, H, 8.63, N, 5.28. $C_{14}H_{20}ClN.1/2\ H_2O$ requires C, 68.13, H, 8.57, N, 5.67%).

16d. M.P. 222°C; IR (cm^{-1}) 3388 (N–H); EIMS *m/z* 233 (M^+); ^1H NMR (D_2O) δ 1.14 (m, 5H, 2×CH_2 and CH), 1.72 (m, 6H, 3×CH_2), 2.30 (m, 1H, CH_2–Ar), 2.68 (m, 1H, CH_2–Ar), 2.84 (m, 1H, CH–NH_2), 3.70 (s, 3H, Ar–OCH_3), 6.76 (d, 2H, J=9 Hz, Ar–H), 7.02 (d, 2H, J=9 Hz, Ar–H) (Found: C, 83.39, H, 10.07, N, 5.84. $C_{15}H_{23}NO_2$ requires C, 83.65, H, 9.93, N, 6.00%).

16e. M.P. oil; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 263 (M^+); ^1H NMR (D_2O) δ 0.90 (m, 5H, 2×CH_2 and CH), 1.48 (m, 6H, 3×CH_2), 2.41 (m, 1H, CH_2–Ar), 2.72 (m, 1H, CH_2–Ar), 3.06 (m, 1H, CH–NH_2), 3.52 (s, 6H, 2×Ar–OCH_3), 6.64 (s, 3H, Ar–H), (Found: C, 73.12, H, 9.81, N,5.22. $C_{16}H_{25}NO_2$ requires C, 72.97, H, 9.57, N, 5.32%).

17a. M.P. oil; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 217 (M^+); ^1H NMR (D_2O) δ 1.19 (m, 7H, 3×CH_2 and CH), 1.94 (m, 6H, 3×CH_2), 2.54 (m, 1H, CH_2–Ar), 2.80 (m, 1H, CH_2–Ar), 3.18 (m, 1H, CH–NH_2), 7.10 (m, 5H, Ar–H), (Found: C, 82.90, H, 10.51, N,6.29. $C_{15}H_{23}N$ requires C, 82.90, H, 10.66, N, 6.45%).

17b. M.P. 42°C; IR (cm^{-1}) 3390 (N–H); EIMS *m/z* 231 (M^+); ^1H NMR (D_2O) δ 1.52 (m, 7H, 3×CH_2 and CH), 1.74 (m, 6H, 3×CH_2), 2.32 (s, 3H, Ar–CH_3), 2.39 (m, 1H, CH_2–Ar), 2.78 (m, 1H, CH_2–Ar), 2.88 (m, 1H, CH–NH_2), 7.09 (m, 4H, Ar–H), (Found: C, 82.80, H, 10.66, N, 6.25. $C_{16}H_{25}N$ requires C, 83.07, H, 10.89, N, 6.06%).

17c. M.P. 207°C; IR (cm^{-1}) 3405 (N–H); EIMS *m/z* 251 (M^+); ^1H NMR δ 1.49 (m, 7H, 3×CH_2 and CH), 1.74 (m, 6H, 3×CH_2), 2.98 (m, 1H, CH_2–Ar), 3.14 (m, 1H, CH_2–Ar), 3.38 (m, 1H, CH–NH_2), 7.28 (m, 4H, Ar–H), 8.42 (brs, 2H, NH_2), (Found: C, 71.21, H, 8.81, N,5.42. $C_{15}H_{22}ClN$ requires C, 71.54, H, 8.80, N, 5.56%).

17d. M.P. 197–198°C; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 247 (M^+); ^1H NMR (D_2O) (δ 1.48 (m, 7H, 3×CH_2 and CH), 1.72 (m, 6H, 3×CH_2), 2.92 (m, 1H, CH_2–Ar), 3.06 (m, 1H, CH_2-Ar), 3.32 (m, 1H, CH–NH_2), 3.78 (s, 3H, Ar–OCH_3), 6.74 (d, 2H, J=9 Hz, Ar–H), 7.16 (d, 2H, J=9 Hz, Ar–H) (Found: C, 77.84, H, 9.91, N,5.35. $C_{16}H_{25}NO$ requires C, 77.69, H, 10.19, N, 5.66%).

17e. M.P. oil; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 277 (M^+); ^1H NMR δ 1.48 (m, 7H, 3×CH_2 and CH), 1.64 (m, 6H, 3×CH_2), 2.42 (m, 1H, CH_2–Ar), 2.62 (m, 1H, CH_2–Ar), 2.69 (m, 1H, CH–NH_2), 3.68 (s, 6H, 2×Ar–OCH_3), 6.76 (m, 3H, Ar–H) (Found: C, 73.47, H, 9.53, N, 5.08. $C_{17}H_{27}NO_2$ requires C, 73.61, H, 9.81, N, 5.05%).

18a. M.P. oil; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 231 (M^+); ^1H NMR (D_2O) δ 1.08 (m, 9H, 4×CH_2 and CH), 1.34 (m, 6H, 3×CH_2), 2.48 (m, 1H, CH_2–Ar), 2.66 (m, 1H, CH_2–Ar), 2.94 (m, 1H, CH–NH_2), 7.08 (m, 5H, Ar–H) (Found: C, 83.29, H, 10.51, N,5.88. $C_{16}H_{25}N$ requires C, 83.07, H, 10.89, N, 6.06%).

18b. M.P. oil; IR (cm^{-1}) 3410 (N–H); EIMS *m/z* 245 (M^+); ^1H NMR δ 1.50 (m, 9H, 4×CH_2 and CH), 1.66 (m, 6H, 3×CH_2), 2.34 (s, 3H, CH_3–Ar), 2.86 (m, 1H, CH_2–Ar), 3.22 (m, 1H, CH_2–Ar), 3.34 (m, 1H, CH–NH_2), 6.54 (d, 2H, J=9 Hz, Ar–H), 7.06 (d, 2H, J=9 Hz, Ar–H) (Found: C, 83.40, H, 11.15, N, 5.72. $C_{17}H_{27}N$ requires C, 83.19, H, 11.08, N, 5.70%).

18c. M.P. 220–221°C; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 265 (M^+); ^1H NMR δ 1.50 (m, 9H, 4×CH_2 and CH), 1.68 (m, 6H, 3×CH_2), 2.96 (m, 1H, CH_2–Ar), 3.14 (m, 1H, CH_2–Ar), 3.36 (m, 1H, CH–NH_2), 7.28 (m, 4H, Ar–H), 8.42 (brs, 2H, NH_2) (Found: C, 71.96, H, 9.32, N, 5.28. $C_{16}H_{24}ClN$ requires C, 72.29, H, 9.10, N, 5.26%).

18d. M.P. 203–204°C; IR (cm^{-1}) 3410 (N–H); EIMS *m/z* 261 (M^+); ^1H NMR δ 1.46 (m, 9H, 4×CH_2 and CH), 1.76 (m, 6H, 3×CH_2), 2.90 (s, 3H, CH_2–Ar), 3.04 (m, 1H, CH_2–Ar), 3.27 (m, 1H, CH–NH_2), 3.79 (s, 3H, Ar–OCH_3), 6.86 (d, 2H, J=9 Hz, Ar–H), 7.18 (d, 2H, J=9 Hz, Ar–H) (Found: C, 78.19, H, 10.28, N, 5.35. $C_{17}H_{27}NO$ requires C, 78.12, H,10.41, N, 5.36%).

18e. M.P. oil; IR (cm^{-1}) 3400 (N–H); EIMS *m/z* 291 (M^+); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 1.52 (m, 9H, 4×CH_2 and CH), 1.62 (m, 6H, 3×CH_2), 2.38 (m, 1H, CH_2–Ar), 2.78 (m, 1H, CH_2–Ar), 2.86 (m, 1H, CH–NH_2), 3.76 (s, 6H, 2×Ar–OCH_3), 6.79 (m, 3H, Ar–H) (Found: C, 73.88, H, 10.20, N, 4.99. $C_{18}H_{29}NO_2$ requires C, 74.19, H, 10.03, N, 4.81%).

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