ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Design, Synthesis and Evaluation of Novel Benzoxazole, Benzimidazole and Benzthiazole Based Cationic Lipids as Anticancer agents.

Amarnath Velidandi[1], Kranthi Kumar Gadidasu[2], and Srilakshmi V Patri[1]*.

[1]Department of Chemistry, National Institute of Technology, Warangal 506004, Telangana, India.
[2]Department of Biotechnology, Kakatiya University, Warangal 506009, Telangana, India.

ABSTRACT

Herein, we report on the design, synthesis and cytotoxicities of a series of novel benzoxazole, benzimidazole and benzthiazole based cationic lipids (1a-12b) in breast and lung cancer cell lines. The in vitro cytotoxicities of these lipids were evaluated using MTT assay. The results of the present structure-activity investigation convincingly demonstrate that the benzthiazole based lipids with protonated ammonium group in its headgroup region and C14 hydrocarbon chain as anchoring group showed highest anticancer activity among the series of benzoxazole, benzimidazole and benzthiazole based lipids studied presently. The results indicated that the designed systems are quite capable as anti cancer agents.

Keywords: Benzoxazole, Benzimidazole, Benzthiazole, anticancer activity

Corresponding author

INTRODUCTION

The cationic lipids formulated as cationic liposomes have found applications as drug delivery systems against diseases [1-3] and gene transfection [4-6]. In addition, lysophospholipid analogs (LPAs) viz., edelfosine, miltefosine and other amphiphilic molecules are known to exhibit anticancer activities [7-9]. These anticancer lipids known to achieve their cytotoxic activities through various mechanisms [10] viz., membrane perturbation, induction of differentiation, and activation of macrophages resulting in cell cycle arrest and apoptosis possibly through inhibition of important cell growth regulating enzymes like PKC, PLC, and Akt etc., [11-13]. The mitogenic compound lysophosphatidic acid (LPA) has been found to induce rather than inhibit Akt phosphorylation [11], indicating that the ammonium based cationic head group is of crucial importance for the ability of these lipids to inhibit Akt and cause growth inhibition.

The derivatives of benzoxazoles, benzthiazoles and benzimidazoles were studied extensively for their antitumor [14-20] antiviral [21-26] and antimicrobial activities [27-32]. HIV-1 reverse transcriptase and/or DNA gyrase inhibitors [24-26]. The essential attributes for an anticancer drug to have efficient anticancer activity are (i) possess significant cytotoxicity and (ii) uptake by the cancer cell. To incorporate these attributes in a single molecule, taking the impressive biological properties of benzoxazole, benzthiazole and benzimidazole derivatives and cytotoxicities of various ammonium based cationic lipids into consideration, we developed a series of benzothiazole, benzoxazole and benzimidazole based cationic lipids containing two units (i) hetero cyclic group as the head group which is responsible for the anticancer activity and (ii) anchoring groups impart lipid like structure to the molecule, (iii) the cationic charge to enhance the uptake by the cancer cell lines.

MATERIALS AND METHODS

Experimental section

General procedures and materials

Mass spectral data were acquired by using a commercial LCQ ion trap mass spectrometer (ThermoFinnigan, San Jose, CA, USA) equipped with an ESI source. ^{1}H NMR spectra were recorded on a Varian FT 300 MHz NMR Spectrometer. All the starting materials were obtained from Aldrich or Fluka and used as received. The progress of the reaction was monitored by thin-layer chromatography using 0.25-mm silica gel plates. Column chromatography was performed using silica gel (Acme Synthetic Chemicals, India; finer than 200 and 60–120 mesh).

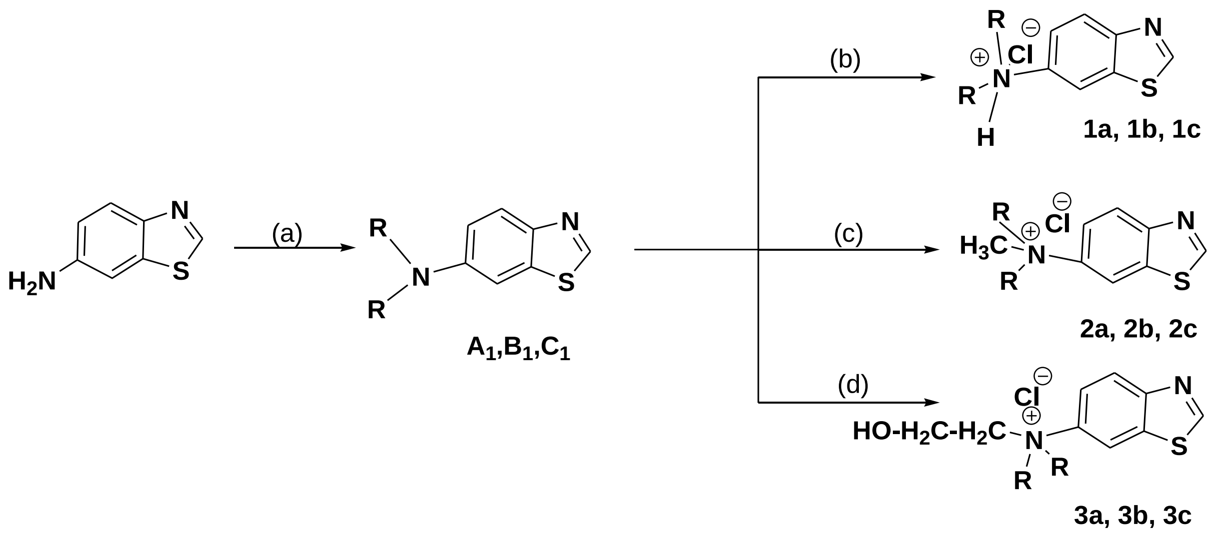
Cytotoxic Assay

Cell Culture: MCF-7 (Breast cancer cell lines) and A549 (Lung cancer cell lines) Cells were grown in monolayer cultures in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% foetal bovine serum, 100 U/ml penicillin, 10 µg/ml streptomycin and maintained at 37 $^{\circ}$C in a 5% CO_2 incubator. The cells were washed with PBS (phosphate buffer saline) and harvested by tripsinization. The cells were plated (10^4 cell/well) in 96-well plates, and incubated for 24h at 37 $^{\circ}$C in the incubator. They were exposed to different concentrations of the lipids synthesised (1a – 12b) for further 72h. At the end of this period MTT assay as described below was performed [33].

MTT Assay

This assay measures the metabolism of 3-(4,5-dimethylthiazol-2yl)-2,5-biphenyl tetrazolium bromide to form an insoluble formazan precipitated by mitochondrial dehydrogenases, which are present only in viable cells. 50µl of MTT solution was added in each well of the 96-well plate and incubated at 37 $^{\circ}$C for 4 h followed by the removal of the medium by aspiration and addition of 200µl DMSO per well. The plate was shaken for 30 sec and the absorbance at 570 nm is measured using ELISA microtiter plate reader. Viability was defined as the ratio (expressed as a percentage) of absorbance of treated cells to untreated cells that served as control [33-34].

Scheme 1

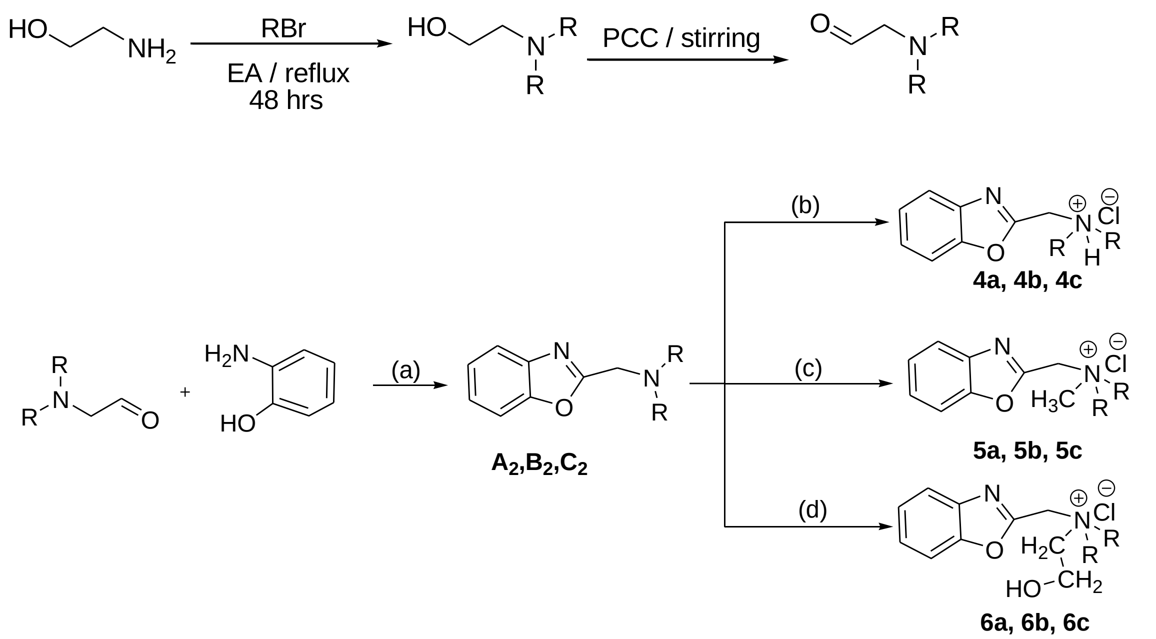


where A $_1$ R = n-$C_{14}H_{29}$; B_1 R = n-$C_{16}H_{33}$; C_1 R = n-$C_{18}H_{37}$

where 1a, 2a, 3a R = n-$C_{14}H_{29}$; 1b, 2b, 3b R = n-$C_{16}H_{33}$; 1c, 2c, 3c: R = n-$C_{18}H_{37}$

(a) Alkyl bromide, K_2CO_3, Ethyl acetate, rt, 24 hrs. (b) 1N HCl, MeOH: $CHCl_3$ (1:1), rt, 12 hrs. (c) MeI, K_2CO_3, Ethyl acetate, Amberlyst anion exchange resin, rt, 12 hrs (d) Chloro ethanol, K_2CO_3, Ethyl acetate, reflux, 4 days.

Scheme 2:



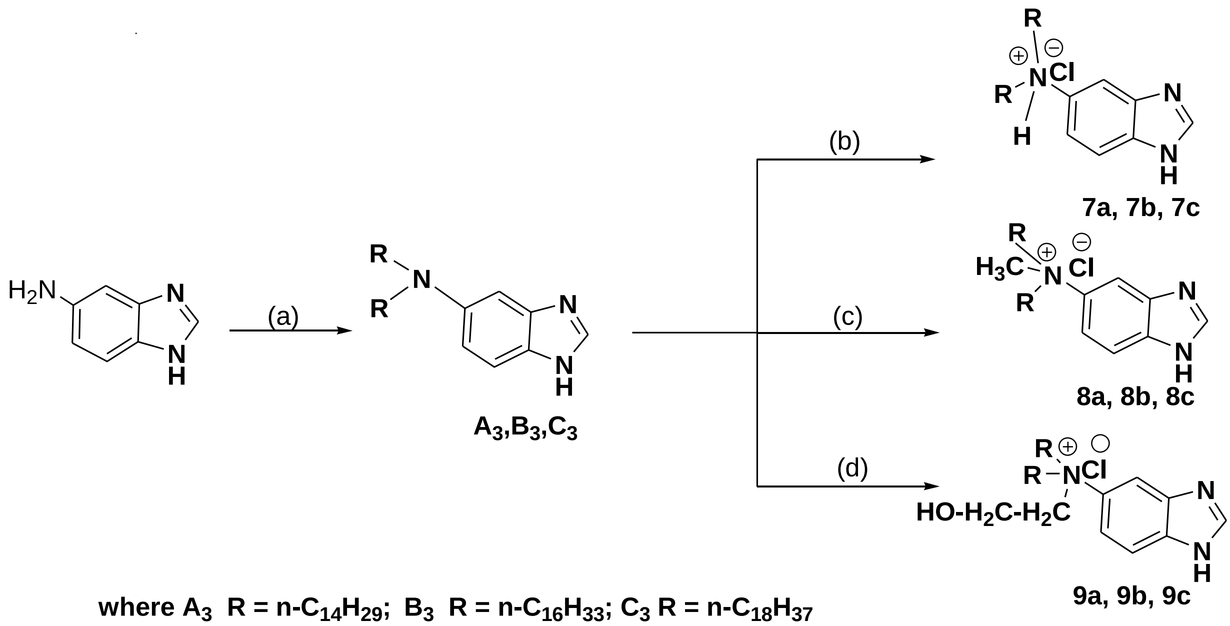
where A $_2$ R = n-$C_{14}H_{29}$; B_2 R = n-$C_{16}H_{33}$; C_2 R = n-$C_{18}H_{37}$

where 4a, 5a, 6a R = n-$C_{14}H_{29}$; 4b, 5b, 6b R = n-$C_{16}H_{33}$; 4c, 5c, 6c: R =n-$C_{18}H_{37}$

ISSN: 0975-8585

(a) $FeCl_3$, Pyridine, EtOH, reflux, 2.5 hrs. (b) 1N HCl, MeOH: $CHCl_3$ (1:1), rt, 12 hrs. (c) MeI, K_2CO_3, Ethylacetate, rt, 12 hrs, Amberlyst anion exchange resin (d) Chloro ethanol, K_2CO_3, Ethylacetate, reflux, 4 days.

Scheme 3

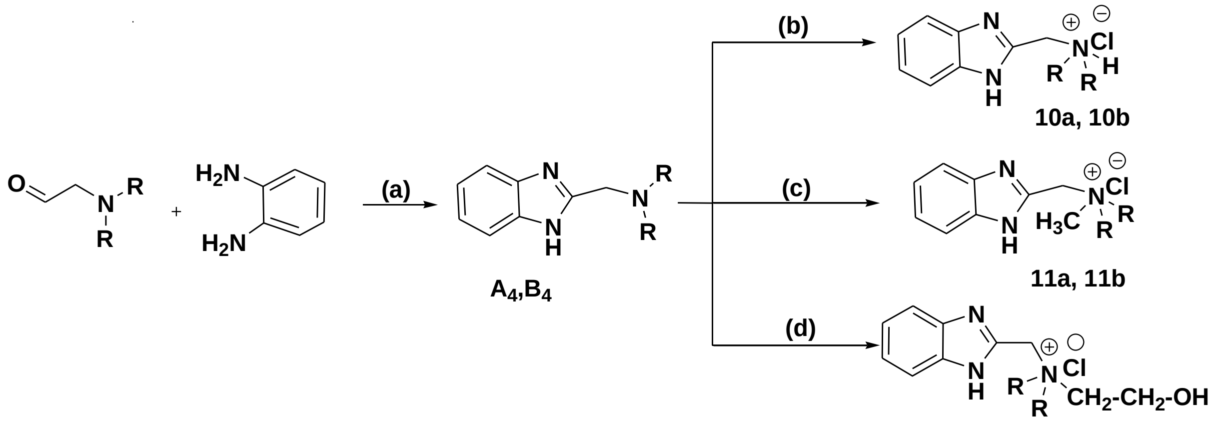


where A_3 R = n-$C_{14}H_{29}$; B_3 R = n-$C_{16}H_{33}$; C_3 R = n-$C_{18}H_{37}$

where 7a, 8a, 9a R = n-$C_{14}H_{29}$; 7b, 8b, 9b R = n-$C_{16}H_{33}$; 7c, 8c, 9c: R = n-$C_{18}H_{37}$

(a) Alkyl bromide, K_2CO_3, Ethyl acetate, rt, 24 hrs. (b) 1N HCl, MeOH: $CHCl_3$ (1:1), rt, 12 hrs. (c) MeI, K_2CO_3, Ethyl acetate, rt, 12 hrs. Amberlyst anion exchange resin (d) Chloro ethanol, K_2CO_3, Ethyl acetate, reflux, 4 days.

Scheme 4



where A_4 R = n-$C_{14}H_{29}$;B_4 R = n-$C_{18}H_{37}$

where 10a, 11a, 12a R = n-$C_{14}H_{29}$; 10b, 11b, 12b: R = n-$C_{18}H_{37}$

(a) Alkyl bromide, K_2CO_3, Ethyl acetate, rt, 24 hrs. (b) 1N HCl, MeOH: $CHCl_3$ (1:1), rt, 12 hrs. (c) MeI, K_2CO_3, Ethyl acetate, rt, 12 hrs. Amberlyst anion exchange resin (d) Chloro ethanol, K_2CO_3, Ethyl acetate, reflux, 4 days.

Synthesis

Scheme 1

***N*, *N*-di(n-tetradecyl)-benzothiazol-6-amine (intermediate A_1):** To a solution of benzothiazol-6-amine (2 g, 13 mmol) in 20 mL of ethyl acetate, alkylbromide (4.4 g, 16.0 mmol) and catalytic amount of K_2CO_3 were added and the reaction mixture was stirred at room temp for 24 hours. The reaction mixture was washed with water (2 X 50ml) and the product is extracted in chloroform (2 X 20ml). The organic layer was dried on anhydrous sodium sulfate, the solvent was evaporated, and the sample was purified by column chromatography using 6-7% ethylacetate in hexane afforded pure intermediate A_1 (3.8 g, 52%, Rf = 0.9, 20% ethylacetate in Hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.2-1.4 [m, 44H, N-CH_2- CH_2- $(CH_2)_{11}$- CH_3], 1.7 [m, 4H, N-CH_2- CH_2-$(CH_2)_{11}$ -CH_3], 3.4 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 7.1 [m, 1H, aromatic], 7.5 [m, 1H, aromatic], 7.9 [d, 1H ,aromatic, *J* = 7.5 Hz], 9.1 [s, 1H, =CH-S-]. Mass spectrum (LCM): m/z 543 [M^+] for $C_{35}H_{62}N_2S$.

***N*, *N*-di(n-hexadecyl)-benzothiazol-6-amine (intermediate B_1):** (5 g, 62%, Rf = 0.9, 20% ethylacetate in Hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.8-0.9 [t, 6H, N-CH_2- CH_2- $(CH_2)_{13}$-CH_3], 1.2-1.3 [m, 52H, N-CH_2- CH_2- $(CH_2)_{13}$- CH_3], 1.6-1.8 [m, 4H, N-CH_2- CH_2-$(CH_2)_{13}$ -CH_3], 3.4 [t, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 7.1 [m, 1H, aromatic], 7.4 [m, 1H, aromatic], 7.9 [d, 1H ,aromatic, *J* = 7.5 Hz], 9.1 [s, 1H, =CH-S-]. Mass spectrum (LCM): m/z 613 [M+15] for $C_{39}H_{70}N_2S$.

***N*, *N*-di(n-octadecyl)-benzothiazol-6-amine (intermediate C_1):** (4.5 g, 51.5%, Rf = 0.9, 20% ethylacetate in Hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2- CH_2- $(CH_2)_{15}$-CH_3], 1.3-1.4 [m, 60H,N-CH_2- CH_2- $(CH_2)_{15}$- CH_3], 1.8-1.9 [m, 4H, N-CH_2- CH_2-$(CH_2)_{15}$ -CH_3], 3.4-3.5 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 7.1 [m, 1H, aromatic] ,7.4 [m, 1H, aromatic], 8.0 [d, 1H ,aromatic, *J* = 7.5 Hz] , 9.1 [s, 1H, =CH-S-]. Mass spectrum (LCM): m/z 672 $[MNH_4]^+$ for $C_{43}H_{78}N_2S$.

(Benzothiazol-6-yl)-di(n-tetradecyl)-ammonium chloride (1a): To a solution of 0.5 g (0.94 mmol) of purified intermediate A1 dissolved in 5 mL of (1:1 v/v) a mixture of chloroform and methanol, added 1 mL of 1 N HCl at 0^0C. The resulting solution was left stirred at room temperature for overnight. Excess HCl was removed by flushing with nitrogen to give the title compound as a hydrochloride salt. Column chromatographic purification using 230-400 mesh size silica gel and 3-4% methanol in chloroform as eluent (0.4 g, yield 80%, Rf = 0.2, 6% methanol in chloroform) yielded the title compound 1a. 1b & 1c also prepared in the same way from the respective intermediate B1 and C1. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.2-1.3 [m, 44H, N-CH_2- CH_2- $(CH_2)_{11}$- CH_3], 1.8 [m, 4H, N-CH_2- CH_2-$(CH_2)_{11}$ -CH_3], 3.4 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 7.8 [d, 1H, aromatic, *J* = 7.2 Hz], 7.9 [s, 1H, aromatic], 8.1 [d, 1H ,aromatic, *J* = 7.5 Hz], 8.3 [s, 1H, -CH_2- CH_2-N*H*-CH_2-CH_2-], 9.1 [s, 1H, =C*H*-S-, aromatic]. Mass spectrum (LCM): m/z 544 [M^+] for $C_{35}H_{63}N_2S^+$. Elemental Analysis: Calculated : %N: 5.15, %C: 77.28, %H: 11.67, %S: 5.89. Observed : %N: 5.21, %C: 77.32, %H: 11.41, %S: 5.99.

(Benzothiazol-6-yl)-di(n-hexadecyl)-ammonium chloride (1b): (0.45 g, yield 90%, Rf = 0.2, 6% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.85 [t, 6H, N-CH_2- CH_2- $(CH_2)_{13}$-CH_3], 1.2-1.3 [m, 52H, N-CH_2- CH_2- $(CH_2)_{13}$- CH_3], 2.0 [m, 4H, N-CH_2- CH_2-$(CH_2)_{13}$ -CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 8.2 [d, 1H, aromatic, *J* = 7.2 Hz], 8.3 [s, 1H, -CH_2- CH_2-N*H*-CH_2- CH_2-], 8.6 [d, 1H ,aromatic, *J* = 7.5 Hz], 8.8 [s, 1H ,aromatic], 9.2 [s, 1H, =CH-S-, aromatic]. Mass spectrum (LCM): m/z 600 [M^+] for $C_{39}H_{71}N_2S^+$. Elemental Analysis: Calculated : %N: 4.67, %C: 78.06, %H: 11.93, %S: 5.34. Observed : %N: 4.78, %C: 78.01, %H: 11.83, %S: 5.25.

(Benzothiazol-6-yl)-di(n-octadecyl)-ammonium chloride (1c): (0.46 g, yield 92%, Rf = 0.2, 6% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2- CH_2- $(CH_2)_{15}$-CH_3], 1.2-1.3 [m, 60H,N-CH_2- CH_2- $(CH_2)_{15}$- CH_3], 1.9 [m, 4H, N-CH_2- CH_2-$(CH_2)_{15}$ -CH_3], 3.3 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 8.2 [d, 1H, aromatic, *J* = 7.2 Hz], 8.3 [s, 1H, - CH_2-N*H*-CH_2-], 8.6 [d, 1H ,aromatic, *J* = 7.5 Hz], 8.8 [s, 1H ,aromatic], 9.2 [s, 1H, =CH-S-]. Mass spectrum (LCM): m/z 656 [M+1] for $C_{43}H_{79}N_2S^+$. Elemental Analysis: Calculated : %N: 4.27, %C: 78.71, %H: 12.14, %S: 4.89. Observed : %N: 4.17, %C: 78.80, %H: 12.05, %S: 4.95.

(Benzothiazol-6-yl)-Methyl-di(n-tetradecyl)-ammonium chloride (2a): In a 25 mL round bottom flask, methyl iodide (1.25 g, 8.8 mmol) was added to intermediate A_1 (2 g, 3.6 mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated and the residue upon column chromatographic purification using 230-400 mesh size silica gel and 4-5% methanol in chloroform as eluent followed by chloride ion exchange (using Amberlyst A-26 with methanol as eluent) afforded the pure 2a (1 g, 48%, Rf = 0.5, 10% methanol in chloroform). 2b & 2c are also synthesised using the above procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.2-1.3 [m, 44H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.5-1.6 [m, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.7 [s, 3H, N-CH_3] ,8.2 [m, 1H, aromatic], 8.6 [m, 1H, aromatic], 8.8 [m, 1H, aromatic], 9.2 [s, 1H, =CH-S-] Mass spectrum (LCM): m/z 557 [M^+] for $C_{36}H_{65}N_2S^+$. Elemental Analysis: Calculated : %N: 5.02, %C: 77.49, %H: 11.74, %S: 5.75. Observed : %N: 5.13, %C: 77.60, %H: 11.65, %S: 5.61.

(Benzothiazol-6-yl)-Methyl-di(n-hexadecyl)-ammonium chloride (2b): (1.2 g, 58%, Rf = 0.5, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9-1.0 [t, 6H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.3-1.4 [m, 52H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.6 [m, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.1-3.2 [t, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.7 [s, 3H, N-CH_3], 8.1 [m, 1H, aromatic], 8.5 [m, 1H, aromatic], 8.7 [m, 1H, aromatic], 9.2 [s, 1H, =CH-S-]. Mass spectrum (LCM): m/z 614 [M^+] for $C_{40}H_{73}N_2S^+$. Elemental Analysis: Calculated: %N: 4.56, %C: 78.23, %H: 11.98, %S: 5.22. Observed : %N: 4.48, %C: 78.35, %H: 11.86, %S: 5.35.

(Benzothiazol-6-yl)-Methyl-di(n-octadecyl)-ammonium chloride (2c): (1.3 g, 63%, Rf = 0.5, 10% methanol in chloroform) ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.1-1.3 [m, 60H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.7 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.7 [s, 3H, N-CH_3], 8.2 [m, 1H, aromatic], 8.5 [m, 1H, aromatic], 8.7 [m, 1H, aromatic], 9.2 [s, 1H, =CH-S-]. Mass spectrum (LCM): m/z 671 [M+1] for $C_{44}H_{81}N_2S^+$. Elemental Analysis: Calculated: %N: 4.18, %C: 78.85, %H: 12.18, %S: 4.78. Observed : %N: 4.27, %C: 78.65, %H: 12.35, %S: 4.69.

(Benzothiazol-6-yl)-(2-hydroxy-ethyl)-di(n-tetradecyl)-ammonium chloride (3a): The intermediate tertiary amine (A_1) (2 g, 3.6 mmol) was taken in a 25 mL round-bottomed flask and chloroethanol (0.35 g, 4.4 mmol) was added to it. After refluxing the reaction mixture for four days, the solvent was removed on a rotary evaporator. The column chromatographic purification of the resulting residue using 230-400 mesh size silica and 4-5% methanol in chloroform as eluent afforded the title compound as a quaternary chloride salt 3a, (1.3 g, 60% yield, R_f = 0.5, 10% methanol in chloroform). 3b & 3c are also prepared using the same procedure described above. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.3-1.4 [m, 44H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.7-1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.1-3.2 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.5-3.6[t, 2H, N-CH_2-CH_2-OH], 3.8-3.9 [t, 2H, N-CH_2-CH_2-OH] , 4.5 [br, 1H, N-CH_2-CH_2-OH] ,8.2 [m, 1H, aromatic], 8.5-8.6 [m, 1H, aromatic], 8.9 [m, 1H, aromatic], 9.3 [s, 1H, =CH-S-]. Mass spectrum (TOFMS): m/z 589 [M+1] for $C_{37}H_{67}OSN_2^+$. Elemental Analysis: Calculated: %N: 4.76, %C: 75.58, %H: 11.48, %S: 5.45. Observed : %N: 4.65, %C: 75.47, %H: 11.59, %S: 5.55.

(Benzothiazol-6-yl)-(2-hydroxy-ethyl)-di(n-hexadecyl)-ammonium chloride (3b): (1.2 g, 58 % yield, R_f = 0.5, 10% methanol in chloroform. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.3-1.4 [m, 52H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.1-3.2 [t, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.6-3.7 [t, 2H, N-CH_2-CH_2-OH], 3.9 [t, 2H, N-CH_2-CH_2-OH], 4.6 [br, 1H, N-CH_2-CH_2-OH], 8.2 [m, 1H, aromatic], 8.6 [m, 1H, aromatic], 8.9 [m, 1H, aromatic], 9.3 [s, 1H, =CH-S-]. Mass spectrum (TOFMS): m/z 644 [M^+] for $C_{41}H_{75}OSN_2^+$. Elemental Analysis: Calculated: %N: 4.35, %C: 76.45, %H: 11.74, %S: 4.98. Observed : %N: 4.44, %C: 76.55, %H: 11.65, %S: 4.87.

(Benzothiazol-6-yl)-(2-hydroxy-ethyl)-di(n-octadecyl)-ammonium chloride (3c): (1.2 g, 56% yield, R_f = 0.5, 10% methanol in chloroform. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm0.8-0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.3-1.4 [m, 60H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.8-1.9 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.1 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.5 [t, 2H, N-CH_2-CH_2-OH], 3.9 [t, 2H, N-CH_2-CH_2-OH] , 4.5 [br, 1H, N-CH_2-CH_2-OH], 8.2 [m, 2H, aromatic], 8.5 [m, 1H, aromatic], 8.9 [m, 1H, aromatic], 9.3 [s, 1H, =CH-S-]. Mass spectrum (TOFMS): m/z 717 $[MNH_4]^+$ for $C_{45}H_{83}OS$ N_2^+. Elemental Analysis: Calculated: %N: 4.00, %C: 77.19, %H: 11.95, %S: 4.58. Observed : %N: 4.09, %C: 77.30, %H: 11.84, %S: 4.49.

Scheme 2

Synthesis of 2-*N,N*-di(n-tetradecyl) amino-ethanol : To a solution of 2-aminoethanol (0.5 g, 8.1 mmol) in 20 ml of ethylacetate, 1-bromotetradecane (5.4 g, 19.6 mmol) and catalytic amount of potassium carbonate were added and refluxed it for 48 h. The solvent was evaporated under reduced pressure and the residue was taken in chloroform and washed with water 2 X 50 ml. The organic layer was separated and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to obtain 5.8 g (yield 64% Rf = 0.4, 50:50

ethylacetate:hexane (v/v)) of 2-ditetradecylamino-ethanol following the same procedure for 2-di -hexa & di octa decyl amino alcohols .

Synthesis of 2-*N,N*-di(n-hexadecyl) amino-ethanol: 6.2 g (yield 62% Rf = 0.4, 50:50 ethylacetate:hexane (v/v)) of 2-dihexadecylamino-ethanol.

Synthesis of 2-*N,N*-di(n-octadecyl) amino-ethanol: 7.3 g (yield 65% Rf = 0.4, 50:50 ethylacetate:hexane (v/v)) of 2-dioctadecylamino-ethanol.

Synthesis of 2-*N,N*-di(n-tetradecyl) amino-acetaldehyde: To a solution of Pyridinium chloro chromate (0.94 g, 4.4 mmol) dissolved in 20 mL of anhydrous DCM added in portions a solution of 2-ditetradecylamino-ethanol (2 g, 4.4 mmol) in 10 mL of anhydrous DCM and stirred for one and half hour. To the reaction mixture 50 mL of dry ether was added and the supernatant solution decanted from black gum. The residue was extracted thoroughly with 3 X 50 mL of anhydrous ether and the combined organic solvents were dried over anhydrous sodium sulphate and the solvent removed by evaporation under reduced pressure to obtain 0.95 g (yield 47%, R_f =0.5, 50% ethylacetate in hexane) of ditetradecylamino-acetaldehyde in the same way di hexa & diocta decylamino-acetaldehyde are prepared .

Synthesis of 2-*N*, *N*-di(n-hexadecyl) amino-acetaldehyde: 0.98 g (yield 49% R_f =0.5, 50% ethylacetate in hexane) of dihexadecylamino-acetaldehyde.

Synthesis of 2-*N*, *N*-di(n-octadecyl) amino-acetaldehyde: 0.96 g (yield 48% R_f =0.5, 50% ethylacetate in hexane) of di hexadecylamino-acetaldehyde.

Synthesis of *N*-(benzoxazol-2-yl) methyl)-*N*-n-tetradecyltetradecan-1-amine (A_2): To a solution of 2-*N*, *N*-ditetradecylamino-acetaldehyde (2 g, 4.4 mmol) dissolved in 20 mL of absolute ethanol, 2-amino phenol (0.483 g, 4.4 mmol), 1mL of pyridine and catalytic amount of ferric chloride added. The reaction mixture was refluxed for two and half hour. The residue was taken in chloroform and washed with water 2 X 50 ml. The organic layer was separated and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure the sample was purified by column chromatography using 100-200 mesh size silica gel and 10-12% of ethylacetate in Hexane as eluent to obtain 1.3 g (yield 54% Rf = 0.8, 50% ethylacetate in hexane) of A_2. B_2 & C_2 were prepared using the same procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9-1.0 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.2-1.5 [m, 48H, N-CH_2- $(CH_2)_{12}$- CH_3], 2.3-2.4 [t, 4H, N-CH_2-(CH_2)$_{12}$-CH_3], 3.7 [s, 2H, N-CH_2-C=], 7.3 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 558 $[MNH_4]^+$ for $C_{36}H_{64}N_2O$.

Synthesis of *N*-(benzoxazol-2-yl) methyl)-*N*-n-hexadecylhexadecan-1-amine (B_2): 1.38 g (yield 58% Rf = 0.8, 50% ethylacetate in hexane) of B_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9-1.0 [t, 6H, N-CH_2-$(CH_2)_{14}$-CH_3], 1.2-1.5 [m, 56H, N-CH_2- $(CH_2)_{14}$- CH_3], 2.3-2.4 [t, 4H, N-CH_2-(CH_2)$_{14}$-CH_3], 3.7 [s, 2H, N-CH_2-C=], 7.4 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 598 [M+1] for $C_{40}H_{72}N_2O$.

Synthesis of *N*-(benzoxazol-2-yl) methyl)-*N*-n-octadecyloctadecan-1-amine (C_2): 1.15 g (yield 49% Rf = 0.8, 50% ethylacetate in hexane) of C_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{16}$-CH_3], 1.2-1.4 [m, 64H, N-CH_2- $(CH_2)_{16}$- CH_3], 2.3 [t, 4H, N-CH_2-(CH_2)$_{16}$-CH_3], 3.7 [s, 2H, N-CH_2-C=], 7.4 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 655 [M+2] for $C_{44}H_{80}N_2O$.

Benzoxazol-2-yl methyl-di-n-tetradecyl-ammonium chloride (4a): 0.5 g (0.92 mmol) of purified A_2 was dissolved in 5 mL of (1:1 v/v) a mixture of chloroform and methanol, and 1 mL of 1 N HCl was added at 0^0C. The resulting solution was left stirred at room temperature for overnight. Excess HCl was removed by flushing with nitrogen to give the title compound as a hydrochloride salt. Column chromatographic purification using 230-400 mesh size silica gel and 3-4% methanol in chloroform as eluent to obtain 0.3 g (yield 59%, Rf = 0.2, 6% methanol in chloroform) of 4a in the same way 4b & 4c were prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.0 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.2-1.4 [m, 48H, N-CH_2- (CH_2)$_{12}$- CH_3], 2-2.2 [t, 4H, N-CH_2-(CH_2)$_{12}$-CH_3], 3.7 [s, 2H, N-CH_2-C=], 7.4 [s, 4H, aromatic], 7.6 [s, 1H, -CH_2-NH-CH_2]. Mass spectrum (LCM): m/z 542 $[M^+]$ for $C_{36}H_{65}N_2O^+$. Elemental Analysis: Calculated : %N: 5.17, %C: 79.79, %H: 12.09. Observed : %N: 5.20, %C: 79.85, %H: 12.01.

Benzoxazol-2-ylmethyl-di-n-hexadecyl-ammonium chloride (4b): 0.29 g (yield 57%, Rf = 0.2, 6% methanol in chloroform) of 4b. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9-1.0 [t, 6H, N-CH_2-$(CH_2)_{14}$-CH_3], 1.2-1.4 [m, 56H, N-CH_2-

ISSN: 0975-8585

(CH_2)$_{14}$- CH_3], 2.3-2.5 [t, 4H, N-CH_2-(CH_2)$_{14}$-CH_3], 3.8 [s, 2H, N-CH_2- Ar], 7.4 [m, 4H, aromatic], 7.6 [s, 1H, -CH_2-NH-CH_2]. Mass spectrum (LCM): m/z 598 [M^+] for $C_{40}H_{73}N_2O^+$. Elemental Analysis: Calculated : %N: 4.68, %C: 80.34, %H: 12.30. Observed : %N: 4.64, %C: 80.45, %H: 12.15.

Benzoxazol-2-ylmethyl-di-n-octadecyl-ammonium chloride (4c): 0.26 g (yield 51%, Rf = 0.2, 6% methanol in chloroform) of 4c. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.0 [t, 6H, N-CH_2-(CH_2)$_{16}$-CH_3], 1.2-1.4 [m, 64H, N-CH_2-(CH_2)$_{16}$- CH_3], 2.4 [t, 4H, N-CH_2-(CH_2)$_{16}$-CH_3], 3.8 [s, 2H, N-CH_2-C=], 7.5 [m, 4H, aromatic], 7.6 [s, 1H, -CH_2-NH-CH_2]. Mass spectrum (LCM): m/z 654 [M+1] for $C_{44}H_{81}N_2O^+$. Elemental Analysis: Calculated : %N: 4.28, %C: 80.79, %H: 12.48. Observed : %N: 4.30, %C: 80.65, %H: 12.60.

Benzoxazol-2-ylmethyl-methyl-dioctadecyl-ammonium (5a): In a 25 mL round bottom flask, methyl iodide (0.28 g, 2 mmol) was added to intermediate A_2 (0.5 g, 0.92 mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated and the residue upon column chromatographic purification using 230-400 mesh size silica gel and 4-5% methanol in chloroform as eluent followed by chloride ion exchange (using Amberlyst A-26 with methanol as eluent)afforded the pure 5a (0.25 g, 49%, Rf = 0.6, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 1.2-1.4 [m, 44H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 1.9 [m, 4H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 3.5 [s, 3H, N-CH_3], 4.5 [s, 2H, 1N(-CH_2)-C=], 7.4 [s,4H, aromatic]. Mass spectrum (LCM): m/z 557 [M+1] for $C_{37}H_{67}N_2O^+$. Elemental Analysis: Calculated : %N: 5.04, %C: 79.94, %H: 12.15. Observed : %N: 5.05, %C: 79.85, %H: 12.25.

Benzoxazol-2-ylmethyl-methyl-dihexadecyl-ammonium (5b): (0.2g, 39%, Rf = 0.6, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.0 [t, 6H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 1.2-1.4 [m, 52H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 1.9 [m, 4H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 3.5 [s, 3H, N-CH_3], 4.5 [s, 2H, 1N(-CH_2)-C=], 7.4 [s,4H, aromatic]. Mass spectrum (LCM): m/z 613 [M+1] for $C_{41}H_{75}N_2O^+$. Elemental Analysis: Calculated : %N: 4.58, %C: 80.46, %H: 12.35. Observed : %N: 4.60, %C: 80.35, %H: 12.47.

Benzoxazol-2-ylmethyl-methyl-dioctadecyl-ammonium (5c): (0.21 g, 41%, Rf = 0.6, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 1.2-1.4 [m, 60H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 1.9 [m, 4H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 3.5 [s, 3H, N-CH_3], 4.5 [s, 2H, 1N(-CH_2)-C=], 7.4 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 668 [M^+] for $C_{45}H_{83}N_2O^+$. Elemental Analysis: Calculated : %N: 4.19, %C: 80.89, %H: 12.52. Observed : %N: 4.25, %C: 80.54, %H: 12.86.

Benzoxazol-2-ylmethyl-(2-hydroxy-ethyl)-di-n-tetradecyl-ammonium chloride (6a): The N-(benzoxazol-2-yl) methyl)-N-tetradecyltetradecan-1-amine (0.5 g, 0.92 mmol) was taken in a 25 mL round-bottomed flask and chloroethanol (0.08 g, 1 mmol) was added to it. After refluxing the reaction mixture for four days, the solvent was removed on a rotary evaporator. The column chromatographic purification of the resulting residue using 230-400 mesh size silica and 4-5% (v/v) methanol in chloroform as eluent afforded the title compound as a quaternary chloride salt (0.2 g, 37% yield, R_f = 0.5, 10% methanol in chloroform) 6b & 6c were prepared in the same way. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.8-0.9 [t, 6H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 1.2-1.3 [m, 44H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 1.7-1.8 [m, 4H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-(CH_2)$_{11}$-CH_3], 3.3-3.4 [t, 2H, N-CH_2-CH_2-OH], 3.9 [t, 2H, N-CH_2-CH_2-OH], 4.4 [br, 1H, N-CH_2-CH_2-OH], 4.5 [s, 2H, N-CH_2-C=], 7.3 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 586 [M^+] for $C_{38}H_{69}N_2O_2^+$. Elemental Analysis: Calculated : %N: 4.78, %C: 77.89, %H: 11.87. Observed : %N: 4.90, %C: 77.75, %H: 11.80.

Benzoxazol-2-ylmethyl-(2-hydroxy-ethyl)-di-n-hexadecyl-ammonium chloride (6b): (0.22 g, 41% yield, R_f = 0.5, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 1.2-1.4 [m, 52H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 1.8 [m, 4H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-(CH_2)$_{13}$-CH_3], 3.4-3.5 [t, 2H, N-CH_2-CH_2-OH], 3.9 [t, 2H, N-CH_2-CH_2-OH], 4.4 [br, 1H, N-CH_2-CH_2-OH], 4.5 [s, 2H, N-CH_2-C=], 7.3 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 643 [M+1] for $C_{42}H_{77}O_2N_2^+$. Elemental Analysis: Calculated : %N: 4.36, %C: 78.57, %H: 12.09. Observed : %N: 4.55, %C: 78.38, %H: 12.15.

Benzoxazol-2-ylmethyl-(2-hydroxy-ethyl)-di-n-octadecyl-ammonium chloride (6c): (0.24 g, 45% yield, R_f = 0.5, 10% methanol:chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm0.9 [t, 6H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 1.2-1.4 [m, 60H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 1.8 [m, 4H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 3.2[t, 4H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 3.5[t, 2H, N-CH_2-CH_2-OH], 3.9 [t, 2H, N-CH_2-CH_2-OH] , 4.4 [br, 1H, N-CH_2-CH_2-OH] , 4.5 [s, 2H, N-CH_2-C=] ,7.3 [s, 4H, aromatic]. Mass spectrum (LCM): m/z 699 [M+1] for $C_{46}H_{85}O_2 N_2^+$. Elemental Analysis: Calculated : %N: 4.01, %C: 79.13, %H: 12.27. Observed : %N: 4.08, %C: 79.05, %H: 12.35.

Scheme 3

***N*, *N*-di-n-tetradecyl benzimidazol-5-amine (A_3)** : To a solution of benzimidazol-5-amine (2 g, 15 mmol) in 20mL of ethyl acetate , n-tetradecylbromide (10.41 g, 37.5 mmol), and catalytic amount of K_2CO_3 were added and the reaction mixture was stirred at room temp for 24 hours. The reaction mixture was poured in to water, to this chloroform was added and extracted the product in Chloroform. The organic layer was dried on anhydrous sodium sulfate, the solvent was evaporated, and the residue was purified by column chromatography using 100-200 mesh size silica gel and 9-10% of ethylacetate in Hexane as eluent to afford the intermediate tertiary amine A_3. (3.31 g, 42%, Rf = 0.9, 15% ethylacetate in hexane). B_3 and C_3 were also prepared as discussed above. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.83-0.84 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 0.85 [m, 4H, N-CH_2-$(CH_2)_{11}$-CH_2-CH_3], 1.23-1.39 [m, 40H, N-CH_2- CH_2-$(CH_2)_{10}$ -CH_2-CH_3], 1.78-1.82 [m, 4H, N-CH_2-CH_2-$(CH_2)_{10}$-CH_2-CH_3], 4.31-4.34 [t, 4H, N-C*H2*] , 7.86[m 1H, aromatic], 7.88 [m, 1H, aromatic], 8.17[m, 1H ,aromatic], 8.19 [s,1H, aromatic] 8.55-8.57 [s, 1H, -NH, D_2O, exchangeable].ESIMS: m/z: 527 [M+1] for $C_{35}H_{63}N_3$.

***N*,*N*-di-n-hexadecyl benzimidazol-5-amine (B_3):** (3.93 g, 45%, Rf = 0.9, 15% ethylacetate in Hexane) the intermediate tertiary amine**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.8-0.9 [t, 6H, N-CH_2-$(CH_2)_{14}$-CH_3], 0.9-1.0 [m, 4H, N-CH_2-$(CH_2)_{13}$-CH_2-CH_3], 1.2-1.4 [m, 48H, N-CH_2- CH_2-(CH_2)$_{12}$ -CH_2-CH_3], 1.6-1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{12}$-CH_2-CH_3], 4.1-4.2 [t, 4H, N-C*H2*] , 7.7[m, 1H, aromatic], 7.9 [m, 1H, aromatic], 8.1[m, 1H ,aromatic] , 8.2-8.3 [s,1H, aromatic] 8.5-8.6 [s, 1H, -NH, D_2O, exchangeable]. ESIMS:m/z:597 [M+15] for $C_{39}H_{71}N_3$.

***N*,*N*-di-n-octadecylbenzimidazol-5-amine (C_3):** (4.98 g, 52%, Rf = 0.9, 15% ethylacetate in Hexane) the intermediate tertiary amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.8 [t, 6H, N-CH_2-$(CH_2)_{16}$-CH_3], 0.9 [m, 4H, N-CH_2-$(CH_2)_{15}$-CH_2-CH_3], 1.1-1.3 [m, 56H, N-CH_2- CH_2-(CH_2)$_{14}$ -CH_2-CH_3], 1.4-1.5 [m, 4H, N-CH_2-CH_2-$(CH_2)_{14}$-CH_2-CH_3], 4.2-4.4 [t, 4H, N- CH_2], 7.6-7.7[m, 1H, aromatic], 7.8-7.9 [m, 1H, aromatic], 8.1[m, 1H ,aromatic], 8.3 [s,1H, aromatic], 8.5[s, 1H, -NH, D_2O, exchangeable]. ESIMS: m/z: 663 [M+Na] for $C_{43}H_{79}N_3$.

(Benzimidazol-5-yl)-di-n-tetradecyl-ammonium chloride (7a): 0.5 g (0.94 mmol) of purified A_3 was dissolved in 5mL of (1:1 v/v) a mixture of chloroform and methanol, and 1 mL of 1 N HCl was added at 0^0C. The resulting solution was left stirred at room temperature for overnight. Excess HCl was removed by flushing with nitrogen to give the title compound as a hydrochloride salt. Column chromatographic purification using 230-400 mesh size silica gel and 3-4% (v/v) methanol/chloroform as eluent yielded the compound 7a. (0.45 g, yield 90%, Rf = 0.2, 6% methanol in chloroform). 7b &7c were prepared using the same procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.96 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.30 [m, 44H, N-CH_2- CH_2-(CH_2)$_{11}$-CH_3], 1.9 [m, 4H, N-CH_2-CH_2-$(CH_2)_{10}$-CH_2-CH_3], 3.8 [t, 4H, N-C*H2*] , 7.8[m 1H, aromatic], 8.1-8.2 [m, 2H, aromatic], 8.3 [s, 1H ,aromatic] , 8.4 [s,1H, -NH-] 8.5 [s, 1H, Ar-NH, D_2O, exchangeable]. ESIMS: m/z: 527 [M^+] for $C_{35}H_{64}N_3^+$. Elemental Analysis: Calculated : %N: 7.97, %C: 79.78, %H: 12.24. Observed : %N: 7.92, %C: 79.25, %H: 12.80.

(Benzimidazol-5-yl)-di-n-hexadecyl-ammonium chloride (7b): (0.42 g, yield 84%, Rf = 0.2, 6% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{14}$-CH_3], 1.3 [m, 52H, N-CH_2- CH_2-(CH_2)$_{13}$-CH_3], 1.6-1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{12}$-CH_2-CH_3], 3.9-4.1 [t, 4H, N-C*H2*] , 7.9[s, 1H, aromatic], 8.1 [s, 2H, aromatic], 8.3 [s,1H, aromatic] , 8.4 [s,1H, -N*H*-],8.5 [s, 1H, Ar-N*H*, D_2O, exchangeable]. ESIMS:m/z:584 [M^++1] for $C_{39}H_{72}N_3^+$. Elemental Analysis: Calculated : %N: 7.21, %C: 80.34, %H: 12.45. Observed : %N: 7.31, %C: 80.54, %H: 12.35.

(Benzimidazol-5-yl)-di-n-octadecyl-ammonium chloride (7c): (0.40 g, yield 80%, Rf = 0.2, 6% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{16}$-CH_3], 1.2-1.3 [m, 60H, N-CH_2-CH_2-(CH_2)$_{15}$-CH_3], 2.0 [m, 4H, N-CH_2-CH_2-$(CH_2)_{14}$-CH_2-CH_3], 3.8 [t, 4H, N- CH_2] , 7.9 [s, 1H, aromatic], 8.1-8.2 [m, 2H, aromatic], 8.3 [s,1H, aromatic], 8.4 [s,1H, -N*H*-], 8.5 [s, 1H, Ar-N*H*, D_2O, exchangeable]. ESIMS: m/z: 639 [M^+] for $C_{43}H_{80}N_3^+$. Elemental Analysis: Calculated : %N: 6.57, %C: 80.81, %H: 12.62. Observed : %N: 6.85, %C: 80.55, %H: 12.58.

(Benzimidazol-5-yl)-Methyl-di-n-tetradecyl-ammonium chloride (8a): In a 25 mL round bottom flask, methyl iodide (0.29 g, 2 mmol) was added to intermediate A_3 (0.5 g, 0.95 mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated and the residue upon column chromatographic purification using 230-400 mesh size silica gel and 4-5% methanol in chloroform as eluent followed by chloride ion exchange (using Amberlyst A-26 with methanol as eluent) afforded the pure 8a (0.41 g, 81%, Rf = 0.6, 10% methanol in chloroform). 8b & 8c were also prepared as described above. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9-1.0 [t, 6H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.3-1.5 [m, 44H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.7-1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.9 [s, 3H, N-CH_3], 7.9 [m, 1H, aromatic], 8.0 [m, 1H, aromatic], 8.1 [s, 1H, aromatic], 8.4 [m, 1H, aromatic]], 8.6 [s, 1H, -NH, D_2O, exchangeable]. ESIMS: m/z :557 $[MNH_4]^+$ for $C_{36}H_{66}N_3^+$. Elemental Analysis: Calculated: %N: 7.77, %C: 79.93, %H: 12.30. Observed : %N: 7.85, %C: 79.80, %H: 12.31.

(Benzimidazol-5-yl)-Methyl-di-n-hexadecyl-ammonium chloride (8b): (0.384 g, 75%, Rf = 0.6, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9-1.0 [t, 6H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.2-1.4 [m, 52H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.7 [m, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.9 [s, 3H, N-CH_3],7.9-8.0 [m, 2H, aromatic], 8.1 [s, 1H, aromatic], 8.3 [m, 1H, aromatic] , 8.6 [s, 1H, -NH, D_2O, exchangeable]. ESIMS:m/z:595 [M-1] for $C_{40}H_{74}N_3^+$. Elemental Analysis: Calculated: %N: 7.04, %C: 80.47, %H: 12.49. Observed : %N: 7.05, %C: 80.35, %H: 12.55.

(Benzimidazol-5-yl)-Methyl-di-n-octadecyl-ammonium chloride (8c): (0.4 g, 75%, Rf = 0.6, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.3 [m, 60H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.7 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.9 [s, 3H, N-CH_3] ,7.9 [m, 1H, aromatic], 8.0 [m, 1H, aromatic], 8.1 [s, 1H, aromatic], 8.3 [m, 1H, aromatic] , 8.6 [s, 1H, -NH, D_2O, exchangeable]. ESIMS:m/z:652 $[M^+]$ for $C_{44}H_{82}N_3^+$. Elemental Analysis: Calculated: %N: 6.43, %C: 80.91, %H: 12.65. Observed : %N: 6.35, %C: 80.85, %H: 12.70.

(Benzimidazol-5-yl)-(2-hydroxy-ethyl)-di-n-tetradecyl-ammonium chloride (9a): The intermediate tertiary amine (A_3) (0.5 g, 0.95 mmol) was taken in a 25 mL round-bottomed flask and chloroethanol (0.09g, 1.1mmol) was added to it. After refluxing the reaction mixture for four days, the solvent was removed on a rotary evaporator. The column chromatographic purification of the resulting residue using 230-400 mesh size silica and 4-5% (v/v) methanol in chloroform as eluent afforded the title compound as a quaternary chloride salt, 9a (0.35 g, 65% yield, R_f = 0.5, 10% methanol in chloroform). 9b & 9c were also prepared as discussed above. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.8-0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.2-1.4 [m, 44H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.7-1.9 [m, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.4 [d, 2H, N-CH_2-CH_2-OH], 4.0 [m, 2H, N-CH_2-CH_2-OH] , 4.5 [br, 1H, N-CH_2-CH_2-OH], 7.8-7.9 [m, 2H, aromatic], 8.2 [s, 1H, aromatic], 8.4 [m, 1H, aromatic], 8.6 [s, 1H, -NH, D_2O, exchangeable]. (MS.LCM): m/z: 571 $[M^+]$ for $C_{37}H_{68}N_3O^+$. Elemental Analysis: Calculated: %N: 7.36, %C: 77.83, %H: 12.00. Observed : %N: 7.31, %C: 77.80, %H: 12.05.

(Benzimidazol-5-yl)-(2-hydroxy-ethyl)-di-n-hexadecyl-ammonium chloride (9b): (0.40 g, 80% yield, R_f = 0.5, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.2-1.3 [m, 52H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 1.6 [m, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.1-3.2[t, 4H, N-CH_2-CH_2-$(CH_2)_{13}$-CH_3], 3.4[d, 2H, N-CH_2-CH_2-OH], 4.0-4.1 [m, 2H, N-CH_2-CH_2-OH] , 4.5 [br, 1H, N-CH_2-CH_2-OH] ,7.9 [m, 2H, aromatic], 8.2 [s, 1H, aromatic], 8.4 [m, 1H, aromatic], 8.6 [s, 1H, -NH, D_2O, exchangeable]. (MS.LCM): m/z 650 $[M^+$+Na] for $C_{41}H_{76}N_3O^+$. Elemental Analysis: Calculated: %N: 6.7, %C: 78.53, %H: 12.22. Observed : %N: 6.9, %C: 78.50, %H: 12.25.

(Benzimidazol-5-yl)-(2-hydroxy-ethyl)-di-n-octadecyl-ammonium chloride (9c): (0.43 g, 81% yield, R_f = 0.5, 10% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.2-1.4 [m, 60H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.5-1.6 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.1-3.2 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.4 [d, 2H, N-CH_2-CH_2-OH], 4.2 [m, 2H, N-CH_2-CH_2-OH] , 4.4-4.5 [br, 1H, N-CH_2-CH_2-OH] ,7.9 [m, 2H, aromatic], 8.1 [s, 1H, aromatic], 8.4 [m, 1H, aromatic], 8.6 [s, 1H, -NH, D_2O, exchangeable]. (MS.LCM): m/z 682 $[M^+]$ for $C_{45}H_{84}N_3O^+$. Elemental Analysis: Calculated: %N: 6.15, %C: 79.11, %H: 12.39. Observed : %N: 6.2, %C: 79.25, %H: 12.23.

Scheme 4

***N*-(benzimidazol-2-yl) methyl)-*N*-n-tetradecyl-n-tetradecan-1-amine (A_4):** To a solution of 2-*N*,*N*-ditetradecylamino-acetaldehyde (2 g, 4.4 mmol) dissolved in 20 mL of absolute ethanol, benzene-1,2-diamine(0.478 g, 4.4 mmol),1mL of piperidine and catalytic amount of ferric chloride added. The reaction mixture was refluxed for two and half hour. The residue was taken in chloroform and washed with water 2 X 50 ml. The organic layer was separated and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure the sample was purified by column chromatography using 100-200 mesh size silica gel and 10-12% of ethylacetate in Hexane as eluent to obtain 1.4g (yield 58% Rf = 0.8, 50% ethylacetate in hexane) of A_4 , in similar way B_4 was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.2-1.4[m, 48H, N-CH_2- $(CH_2)_{12}$- CH_3], 2.4 [m, 4H, N-CH_2-$(CH_2)_{12}$-CH_3], 3.6 [s, 2H, N-CH_2-C=], 7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic],8.7-8.8[br,1H, NH]. Mass spectrum (LCM): m/z 541 [M+1] for $C_{36}H_{65}N_3$.

***N*-(benzimidazol -2-yl) methyl)-*N*-n-octadecyl-n-octadecan-1-amine (B_4)**: 1.1 g (yield 47% Rf = 0.8, 50% ethylacetate in hexane).^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{16}$-CH_3], 1.2-1.4[m, 64H, N-CH_2-$(CH_2)_{16}$- CH_3], 2.4 [m, 4H, N-CH_2-$(CH_2)_{16}$-CH_3], 3.6 [s, 2H, N-CH_2-C=], 7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic],8.7-8.8[br,1H, NH]. Mass spectrum (LCM): m/z 653 [M+1] for $C_{44}H_{81}N_3$.

(1H-Benzoimidazol-2-ylmethyl)-di-n-tetradecyl-ammonium chloride (10a): 2 g (3.7 mmol) of purified A_4 was dissolved in 5mL of (1:1 v/v) a mixture of chloroform and methanol, and 1 mL of 1 N HCl was added at 0^0C. The resulting solution was left stirred at room temperature for overnight. Excess HCl was removed by flushing with nitrogen to give the title compound as a hydrochloride salt. Column chromatographic purification using 230-400 mesh size silica gel and 3-4% (v/v) methanol/chloroform as eluent to obtain 0.9 g (yield 45%, Rf = 0.2, 6% methanol in chloroform) of 10a ,10b was also prepared using the same procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.3-1.4[m, 48H, N-CH_2- $(CH_2)_{12}$- CH_3], 2.3 [m, 4H, N-CH_2-$(CH_2)_{12}$-CH_3], 3.8 [s, 2H, N-CH_2-C=], 7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic], 8.4 [s, 1H, -N*H*-],8.8[br,1H, Ar-N*H*]. Mass spectrum (LCM): m/z 541 [M^+] for $C_{36}H_{66}N_3^+$. Elemental Analysis: Calculated : %N: 7.77, %C: 79.93, %H: 12.30. Observed : %N: 7.75, %C: 79.80, %H: 12.40.

(1H-Benzoimidazol-2-ylmethyl)-di-n-octadecyl-ammonium chloride (10b): 0.8g (yield 40%, Rf = 0.2, 6% methanol in chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{16}$-CH_3], 1.3-1.4 [m, 64H, N-CH_2- $(CH_2)_{16}$- CH_3], 2.3 [m, 4H, N-CH_2-$(CH_2)_{16}$-CH_3], 3.5 [s, 2H, N-CH_2-C=], 7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic],8.4 [s, 1H, -N*H*-], 8.8 [br,1H, Ar-N*H*]. Mass spectrum (LCM): m/z 653 [M^+] for $C_{44}H_{82}N_3^+$. Elemental Analysis: Calculated : %N: 6.43, %C: 80.91, %H: 12.65. Observed : %N: 6.35, %C: 80.70, %H: 12.80.

(1H-Benzoimidazol-2-ylmethyl)-methyl-di-n-tetradecyl-ammonium chloride (11a): In a 25 mL round bottom flask, methyl iodide (1.15g, 8.1mmol) was added to A_4 (2g, 3.7mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated and the residue upon column chromatographic purification using 230-400 mesh size silica gel and 4-5% methanol in chloroform as eluent followed by chloride ion exchange (using Amberlyst A-26 with methanol as eluent)afforded the pure 11a (1.1 g, 53%, Rf = 0.6, 10% methanol in chloroform) , 11b was also prepared as discussed. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.9 [t, 6H, N-CH_2-$(CH_2)_{12}$-CH_3], 1.3-1.4 [m, 48H, N-CH_2- $(CH_2)_{12}$- CH_3], 1.7 [t, 4H, N-CH_2-$(CH_2)_{12}$-CH_3], 3.2 [m, 4H, N-CH_2-$(C\ H_2)_{12}$-CH_3] ,3.3 [s, 3H, -NCH_3] ,4.5 [s, 2H, N-CH_2-C=], 7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic],8.8 [br,1H, NH]. Mass spectrum (LCM): m/z 555 [M^++1] for $C_{37}H_{68}N_3^+$. Elemental Analysis: Calculated: %N: 7.57, %C: 80.08, %H: 12.35. Observed : %N: 7.52, %C: 80.20, %H: 12.25.

(1H-Benzoimidazol-2-ylmethyl)-methyl-di-n-octadecyl-ammonium chloride (11b): (0.95 g, 46%, Rf = 0.6, 10% methanol in chloroform). NMR (300 MHz, $CDCl_3$) δ/ppm 0.8 [t, 6H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.2-1.3 [m, 60H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.8-1.9 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.2 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.4 [s, 3H, N-CH_3] ,4.4 [s, 2H, 1N(-CH_2)-C=], 7.2 [s,2H, aromatic], 7.7 [s, 2H, aromatic],8.8[br,1H, NH], Mass spectrum (LCM): m/z 667 [M^+] for $C_{45}H_{84}N_3^+$. Elemental Analysis: Calculated: %N: 6.30, %C: 81.01, %H: 12.69. Observed : %N: 6.15, %C: 81.50, %H: 12.30.

(1H-Benzoimidazol-2-ylmethyl)-(2-hydroxy-ethyl)-di-n-tetradecyl-ammonium chloride (12a): The A_4 (2 g, 3.7 mmol) was taken in a 25 mL round-bottomed flask and chloroethanol (0.32g, 4 mmol) was added . After refluxing the reaction mixture for four days, the solvent was removed on a rotary evaporator. The column chromatographic purification of the resulting residue using 230-400 mesh size silica and 4-5% (v/v) methanol in chloroform as eluent afforded the title compound as a quaternary chloride salt (1 g, 46% yield, R_f = 0.5, 10% methanol:chloroform), in similar way 12b was prepared. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 0.8-0.9 [t, 6H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.2-1.4 [m, 44H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{11}$-CH_3], 3.5-3.6[t, 2H, N-CH_2-CH_2-OH], 4.0[t, 2H, N-CH_2-CH_2-OH] , 4.3-4.4 [br, 1H, N-CH_2-CH_2-O*H*] , 4.5[s, 2H, N-CH_2-C=] ,7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic], 8.8 [br, 1H, N*H*]. Mass spectrum (LCM): m/z 586 [M+1] for $C_{38}H_{70}ON_3^+$. Elemental Analysis: Calculated: %N: 7.18, %C: 78.02, %H: 12.06. Observed : %N: 7.21, %C: 78.08, %H: 12.01.

(1H-Benzoimidazol-2-ylmethyl)-(2-hydroxy-ethyl)-di-n-octadecyl-ammonium chloride (12b): (1.1 g, 52% yield, R_f = 0.5, 10% methanol:chloroform). ^1H NMR (300 MHz, $CDCl_3$) δ/ppm0.8 [t, 6H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.2-1.4 [m, 60H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 1.8 [m, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.2-3.3 [t, 4H, N-CH_2-CH_2-$(CH_2)_{15}$-CH_3], 3.6 [t, 2H, N-CH_2-CH_2-OH], 4.0 [t, 2H, N-CH_2-CH_2-OH] , 4.4 [br, 1H, N-CH_2-CH_2-OH] , 4.5 [s, 2H, N-CH_2-C=] , 7.3 [s, 2H, aromatic], 7.7 [s, 2H, aromatic], 8.8 [br, 1H, NH]. Mass spectrum (LCM): m/z 699 [M+2] for $C_{46}H_{86}O\ N_3^+$. Elemental Analysis: Calculated: %N: 6.03, %C: 79.25, %H: 12.43. Observed : %N: 6.12, %C: 79.50, %H: 12.25.

RESULTS AND DISCUSSIONS

Chemistry

The key structural elements common to the benzothiazole, bezoxazole and benzimidazole based lipids 1a to 12b described herein include (a) the presence of hydrophobic chains as anchoring groups (i) linked to the positively charged nitrogen atom directly which in turn attached to the benzo group of the heterocyclic ring through a spacer or (ii) linked directly to the benzo group of the heterocyclic ring or (iii) linked through a spacer to the heterocylic ring (b) the presence of heterocyclic ring benzothiazole or benzoxazole or benzimidazole as head group. The details of the synthetic procedures for benzothiazole, benzoxazole and benzimidazole based lipids 1a and 12b shown in Chart 1 are described in the ''Experimental section''. As outlined in Schemes **1** to **4**, the chemistry involved in preparing these new lipids is straightforward. Scheme **1** outlines the general synthetic strategies adopted for preparing lipid 1a – 3c. The steps involved were (a) reacting alkyl bromide with benzothiazole-6-amine. (b) quarternizing the intermediate tertiary amine using hydrochloric acid or methyl iodide or chloro ethanol followed by Ion exchange. Synthesis of lipids 4a – 6c as discussed in scheme **2** the steps involved are (i) alkylation of ethanolamine with alkyl bromide (ii) oxidizing the intermediate alcohol to aldehyde using pyridinium chloro chromate (iii) treating the intermediate aldehyde with 2-amino phenol in presence of ferric chloride and pyridine in ethanol (iv) quarternizing the intermediate tertiary amine using hydrochloric acid or methyl iodide or chloro ethanol followed by Ion exchange. Synthesis of lipid 7a – 9c essentially consists of similar steps as in synthesis of lipid 1a-3c except that instead of reacting alkyl bromide with benzothiazole-6-amine reacted with benzimidazole-5-amine as in Scheme **3**. The steps involved in the synthesis of lipids 10a – 12b are similar as in the synthesis of lipids 4a – 6c except that instead of reacting the intermediate aldehyde with 2-amino phenol reacted with benzene-1,2-diamine as in Scheme **4**.

Biological Activity

Anticancer activity

It is well known that derivative of benzthiazole, benzoxazole and benzimidazoles possess significant biological activities viz., anticancer activity. Cationic lipids are very well known as delivery systems and also they increase the uptake of the drug into cancer cell lines. The essential attributes for an anticancer drug to have efficient anticancer activity are (i) possess significant cytotoxicity and (ii) uptake by the cancer cell. To incorporate these attributes in a single molecule we developed a series of benzothiazole, benzoxazole and benzimidazole based cationic lipids containing two units (i) hetero cyclic group as the head group which is responsible for the anticancer activity and (ii) anchoring groups impart lipid like structure to the molecule, (iii) the cationic charge to enhance the uptake by the cancer cell lines. Herein, we are reporting the relative anticancer activities of synthesized series of benzothiazole, benzoxazole and benzimidazole based lipids in lung and breast cancer cell lines across 30 to 500 microgram/ml concentration of molecules were studied. The IC_{50} values of these lipids are compared with that of commercially available anti cancer drug Cis-platin (Table 1).

The results of figure 1 summerize the cytotoxicity profile of the synthesized lipids 1a – 12b. It is observed from the results that in general, the heterocyclic based lipids with protonated ammonium head group are found to be better cytotoxic than the lipids with methylated or hydroxy ethylated ammonium head groups among all the series of lipids studied in both the cell lines. It is also observed that the benzothiazole based lipid with C14 chain as hydrophobic group and protonated ammonium head group is showing highest cytotoxicity among the series of the lipids studied. The results demonstrate that in mojority cases the lipids with C14 chain are showing better cytotoxicity than the lipids with C16 and C18. The benzimidazole based lipid with methylated ammonium head group is showing least cytotoxicity. It is also observed from the results that the 5-substituted benzimidazole based lipids are more cytotoxic than the 2-substituted benzimidazole based lipids. The results also demonstrate that the benzothiazole based lipids inhibiting the growth of both the cancer cell lines effectively compared to benzoxazole or benzimidazole based lipids.

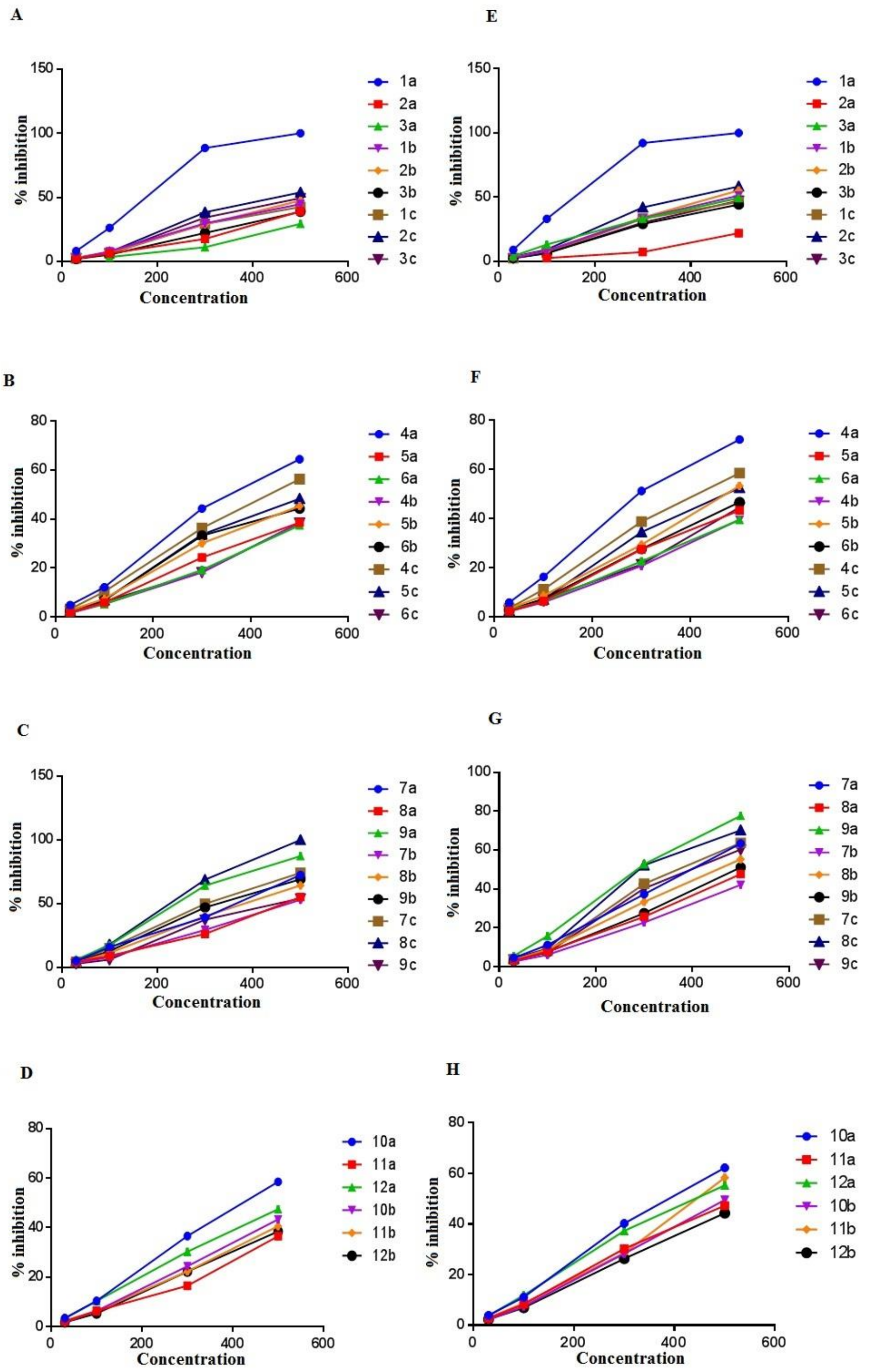


Figure I: Cytotoxicities of lipids (1a – 12b) in MCF-7 cell lines and A549 cell lines using MTT assay. (A) to (D) refers to the cytoxicities of lipids 1a-12b in MCF 7 cell lines and (E) to (H) refers to the cytotoxicities of lipids 1a -12b in A549. The absorption obtained with reduced formazan with cells in the absence of lipids was taken to be 100. The toxicity assays were performed as described in the text. The data presented are the average values of three independent experiments (n=3).

Table 1: IC 50 values of lipids (1a-12b):

Lipids	IC 50 VALUES AGAINST BREAST CANCER	IC 50 VALUES AGAINST LUNG CANCER
1a	205.1373	189.8485
2a	629.2857	575.4588
3a	557.4302	496.4211
1b	539.6739	465.0849
2b	506.4742	427.5877
3b	615.2278	535.413
1c	555.191	504.5
2c	429.3246	408.6967
3c	469.7885	490.798
4a	376.5308	327.625
5a	612.9	543.8111
6a	648.24	626.519
4b	620.6883	606.6625
5b	533.172	455.4299
6b	529.6915	516.0737
4c	433.2	418.084
5c	482.2549	439.8455
6c	649.92	551.5455
7a	393.7302	351.4786
8a	521.7979	457.5888
9a	311.1603	266.6313
7b	571.6706	460.5189
8b	438.4375	382.7
9b	468.9806	348.7958
7c	361.1791	326.4533
8c	327.1267	240.5169
9c	380.8583	420.687
10a	416.0672	395.5873
11a	686.5775	516.7188
12a	522.9787	439.7027
10b	541.3596	477.3762
11b	595.5244	404.3761
12b	612.4937	542.3333
Cis-platin	10 µM	16 µM

CONCLUSIONS

In summary, we have developed and synthesized an efficient and novel series of benzoxazole, benzimidazole and benzthiazole based cationic lipids for use in anticancer activity. The anticancer activity of these new lipids were studied and found that these lipids are active against both breast and lung cancer cell lines. The results indicated that the designed systems are quite capable as anti cancer agents.

ACKNOWLEDGMENT

Financial supports for this work from DST, Government of India, New Delhi (to P. V. Srilakshmi.) is gratefully acknowledged. We sincerely acknowledge the experimental assistance for the studies of anticancer activity received from G. Kranthi Kumar.

REFERENCES

[1] Banerjee RK, Das PK, Srilakshmi GV, Chaudhuri A and Rao NM (1999) J Med Chem 42, 4292.
[2] Srilakshmi GV, Sen J, Chaudhuri A, Ramdas Y and RaO NM (2002) Biochim Biophys Acta 1559, 87.
[3] Sen J and Chaudhuri A (2005) J Med Chem 48, 812.
[4] Kedika Bhavani and Srilakshmi V Patri (2012) Mol Pharmaceutics 9, 1146.
[5] Kumar VV, Pichon C, Refregiers M, Guerin B, Midoux P and Chaudhuri A (2003) Gene Ther 10, 1206.

[6] Rajesh M, Srujan M, Mahidhar YV, Gangamodi NV, Ramakrishna S and Chaudhuri A (2009) Biomaterials 30:2369–2384.
[7] Kuhlencord A , Maniera T, Eibl H and Unger C (1992) Agents Chemother 36,1630.
[8] Unger C, Fleer EA, Kotting J, Neumuller W and Eibl H(1992) Prog Exp Tumor Res 34, 25.
[9] Wieder T, Reutter W, Orfanos CE and Geilen CC (1999) Prog Lipid Res 38(3), 249.
[10] Houlihan WJ, Lohmeyer M, Workman P and Cheon SH (1995) Med. Res. Rev. 15, 157.
[11] Ruiter GA, Zerp SF, Bartelink H, van Blitterswijk WJ and Verheij M (2003) Anticancer Drugs 14, 167.
[12] Eue, I. (2001) Int. J. Cancer 92, 426.
[13] Vivanco I and Sawyers CL (2002) Nat. Rev. Cancer 2, 489.
[14] Shanta D and Stephen JL (2009) PNAS,106(52), 22199.
[15] Ueki M, Ueno K, Miyadoh S, Abe K, Shibata K, Taniguchi M and Oi S (1993) J Antibiot 46(7),1089.
[16] Cheng CC, De Liu and Tc Chou (1993), Heterocycles, 35(2), 775.
[17] Shi D, T.D. Bradshaw, S Wrigley, CJ McCall, P Lelieveld, I Fichtner and MFG Stevens (1996) J. Med. Chem 39, 3375.
[18] Hall IH, Peaty NJ, Henry JR, Easmon J, Heinisch G, Pürstinger G(1993). 332(4), 115.
[19] Kumar D, Jacob MR, Reynolds MB and Kerwin SM (2002) Bioorg Med Chem 10(12), 3997.
[20] Easmon J, Puerstinger G, Roth T, Fiebig HH, Jenny M, Jaeger W, Heinisch G and Hofmann J (2001) Int J Cancer 94(1), 89.
[21] Balani SK, Pitzenberger SM, Kauffman LR, Arison BH, Ramjit HG, Goldman ME, O'Brien JA, King JD, Hoffman JM and Rooney CS (1992) Drug Metab Dispos 20(6), 869.
[22] Hoffman JM, Smith AM, Rooney CS, Fisher TE, Wai JS, Thomas CM, Bamberger DL, Barnes JL, Williams TM and Jones JH (1993) J Med Chem 36(8), 953.
[23] Saari WS, Wai JS, Fisher TE, Thomas CM, Hoffman JM, Rooney CS, Smith AM, Jones JH, Bamberger DL and Goldman ME (1992) J Med Chem 35(21), 3792.
[24] Perrin L, Rakik A, Yerly S, Baumberger C, Kinloch-de Loës S, Pechère M and Hirschel B. (1996) AIDS (11), 1233.
[25] Staszewski S, Massari FE, Kaber A, Gohler R, Durrr S, Anderson KW, Schneider CL, WaterburyJA, Bakshi KK, Taylor CS, Hildebrand C, Kriesl B, Haffstedt WA, Schleif VW and Byrnes (1995) Inhibitor J. Infect. Dis 171, 1159.
[26] Olsen D B, Carroll S S, Culberson J C, Shafer J A, and Kuo L C (1994) Nucleic Acids Res 22(8), 1437.
[27] TEMIZ-ARPACI Ö, ÖREN İ and ALTANLAR N (2002) Il Farmaco (57), 175.
[28] Ersan S, Nacak S, Berkem R and Özden T (1997) Arzneim.Forsch.Drug Res. 47, 963.
[29] Oren I, Temiz O, Yalcin I, Sener E, Akin A and Ucarturk N (1997) Arzneim Forsch/Drug Res 47(12),1393.
[30] Temiz O, Oren I, Sener E, Yalcin I and Ucarturk N (1998) Farmaco 53, 337.
[31] Sener E, I Yalcin, O Temiz, I Oren, A Akin and N Ucarturk (1997) II Farmaco 52 (2), 99.
[32] Yalcin I, I Oren, E Sener, A Akin and N Ucarturk (1992) Eur. J. Med. Chem 27, 401.
[33] Thabrew MI, Mitry RR, Morsy MA and Hughes RD (2005) Life Sciences, 77, 1319.
[34] Sahranavard Shamim , Naghibi Farzaneh, and Mosaddegh Mahmoud (2009) Ethno-Med 3(1), 81.