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SYNTHESIS AND ANTI-MYCOBACTERIAL ACTIVITY OF SOME NOVEL ANACARDIC ACID DERIVATIVES FROM CASHEW NUT SHELL LIQUID

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Keywords:

Synthesis, Anacardic acid, Cashew nut shell liquid, Anti-mycobacterial activity

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ABSTRACT: Synthesis and anti-mycobacterial activity of some novel derivatives of anacardic acid *viz*., 2-Ethoxy-6-pentadecyl benzamide (APHK-1), 1-(2-methoxy-6-pentadecylbenzyl)-4-hydroxy ethylpiperazine (APHK-2), 1- (2-hydroxy-6-pentadecyl)- N- (hydroxyl ethylaminoethyl) benzamide (APHK-3) and compounds 20-34 from saturated anacardic acid which was obtained from natural product cashew nut shell liquid (CNSL) is reported. Anti-mycobacterial activity was performed using *Mycobaterium smegmatis* mc^2 155, taking anacardic acid and ethambutol as standards. Of all the derivatives, 1-(2-hydroxy-6-pentadecyl)-N-(hydroxyethylaminoethyl) benzamide exhibited good anti-mycobacterial activity.

INTRODUCTION: Anacardic acid mixture (1) **Fig. 1** isolated from a natural product cashew nut shell liquid (CNSL) is a by product in cashew industry. These are salicylic acid derivatives with a nonisoprenoid alk(en)yl side chain [1]. Kubo *et al*., reported the separation of anacardic acid into monoene, diene, and triene by preparative HPLC and tested against cancer cells, and found to show moderate cytotoxic activity on BT-20 breast and Hela epithelioid cervix carcinoma cells [2]. Anacardic acid and its derivatives exhibit biological activities like anti-mycobacterial activity [3, 4] lipoxygenase-1 inhibitory activity [5, 6]. Synthesis of benzamide derivatives [7], sidenafil analogues [8], dihydropyridine analogues [9] as calcium channel blockers, isonicotinoyl hydrazones for antimycobacterial activity [10] starting from anacardic acid were reported.

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Recently anacardic acid is found to exhibit a specific activator of kinase activity of Aurora Kinase A, [11, 12] suppress expression of nuclear factor-KB regulated gene products leading to potentiation of apoptosis [13] inhibitor of the HAT activity of recombinant *Plasmodium falciparum* GCN5 [14] and as modulators of histone acetyltransferases [15].

Worldwide spread of HIV infection, which results in weakening of immune system of infected individuals and the development of drug-resistant strains of *Mycobacterium tuberculosis* have contributed to a significant TB increase in recent years [16, 17, 18]. Isoniazide, rifampin, pyrazinamide and ethambutol are the front-line agents that are recommended by world Health Organization (WHO) for the treatment of tuberculosis (TB) [19]. Problems with the current TB treatment regimes are complex and include a prolonged standard course regimen of 6 months, which often results in non-compliance, the emergence of extensively drug-resistant tuberculosis strains [20] (XDRTB); and lack of effective drugs against the latent state.

In the present work the abundantly available anacardic acid has been used as synthon for generating derivatives and studied their anti-mycobacterial activity. This was achieved by (a) alkylation of hydroxyl and carboxylic acid groups (b) hydrolysis of ester to acid (c) converting acid to acid chloride (d) reduction of ester group into alcohol followed by halogenation and finally coupling with suitable pendant groups. The synthesized compounds were tested for anti-mycobacterial activity.

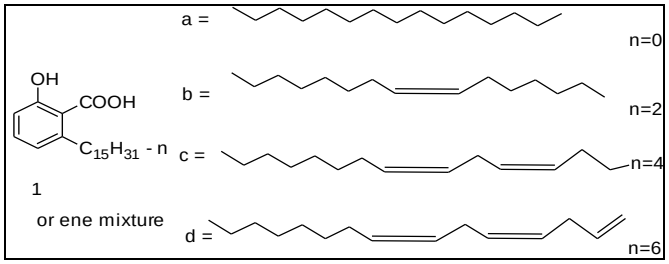

FIG. 1: ANACARDIC ACID MIXTURE

MATERIALS AND METHODS: IR spectra were recorded using Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 at 200 MHz on a Brukar A G Spectrometer. All the chemical shift values are reported in δ units and down field from TMS as internal standard. Mass spectra were recorded using GC MS-QP2010s (Direct probe) and on Q-TOF micro^{TM} AMPS MAX 10/6A system. Melting points were recorded using melting point apparatus Acro steel Pvt. Ltd., All the starting materials and reagents were obtained from commercial source and were used without further purification.

Solvent extracted CNSL containing ene mixture of anacardic acid 63%, cardanol 10.5%, and cardols 22% was obtained from cashew processing industry, Mangalore (Karnataka), India.

Antimycobacterial activity of the compounds were determined using *Mycobaterium smegmatis* mc^{2}155 cells which were grown on saturated Youman-Karlson (YK) broth medium [21] at 37 ºC.

RESULTS AND DISCUSSION: The ene mixture of anacardic acid (1a-d) was isolated from CNSL by a reported method [22]. First, calcium hydroxide was added to the natural CNSL to convert into calcium anacardate, which was isolated and hydrolysed with dil. hydrochloric acid to generate anacardic acid ene mixture of mono ene, diene and triene located at (8'), (8', 11'), and (8', 11', 14') of C15 alkyl chain respectively. 1a saturated anacardic acid was prepared from ene mixture (1a-d) using hydrogen and Pd/C **Fig. 2**.

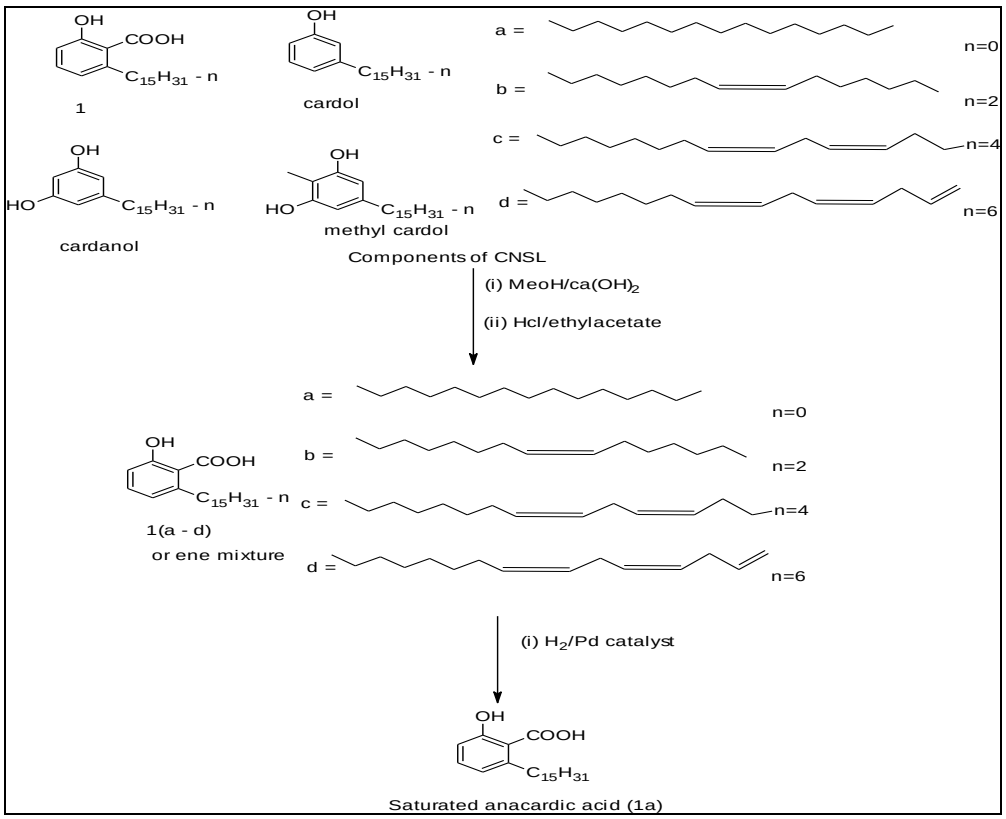

FIG. 2: PREPARATION OF SATURATED ANACARDIC ACID

Saturated anacardic acid (1a) was modified into several synthones (4, 7, 8, 9, 12, 13, 17, 18 and 19) as described in **Fig. 3**.

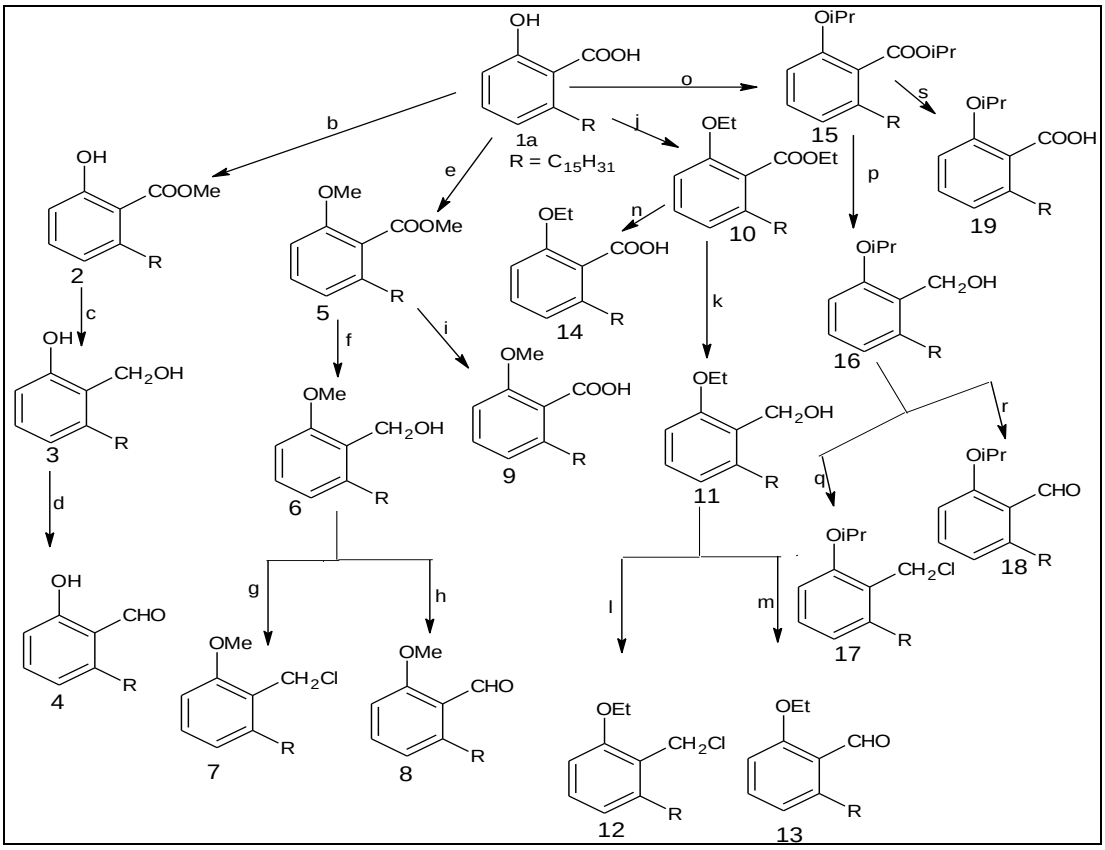

FIG. 3: ANACARDIC ACID SYNTHONES

Reagents and conditions; (b) dimethyl sulphate, K_2CO_3, acetone, <20 ºC; (c) LAH, THF, reflux; (d) PCC, MDC, 20 ºC; (e) dimethyl sulphate, K_2CO_3, acetone, reflux; (f) LAH, THF, reflux; (g) $SOCl_2$, MDC, 40 ºC; (h) PCC, MDC, 20 ºC; (i) DMSO, t-BuOK, 40 ºC, 2h; (j) diethyl sulphate, K_2CO_3, acetone, reflux; (k) LAH, THF, reflux; (l) $SOCl_2$.MDC, 40 ºC; (m) PCC, MDC, 20 ºC; (n) DMSO, t-BuOK, 40 ºC, 2h; (o) i-PrBr, K_2CO_3, acetone, reflux; (p) LAH, THF, reflux; (q) $SOCl_2$, MDC, 40 ºC; (r) PCC, MDC,20 ºC; (s) DMSO, t-BuOK, 40 ºC, 2h.

Compound 1a was esterified using dimethyl sulphate to get methyl 2-hydroxy-6-penta-decylbenzoate 2. This on reduction with LAH gave 2-hydroxy-6-pentadecylbenzyl alcohol 3. Oxidation of 3 using pyridinium chlorochromate (PCC) yielded compound 4. Similarly, O-alkylation and esterification of carboxylic acid group of 1a using dimethyl sulphate, diethyl sulphate and isopropyl bromide obtained compounds 5, 10 and 15 respectively. Reduction followed by oxidation of these compounds obtained synthones 8, 13 and 18. Compounds 7, 12 and 17 were obtained by the treatment of compounds 6, 11 and 16 with thionyl chloride. The synthones 9, 14 and 19 were obtained by the ester hydrolysis of compounds 5, 10 and 15 respectively.

The isonicotinyl hydrazone derivative compounds 20 - 26 were prepared from corresponding aldehydes **Fig. 3** by refluxing with isoniazid to obtain isoniconoylhydrazones of anacardic acid (21 - 23). Reduction of the compounds 21 - 23 obtained another set of isoniazide derivatives 24 - 26 **Fig. 4**.

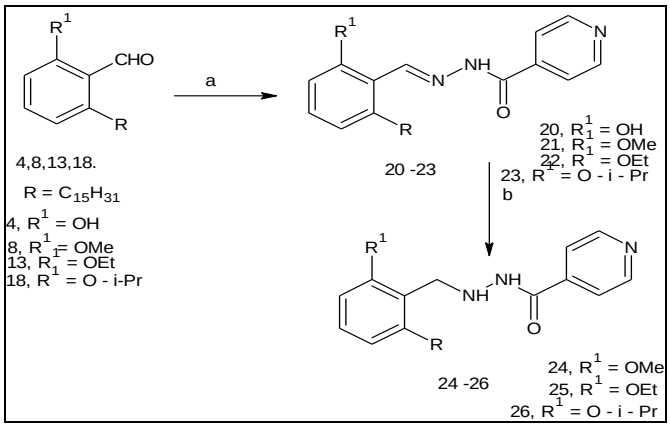

FIG. 4: ISONIAZIDE DERIVATIVES

Reagents and conditions; (a) MeOH, isoniazide, reflux. (b) MeOH, $NaBH_4$, 25 ºC.

Also synthesized pyrazine carboxylic acid (27 - 29) and N-methyl piperazine derivatives of anacardic acid, by reacting 2-alkoxy-6-pentadecylbenzyl chloride with piperazine-2- carboxylic acid and N-methyl piperazine (30 - 32), as shown in **Fig. 5**.

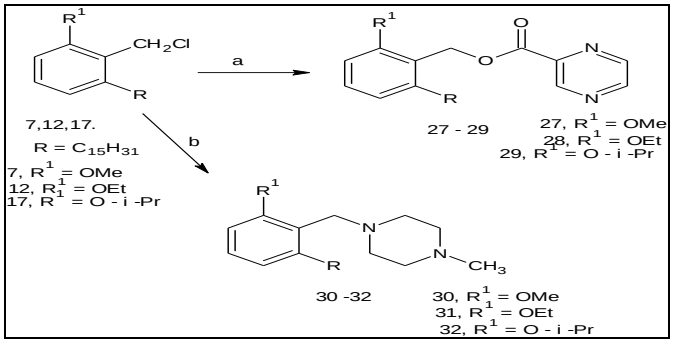

FIG. 5: PIPERAZINE DERIVATIVES

Reagents and conditions; (a) Pyrazine - 2-carboxylic acid, K_2CO_3, DMF, 85 ºC; (b) N-methylpiperazine, aq. NaOH, MDC, TBAB, 40 ºC.

Furthermore, D-cycloserine derivatives of anacardic acid (33, 34) were prepared by reacting corresponding acid chlorides (9, 14) with cycloserine **Fig. 6**. Pure compounds were obtained by recrystallisation and silica gel column purification techniques. All the compounds were fully characterized by using IR, NMR and Mass spectroscopy.

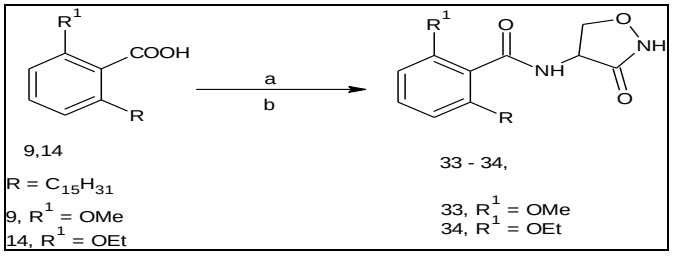

FIG. 6: CYCLOSERINE DERIVATIVES

Reagents and conditions; (a) $SOCl_2$, Hexane, Reflux, 2h; (b) MDC-DMF, TEA, D-Cycloserine, 40 ºC, 1h.

2-Ethoxy-6-pentadecyl benzamide (APHK-1) was synthesized from 14 by treatment with thionyl chloride which gave acid chloride and then coupled with ammonia **Fig. 7**.

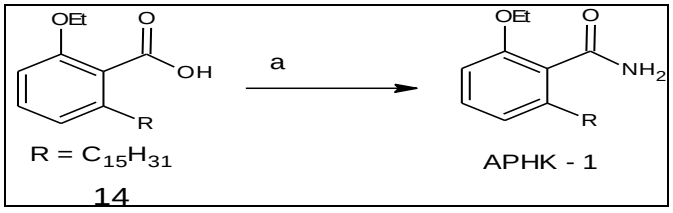

FIG. 7: 2-ETHOXY-6-PENTADECYL BENZAMIDE

Reagents and conditions: (a) Hexane, $SOCl_2$, two drops of DMF, relfux with ammonia in toluene.

Compound APHK-2 was synthesized from 5 by reduction of ester group with LAH/THF, followed by treatment with PBr_3 to give bromo compound 35, which on treatment with hydroxy ethyl piperazine gave APHK-2 **Fig. 8**.

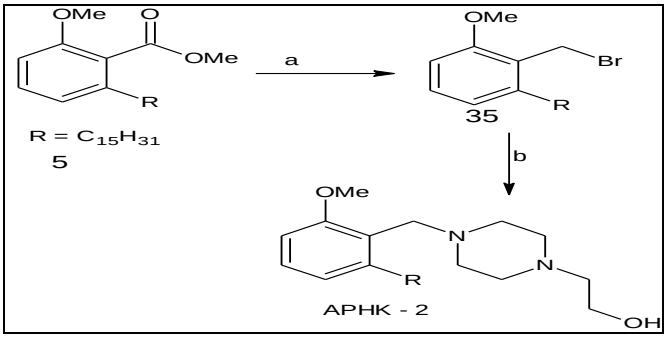

FIG. 8: STRUCTURE OF APHK-2

Reagents and conditions; (a) LAH in THF, PBr_3 (b) N-hydroxy ethyamino piperazine

Title compound APHK-3 was synthesized from 2 by condensation of monoester group with hydroxyl ethyl amino ethyl amine moiety **Fig. 9**.

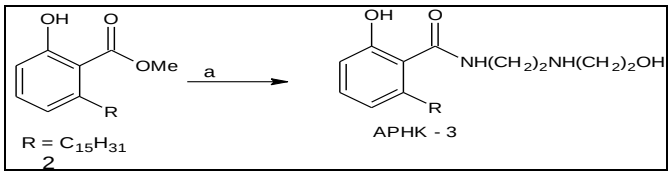

FIG. 9: STRUCTURE OF APHK-3

Reagents and conditions; (a) hydroxyethylaminoethylamine, 120 ºC

Biological Assay: Antimycobacterial activity of the compounds was assayed by the broth dilution method. Stock solutions (10 mg/ml) of the compounds were prepared in methanol and serially diluted using YK culture broth. To all serially diluted solutions, 0.5 ml of suitably diluted inoculums were added (10^6 cfu) and incubated at 37ºC for 24 h.

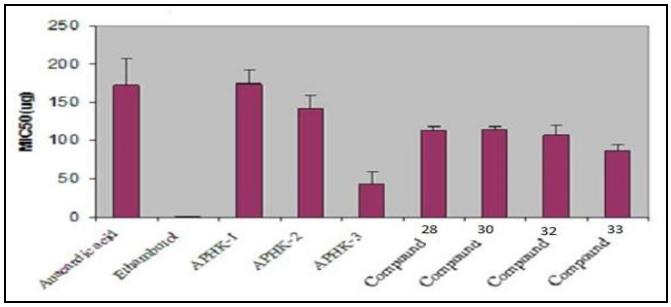

FIG. 10: COMPARISON OF MIC_{50} VALUES OF ANACARDIC ACID DERIVATIVES WITH STANDARDS

The lowest concentrations of the compound that inhibited growth of the organism was taken as

minimum inhibitory concentration (MIC), ethambutol which is an anti-tuberculosis drug was taken as reference compound and values are tabulated in **Table 1** along with bar diagram **Fig. 10**.

TABLE 1: MIC_{50} VALUES OF ANACARDIC ACID DERIVATIVES

Compounds	MIC_{50} (µg)
Anacardic Acid	172.82
Ethambutol	1.76
APHK-1	174.41
APHK-2	140.92
APHK-3	43.75
Compound 20	888.66
Compound 21	340.95
Compound 22	1736.283
Compound 23	302.51
Compound 24	327.21
Compound 25	No Inhibition
Compound 26	No Inhibition
Compound 27	243.01
Compound 28	113.32
Compound 29	292.35
Compound 30	113.65
Compound 31	340.95
Compound 32	107.52
Compound 33	86.07
Compound 34	304.56

CONCLUSION: 1a Saturated anacardic acid was prepared from ene mixture (1a-d) obtained from cashew nut shell liquid (CNSL) using hydrogen and Pd/C and it was used to make isoniazide derivatives (20 - 26), pyrazine analogues (27 - 29) and N-methypiperazine analogues (30 - 32), D-cycloserine analogues (33, 34), APHK-1, APHK-2 and APHK-3. All these anacardic acid analogues were tested against *M. smegmatis* mc^2 155 for antimycobaterial activity taking anacardic acid and ethambutol (TB drug) as standards. APHK-3 (1-(2-hydroxy-6-pentadecyl)-N-(hydroxyethylaminoethyl benzamide) showed good anti-mycobacterial activity compared to anacardic acid.

Experimental Section:

Isolation of Anacardic Acid from Natural CNSL: Commercially available solvent extracted CNSL (100 g) was dissolved in 5% aqueous methanol (600 ml). To the methanolic solution, activated charcoal (20 g) was added and stirred for 15 min. This solution was filtered over celite to remove insoluble plant materials. The clear filtrate was transferred into a round bottom flask fitted with double surface reflux condenser and a mechanical stirrer. Calcium hydroxide (50 g) was added in portions under stirring. After complete addition of calcium hydroxide, the temperature of the reaction mixture was raised to 50 ºC and stirred for 3 h. Supernatant solution was monitored by TLC for the absence of anacardic acid. After the completion of the reaction, the precipitated calcium anacardate was filtered and washed thoroughly with methanol (200 ml) and the cake was dried under vaccum at 45 - 50 ºC and stirred for 2 h (dry weight 110 g). The calcium anacardate was suspended in distilled water (440 ml) and 11 N HCl (60 ml) was added and stirred for one hour. The resultant solution was extracted with ethyl acetate (2 × 150 ml). The combined organic layers were washed with distilled water (2 × 100 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield ene mixture of anacardic acid (60 g). The identity of the compound was confirmed by HPLC and in comparison with standard samples [21].

Preparation of Saturated Anacardic Acid (1a): Ene mixture of anacardic acid (30 g) was dissolved in methanol (120 ml). 5% Pd/C (0.75 g) was added slowly and this solution was transferred into hydrogenation flask. Hydrogenation was carried out with 2.5 Kg/cm^2 pressure for 2 h, and the solution was filtered through a celite bed to obtain catalyst free solution. Organic solvent was evaporated under vacuum to obtain saturated anacardic acid (1a), which was recrystallized from petroleum ether (40 - 60 ºC); Yield = 27 g, MP; 90 - 91 ºC (lit. Mp; 90 - 92 ºC) [32]. IR (KBr); 3140, 2917, 1650, 1655, 1604, 1466, 1308, 1206, 894, 815, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$); δ 0.88 (t, 3H, J = 6.0 Hz), 1.25 (brs, 24H), 1.6 (m, 2H), 2.98(t, 2H, J = 8.0Hz), 6.7 - 6.8 (dd, 2H, J = 8.0Hz), 7.36 (t, 1H, J = 8.0 Hz).

Methyl 2-hydroxy-6-pentadecylbenzoate (2): To a stirred solution of saturated anacardic acid 1a (10 g, 0.028 mol) and powdered potassium carbonate (17.5 g, 0.125 mol) in acetone (75 ml) was added dimethyl sulphate (3.62 g, 0.028 mol) in portions with stirring at 10 ºC. After the addition of dimethyl sulphate, the temperature of the reaction mixture was raised to 15 - 20 ºC and maintained for 4 h. After the completion of the reaction, the solvent was evaporated under reduced pressure. To the residue obtained was added distilled ethyl-acetate (50 ml) and the material was extracted into

ethyl acetate (100 ml) washed with water (2 × 100 ml), finally dried over sodium sulphate and concentrated organic solvent to obtain crude mass (9 g). The crude material was recrystalized from hexane to get title compound 14. Yield; 7.5 g; mp; 40 - 41 ºC (lit mp 40 - 41 ºC); GC-MS (m/z); 362 (M^+).

2-hydroxy-6-pentadecylbenzylalcohol (3): To a stirred solution of compound 2 (7.5 g, 0.022 mol) in THF (40 ml) was added LAH (0.75 g, 0.019 mol) slowly in portions at RT. The reaction mass was refluxed for about 2 h. It was then cooled to 10ºC. 10 ml of ethyl acetate was added slowly to destroy unreacted of LAH. pH of the reaction mixture was adjusted to 1 - 2 with 10% aq. HCl. The product was extracted into ethyl acetate (100 ml). The organic layer was separated and washed with water (2 × 50 ml) and finally dried over anhydrous Na_2SO_4. The organic layer was concentrated and the residue was re-crystalized in hexane to obtain title compound 3. Yield; 5 g, MP; 63 - 65 ºC (Lit mp 63 - 64 ºC); GC-MS (m/z); 334 (M^+).

2-hydroxy-6-pentadecylbenzaldehyde (4): To a stirred solution of compound 3 (5 g, 0.015 mol) and MDC (50 ml) was added pyridinium chloro-chromate (PCC) (6.4 g, 0.03 mol) in portions at 20ºC. After the complete addition of PCC, the reaction mixture was stirred for about 1 h. Hexane (75 ml) was added to the reaction mixture and separated upper layer and passed through celite bed. Finally the organic layer was concentrated to obtain the title compound 4. Yield; 4.5 g; GC-MS (m/z); 332 (M^+).

Methyl 2-methoxy-6-pentadecylbenzoate (5): To a stirred solution of tetrahydroanacardic acid 1a (20 g, 0.057 mol) and powdered potassium carbonate (32 g, 0.232 mol) in acetone (120 ml) was added dimethyl sulphate (14.48 g, 0.112 mol) in portions with stirring at room temperature. After the addition of dimethyl sulphate, the reaction mixture was refluxed for about 3 h. The reaction mixture was cooled to room temperature and inorganic were filtered. The mother liquor was concentrated under reduced pressure. To the residue was added water (100 ml) and the material was extracted into ethyl acetate (200 ml). The organic layer was washed with water (100 ml) and finally dried over anhydrous sodium sulphate. The organic layer was concentrated to obtain title compound 5. Yield; 20g, mp; 37 - 38 ºC (lit mp; 37 - 38 ºC); GC-MS (m/z); 376 (M^+).

2-Methoxy-6-pentadecylbenzylalcohol (6): Title compound was prepared in 80% yield from compound 5 and using the procedure described for compound 3. Mp; 57 - 58 ºC, (lit mp; 57 - 58 ºC); GC-MS (m/z); 348 (M^+).

2-Methoxy-6-pentadecylbenzaldehyde (8): Title compound was prepared in 90% yield from compound 6, and using the procedure described for compound 4. GC-MS, (m/z); 346 (M^+).

Preparation of ethyl-2- ethoxy-6-pentadecyl-benzoate (10): To a stirred solution of 1a (12g, 0.035 mol) in acetone (60 ml) was anhydrous powdered potassium carbonate (14.4 g, 0.104 mol). The diethyl sulphate (10.7 g, 0.069 mol) was added in portions for about 10 min at RT. After the addition was complete, the reaction mass was heated to reflux and stirred for 3 h. The reaction mass was cooled to RT and then concentrated under reduced pressure. Water (100 ml) was added to the reaction mixture and extracted with ethyl acetate (80 ml). The organic layer was evaporated to afford product 10 as viscous liquid. Yield; 12.8 g, 92% (theoretical yield), IR (KBr); 2920, 1730, 1260 cm^{-1} GC-MS (m/z); 404 (M^+).

2-Ethoxy-pentadecylbenzylalcohol (11): Title compound was prepared in 85% yield from compound 10 and using the procedure described for compound 3. Mp; 45 - 46 ºC, (lit mp; 45 - 46 ºC); GC-MS (m/z); 362 (M^+).

2-Ethoxy-6-pentadecylbenzaldehyde (13): Title compound was prepared in 90% yield from compound 11, and using the procedure described for compound 4. GC-MS, (m/z); 360 (M^+).

Isopropyl- 2- isopropoxy- 6- pentadecylbenzoate (15): To a stirred solution of 1a (100 g, 0.29 mol) in methyl isobutyl ketone (700 ml), potassium carbonate (130 g, 0.94 mol) and tetrabutyl-ammonium hydrogen sulphate (2 g), was added isopropyl bromide (90 ml, 0.96 mol). The reaction mass was refluxed for about 24 h, cooled to RT and added water (500 ml) and ethyl acetate (500 ml).

Organic layer was evaporated to obtain compound 27 as brown color liquid in quantitative yield; GC-MS (m/z); 432 (M^+).

2- Isopropyloxy-6-pentadecylbenzylalcohol (16): Title compound was prepared in 85% yield from compound 15, and using the procedure described for compound 3 as brown color liquid; GC-MS (m/z); 376 (M^+).

2- Isopropyloxy-6-pentadecylbenzaldehyde (18): Title compound was prepared in 90% yield from compound 14, and using the procedure described for compound 4 as brown liquid; GC-MS (m/z); 374 (M^+).

General procedure for the preparation of final compounds (20 - 23): To a stirred solution of benzaldehyde (4, 8, 13, 18) (1 M mole) and methanol (10 ml) was added isoniazide (1 M mol). The reaction mixture was refluxed for about 1 h. Reaction mixture was cooled to room temperature and filtered the solid to get title compounds in yield 90%.

N'- [(1E)- (2- hydroxy- 6- pentadecylphenyl) methylene] isonicotinohydrazide (20): Using the starting materials 4 and isoniazid and general procedure described above, the title compound was obtained as cream color solid in 90% yield; mp. 174 - 176 ºC; IR (KBr); 3190, 3163, 3012, 2918, 2850, 1670, 1651, 1620, 1600, 1552, 1462, 1377, 1311, 1211, 1097, 962, 922, 839, 675 cm^{-1}; ^1H NMR (DMSO-D_6, 200 M Hz); δ 0.82 (m, 3H), 1.22 (brs, 24H), 1.54 (brs, 2H), 1.54 (brs, 2H), 2.74 (t, J = 7.0 Hz, 2H), 6.73-6.81 (m, 2H), 7.19-7.27 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 5.6 Hz, 2H), 8.83 (d, J= 5.6 Hz, 2H), 8.92 (s, 1H); GC-MS (m/z); 451 (M^+).

N'- [(1E)- (2- Methoxy- 6- pentadecylphenyl) methylene] isonicotinohydrazide (21): Using the starting materials 8 and isoniazid, the title compound was obtained as white solid in 90% yield; mp. 122 - 124 ºC; IR (KBr); 3196, 3063, 2955, 2918, 2847, 1651, 1606, 1546, 1465, 1373, 1300, 1269, 1116, 1066, 1049, 979, 923, 839, 792, 750, 678 cm^{-1}; ^1H NMR (DMSO-D_6, 200 MHz); δ 0.84-0.90 (m, 3H), 1.24 (brs, 24H), 1.66 (brs, 2H), 2.64-2.74 (m, 2H), 3.85 (s,3H), 6.74-6.91 (m, 2H), 7.21-7.29 (m, 1H), 7.69-7.71 (m, 2H), 8.67-8.73 (m, 3H); ^{13}C NMR (DMSO-D_6, 50 MHz); δ 14.30, 22.88, 29.88, 30.97, 31.28, 32.11, 33.57, 34.22, 55.93, 108.44, 121.53, 123.51, 130.91, 141.21, 143.90, 144.34, 145.53, 149.88, 150.64, 159.42; GC-MS (m/z); 465 (M^+).

N'- [(1E)- (2- ethoxy- 6- pentadecylphenyl) methylene] isonicotinohydrazide (22): Using the starting materials 13 and isoniazid, the title compound was obtained as white solid in 90% yield; mp. 106 - 108 ºC; IR (KBr); 3211, 3063, 2918, 2848, 1654, 1608, 1595, 1546, 1467, 1456, 1369, 1294, 1267, 1112, 1053, 923, 847, 794, 756, 680 cm^{-1}; ^1H NMR (DMSO-D_6, 200 MHz); δ 0.83 (brs, 6H), 1.8-1.51 (m, 24H), 2.96 (m, 2H), 4.07 (m, 2H), 6.70-6.90 (m, 2H), 7.22-7.29 (m, 1H), 7.24 (m, 2H), 8.78 (m, 2H), 8.80 (s, 1H); ^{13}C NMR (DMSO-D6, 50 MHz); δ 13.89, 14.67, 22.05, 28.97, 30.00, 31.24, 33.73, 63.95, 109.86, 121.56, 122.95, 130.37, 141.10, 144.20, 146.20, 149.50, 150.20, 158.10, 162.00; GC-MS (m/z); 479 (M^+).

N'- [(1E)- (2- isopropoxy- 6- pentadecylphenyl) methylene] isonicotinohydrazide (23): Using the starting materials 18 and isoniazid, the title compound was obtained as white solid in 90% yield; mp. 81 - 83 ºC; IR (KBr); 3213, 3061, 2918, 2848, 1654, 1606, 1593, 1573, 1546, 1467, 1373, 1294, 1263, 1116, 1066, 1022, 964, 923, 839, 792, 756, 680 cm^{-1}; ^1H NMR (DMSO-D_6, 200 MHz); δ 0.81-1.53 (m, 35H), 2.97 (m, 2H), 4.59-4.71 (m, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H),7.84 (d, J = 6.0 Hz, 2H), 8.64 (m, 2H), 8.79 (s, 1H); ^{13}C NMR (DMSO-D6, 50 MHz); δ 14.18, 22.19, 22.33, 28.95, 29.26, 31.18, 31.53, 34.10, 70.91, 111.88, 121.85, 123.22, 130.56, 141.05, 144.12, 146.77, 149.68, 150.48, 157.58, 163.40; GC-MS (m/z); 493 (M^+).

General Procedure for the Preparation of Final Compounds (24 - 26): To a stirred solution of imine compound (21-23) (1 M mol) in methanol (5 ml) was added sodium borohydride (1 M mol) at 15 - 20 ºC. The reaction mixture was stirred for about 0.5 h 10% aq. HCl (20 ml) was added and the material was extracted into ethyl acetate (20 ml). Organic layer was washed with water (2 × 10 ml) and dried over sodium sulphate. Organic solvent was concentrated to obtain title compounds in 80% yield.

N'- (2- methoxy- 6-pentadecylbenzyl) isonicotino hydrazide (24): Using the starting materials 21 and general procedure described above, the title

compound was obtained as cream color solid in 80% yield; mp. 86 - 88 ºC; IR (KBr); 3279, 3236, 3061, 2916, 2848, 1666, 1660, 1599, 1581, 1556, 1458, 1323, 1259, 1234, 1118, 1062, 1041, 1001, 983, 902, 846, 817, 746, 686 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); δ 0.84-0.90 (m, 3H), 1.24 (brs, 24H), 1.58 (m, 2H), 2.81 (t, J = 7.2 & 7.8 Hz, 2H), 3.78 (s, 3H), 4.26 (s, 2H), 6.74 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.20-7.28 (m, 1H), 7.47-7.5 (m, 2H), 8.6 (brs, 2H); GC-MS (m/z); 467 (M^+).

N'- (2- ethoxy- 6-pentadecylbenzyl) isonicotino-hydrazide (25): Using the starting materials 22, the title compound was obtained as brown color liquid in 80% yield; IR (KBr); 3213, 2923, 2850, 1690, 1658, 1600, 1550, 1461, 1265, 1130, 1053, 840, 810, 750, 678 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); δ 0.85-0.91 (m, 3H), 1.25 (brs, 24H), 1.38 (m, 5H), 2.89-2.96 (m, 2H), 3.97-4.22 (m, 4H), 6.71-6.82 (m, 2H), 7.16-7.26 (m, 1H), 7.55-7.7 (m, 2H), 8.7 (brs, 2H); GC-MS (m/z); 481 (M^+).

N'-(2-isopropoxy-6-pentadecylbenzyl)isonicotino hydrazide (26): Using the starting materials 23, the title compound was obtained as brown color liquid in 80% yield; IR (KBr); 2923, 2854, 1685, 1593, 1465, 1373, 1261, 1114, 1018, 870, 800, 750, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); δ 0.84-0.90 (m, 3H), 1.25 (brs, 24H), 1.33-1.53 (m, 8H), 2.91 (t, J = 7.4, 8.0 Hz, 2H),4.57-4.71 (m, 3H), 6.76-6.84 (m, 3H), 7.80 (m, 2H), 8.70 (m, 2H); GC-MS (m/z); 495 (M^+).

General Procedure for the Preparation of Final Compounds (27 - 29): To a stirred solution of benzyl alcohol (6, 11, 16) (6 M mol) and MDC (20 ml) was added thionyl chloride (19 M mol). The reaction mixture was stirred at 35 - 40 ºC for about 3 h. The reaction mixture was cooled to 10 ºC and ice-water (20 ml) was added. The organic layer was separated and washed with water (2 × 20 ml), finally dried over sodium sulphate. The organic solvent was concentrated under reduced pressure to obtain corresponding benzyl chlorides (7, 12, 17). The benzyl chlorides obtained were dissolved in DMF (10 ml) and to this reaction mass was added powdered potassium carbonate (12 M mol) and pyrazine-2-carboxylic acid (6 M mol). The reaction mixture was heated to 80 - 90 ºC and stirred for about 3 h. The reaction mixture was cooled to room temperature and DMF was concentrated under reduced pressure. The residue obtained was dissolved in ethyl acetate (20 ml), washed with water (2 × 10 ml) and dried over sodium sulphate. The organic layer was concentrated to get crude material. The title compounds were obtained in pure form by silica-gel column purification with yields 70%.

(2- methoxy- 6- pentadecylbenzyl) pyrazine- 2-carboxylate (27): Using the starting materials 6 and general procedure as described above, the title compound was obtained as white solid in 70% yield; mp. 72 - 73 ºC; IR (KBr); 3053, 3037, 2916, 2848, 1714, 1600, 1585, 1469, 1408, 1375, 1300, 1263, 1134, 1089, 1045, 1014, 927, 898, 783, 742, 723, 582 cm^{-1}; ^1H NMR ($CDCl_3$, 200 M Hz); δ 0.84-0.91 (m, 3H), 1.24 (brs, 24H), 1.51-1.63 (m, 2H), 2.71 (t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 5.6 (s, 2H), 6.78 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 8.72 (s, 2H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 14.52, 23.10, 29.77, 30.08, 32.34, 33.40, 56.12, 60.27, 108.79, 121.22, 122.33, 130.49, 144.50, 144.50, 144.92, 145.33, 146.70, 147.78, 159.37, 164.47; GC-MS (m/z); 430 (M^+).

(2- ethoxy- 6- pentadecylbenzyl) pyrazine- 2-carboxylate (28): Using the starting materials 11, the title compound was obtained as cream color solid in 70% yield; mp. 48 - 50 ºC; IR (KBr); 3041, 2958, 2924, 1728, 1600, 1589, 1464, 1415, 1392, 1373, 1294, 1269, 1168, 1128, 1085, 1045, 1018, 947, 927, 869, 771, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 200 M Hz); δ 0.84-0.90 (m, 3H), 1.25 (brs, 24H), 1.36 (t, J = 7.0 Hz, 3H), 1.51-1.59 (m, 2H), 2.70 (t, J = 7.6 & 8.0 Hz, 2H), 4.04 (qr, J = 7.0 Hz, 2H), 5.62 (s, 2H), 6.75 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H),7.25 (t, J = 8.2 & 7.6 Hz, 1H), 8.72 (s, 2H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 13.58, 14.34, 22.16, 28.84, 29.14, 31.40, 32.52, 59.41, 63.44, 108.81, 120.53, 121.23, 129.45, 143.37, 143.99, 144.26, 145.72, 146.82, 157.80, 163.45; GC-MS (m/z); 468 (M^+).

(2- isopropoxy- 6- pentadecylbenzyl) pyrazine-2-carboxylate (29): Using the starting materials 16, the title compound was obtained as light brown solid in 70% yield; mp. 44 - 45 ºC; IR (KBr); 3039, 2976, 2920, 2847, 1724, 1591, 1462, 1405, 1373, 1296, 1271, 1128, 1045, 1016, 962, 916, 866, 812, 771, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); δ

0.84-0.90 (m, 3H), 1.25 (brs, 24H), 1.31 (d, J = 6.0 Hz, 6H), 1.55-1.59 (m, 2H), 2.26 (s, 3H) 2.33-2.50 (m, 8H), 2.67 (t, J = 7.6 & 8.2 Hz, 2H), 3.53 (s, 2H), 4.42-4.53 (m, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 8.2 & 7.6 Hz, 1H), 8.72 (s, 2H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 14.52, 22.60, 23.10, 29.77, 30.12, 30.48, 32.15, 32.34, 33.21, 46.38, 52.20, 53.12, 55.79, 70.21, 110.40, 121.84, 125.85, 127.95, 145.86, 156.87; GC-MS (m/z); 482 (M^+).

General Procedure for the Preparation of Final Compounds (30 - 32): To a stirred solution of substituted benzyl alcohol (6, 11, 16) (6 M mol) and MDC (20 ml) was added thionyl chloride (19 M mol). The reaction mixture was stirred at 35 - 40 ºC for about 3 h. The reaction mixture was cooled to 10 ºC and ice - water (20 ml) was added. The organic layer was separated and washed with water (2 × 20 ml), finally dried over sodium sulphate. The organic solvent was concentrated under reduced pressure to obtain corresponding benzyl chlorides (7, 12, 17). The benzyl chlorides obtained were dissolved in MDC (10 ml) and to this reaction mass were added N-methyl piperazine (6 M mol), aq. Sodium hydroxide (12 M mol in 1 ml water) and catalytic amount of TBAB. The reaction mixture was heated to reflux and stirred for about 5h. The reaction mixture was cooled to room temperature. The organic layer was washed with water (2 ×10 ml) and dried over sodium sulphate. The organic layer was concentrated to get crude material. The title compounds were obtained in pure form by silica-gel column purification with yields 65%.

1- (2- methoxy- 6- pentadecylbenzyl)- 4- methyl piperazine (30): Using the starting materials 6 & general procedure described above, the title compound was obtained as brown color liquid in 65% yield; IR (KBr); 2920, 2850, 1581, 1467, 1369, 1269, 1091, 1002, 887, 790, 717, cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz); δ 0.85-0.91 (m, 3H), 1.26 (brs, 24H), 1.57 (m, 2H), 2.50 (s, 3H), 2.62-2.80 (m, 10H), 3.66 (s, 2H), 3.78 (s, 3H), 6.71 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 7.15-7.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 14.51, 22.86, 23.09, 29.76, 30.10, 30.37, 32.07, 32.32, 33.07, 44.52, 51.06, 51.50, 54.53, 55.95, 108.33, 122.31, 123.57, 128.73, 145.49, 158.84; GC-MS (m/z); 430 (M^+).

1- (2- ethoxy- 6- pentadecylbenzyl)- 4- methyl piperazine (31): Using the starting materials 11, the title compound was obtained as brown color liquid in 65% yield; IR (KBr); 2923, 2854, 1585, 1461, 1257, 1083, 1010, 880, 791, 736, cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz); δ 0.85-0.91 (m, 3H), 1.26 (brs, 24H), 1.40 (t, J = 7.0 Hz, 3H), 1.56 (m, 2H), 2.43 (s, 3H), 2.56-2.70 (m, 10H), 3.62 (s, 2H), 3.99 (q, J = 7.0 Hz, 2H), 6.69 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 & 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 14.50, 22.90, 23.08, 29.76, 30.09, 30.38, 32.09, 32.32, 33.11, 45.05, 47.38, 51.64, 54.76, 64.20, 109.23, 122.12, 124.12, 128.48, 145.47, 158.18; GC-MS (m/z); 444 (M^+).

1- (2- isopropoxy- 6- pentadecylbenzyl)-4-methyl piperazine (32): Using the starting materials 16, the title compound was obtained as brown color liquid in 65% yield; IR (KBr); 2950, 2850, 2792, 1581, 1461, 1370, 1253, 1118, 1010, 964, 870, 810, 736, cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 M Hz); δ 0.84-0.90 (m, 3H), 1.25 (brs, 24H), 1.31 (d, J = 6.0 Hz, 6H), 1.55-1.59 (m, 2H), 2.26 (s, 3H), 2.33-2.50 (m, 8H), 2.67 (t, J = 7.6 & 8.2 Hz, 2H), 3.53 (s, 2H), 4.42-4.53 (m, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 & 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 14.52, 22.60, 23.10, 29.77, 30.12, 30.48, 32.15, 32.34, 33.21, 46.38, 52.20, 53.12, 55.79, 70.21, 110.40, 121.84, 125.85, 127.95, 145.86, 156.87; GC-MS (m/z); 458 (M^+).

General Procedure for the Preparation of Final Compounds (33 - 34): To a stirred solution of 2-alkoxy-6-pentadecylbenzoic acid (9, 14) (5 M mol) in hexane (10 volumes) was added thionyl chloride (1/2 vol) and catalytic amount of DMF (2 drops). The reaction mixture was refluxed for about 2 h. Distilled off excess thionyl chloride along with hexane under reduced pressure to obtain 2-alkoxy-6-pentadecyl benzoyl chloride. The acid chloride obtained was dissolved in dichloromethane (5 vol) and added slowly to a stirred solution of D-cycloserine (6 M mol) and triethylamine (10 M mol) in DMF (5 vol), by keeping the temperature of the reaction mixture at 20 - 25 ºC. After the complete addition of acid chloride, the reaction mixture was allowed to stir at 40 ºC for about 1 h. The organic solvent was concentrated under reduced pressure. Ice-water was added to the residue.

The product was extracted into ethyl acetate. The organic phase was separated and washed with water. Finally, dried over anhydrous sodium sulphate, filtered and concentrated organic solvent to obtain crude material of title compounds. Pure compounds were obtained by recrystallisation in hexane with yields more than 80%.

2- methoxy- N- (3-oxoisoxazolidin- 4- yl)- 6- pentadecylbenzamide (33): Using 9, D-cycloserine as starting materials and general procedure described above, the title compound 33 was obtained as off-white solid in 85% yield; IR (KBr); 3342, 3340, 3016, 2920, 2848, 1728, 1685, 1658, 1599, 1581, 1525, 1469, 1384, 1300, 1259, 1195, 1114, 1058, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); δ 0.85-0.91 (m, 3H), 1.25 (brs, 24H), 1.56 (m, 2H), 2.49-2.64 (m, 2H), 3.81 (s, 3H), 4.10-4.20 (m, 2H), 4.84-5.09 (m, 2H), 6.46 (d, J = 4.0 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 & 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 14.51, 22.09, 29.76, 30.09, 31.87, 32.32, 33.67, 52.58, 56.20, 75.88, 108.69, 122.31, 124.98, 130.79, 142.77, 156.56, 169.27, 171.45; GC-MS (m/z); 446 (M^+).

2-ethoxy- N- (3- oxoisoxazolidin- 4- yl)- 6- pentadecylbenzamide (34): Using 14, D-cycloserine as starting materials, the title compound 46 was obtained as off-white solid in 90% yield; IR (KBr); 3356, 3257, 3061, 2918, 2848, 1712, 1654, 1645, 1595, 1581, 1529, 1469, 1392, 1303, 1257, 1197, 1116, 1078, 1057, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz); δ 0.84-0.91 (m, 3H), 1.24 (brs, 24H), 1.38 (t, J = 7.0 Hz, 3H), 1.55 (m, 2H), 2.56-2.65 (m, 2H), 3.96-4.15 (m, 3H), 4.88-5.01 (m, 2H), 6.58 (d, J = 4.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 & 8.2 Hz, 1H); GC-MS (m/z); 460 (M^+).

Preparation of 2-ethoxy-6-pentadecylbenzoic acid (14): To a stirred solution of 10 (10 g, 24.7 M mol) in DMSO (50 ml) was added potassium ter-butoxide (3 g, 24.7 M mol) at RT. The reaction mass was stirred for about 2 h at RT and heated to 40 ºC, stirred for another 2 h. The reaction mass was cooled to RT and quenched in ice-water, adjusted pH to 2 with hydrochloric acid. The resulting precipitate was filtered and dried at RT to obtain 14 as brown solid. 6.5 g, Yield = 70%); Mp; 60 - 62ºC. IR (KBr); 2916, 2846, 1705, 1585, 1461, 1396, 1265, 1118, 1076, cm^{-1}, ^1H NMR ($CDCl_3$, 200 MHz); δ 0.88 (t, J = 6.0 Hz, 3H), 1.25 (brs, 24H), 1.45 (t, J = 7.0 Hz, 3H), 1.59 (m, 2H), 2.78 (t, J = 8.0 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), GC-MS, (m/z); 376 (M^+).

Preparation of APHK-1(2-Ethoxy-6-pentadecyl benzamide): To a stirred solution of 14 (5 M mol) in hexane (10 volumes) was added thionyl chloride (1/2 vol) and catalytic amount of DMF (2 drops). The reaction mass was refluxed for about 2 h. Distilled off excess thionyl chloride along with hexane, under reduced pressure to obtain 2-ethoxy-6-pentadecyl benzoylchloride. The acid chloride obtained was dissolved in dichloromethane (5 vol) and added slowly to a pre-saturated ammonia gas purged dichloromethane by keeping the temp. of the reaction mass at 15 - 20 ºC and stirred for 2 h at 25 - 30 ºC.

Filter off white colour solid, ^1H NMR ($CDCl_3$, 200 MHz); δ 0.88 (t, 3H), 1.25 (m, 26H), 1.39 (t, 3H), 2.26 (t, 2H) 4.0 (q, 2H), 5.78 (s, 2H), 6.8 (d, 2H), 7.19 (d, 1H); HR MS 398.3046 (M^+ Na) (cal cd. for $C_{24}H_{41}NO_2$.Na, 398.3035).

Preparation of 2- methoxy- 6- pentadecyl benzylbromide (35): Ester 5 (5 M mol) is added to LAH (20 M mol) in THF at 25 - 30 ºC, stir for 1 h and check TLC for the absence of starting material, then add ethyl acetate stir for 1 h, then charge water, separate organic layer and dried, concentrate the organic layer under vacuum, GC-MS (DI) m/z = 348. This product was taken in two necked RB flask in methanol, cool to 15 - 20 ºC, then added PBr_3 slowly at 15 - 20 ºC, stir for 1 h to give bromo compound 35.

Preparation of APHK-2 (1- (2- methoxy- 6- pentadecylbenzyl)- 4- hydroxyethylpiperazine): To bromo compound 35 (5 M mol) in chloroform, added 1-hydroxyl ethyl piperazine at 25 - 30 ºC, stirred for 2 h to give APHK-2 as off white solid. ^1H NMR ($CDCl_3$, 200 MHz); δ 0.85 (t, 3H) 1.19 (m, 29H), 2.66 (t, 2H), 2.9 (m, 4H) 3.0 (t, 5H), 3.78 (m, 6H), 6.7 (d, 2H), 7.1 (t, 1H). HR MS (M^+ +H) 461.4102 (cal cd for $C_{29}H_{52}O_2N_2$ 461.4107).

Preparation of APHK-3 (2- hydroxy- 6- pentadecyl)- N- (hydroxyl- ethylamino- ethyl) benzamide): Mono ester 2 (5 M mol) and hydroxyl

ethyl amino ethylamine (6 M mol), heat to 120 ºC for 2 h, cool, add acetone filter, gave off white solid; ^{1}H NMR ($CDCl_3$, 200 MHz); δ 0.85 (t, 3H) 1.25 (m, 21H), 1.59 (t, 2H), 2.64 (t, 2H), 2.88-2.9 (m, 11H), 3.7 (m, 3H), 6.1 (b, 1H), 6.7 (d, 2H), 7.15 (t, 1H); MS 435 (M^+).

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