CHAPTER 1
PREPARATION OF ANACARDIC ACID ANALOGUES AND THEIR BIOLOGICAL ACTIVITIES.

1.1 Introduction;

1.1.1 Cashew nut Shell liquid (CNSL)

Cashew nut Shell liquid (CNSL) is a by product in cashew industry, which is sandwiched in a honeycomb layer of tissue between the two walls of the nut shell. Industrial use include automobile brakers, adhesives, paints and varnishes, insecticides, electrical insulation, and anti-microbials.\textsuperscript{1-3} The shell oil is highly caustic, causing moderate to severe skin irritation.

The principal constituents of CNSL are anacardic acid (figure 1.1, 1a-d), cardanol (2a-d), cardol (3a-d) and minor quantities of 2-methyl cardol (4a-d). All these phenolic compounds exist as mixture of saturated, mono, di, and trienes.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of CNSL constituents}
\end{figure}

1.1.2 Industrial Application of Phenol compounds of CNSL;

Cashew nut Shell liquid (CSNL) is used by many companies in Brazil, India and vietnam as a coating additive. The liquid mainly contains anacardic acid, which is used as an antiseptic. When heated, it undergoes de-carboxylation to yield cardanol.
It is cardanol – a phenol with an unsaturated carbon chain attached – that is of interest to chemists.” You can use the unsaturation of the C\textsuperscript{15} side chain to do chemistry like you do on linseed or soyabean oils, or you can do traditional phenolic chemistry” says Doug Rhubright, technical director at palmer international. Skipkack, Pa. USA

Cardolite, in Newark, N. J., pioneered the CNSL commercialization in the 1920s. The first successful product developed was friction particles and these particles are the result of polymerization of cardanol’s side chain. The phenol part of the molecule is then reacted with formaldehyde, much in the same way that of traditional phenol – formaldehyde resins are made, to yield a cardanol – formaldehyde resin. The cashew – based resin found use in vehicle brakers. In the 1920s, the automotive industry was experimenting with braking systems. The coefficient of friction of brakes based on phenol – formaldehyde resins and asbestos varied with changing temperatures, making them unreliable. Where as cardanol–formaldehyde resin, “stabilized the coefficient of friction. Looking beyond the mature automotive market is CSNL-derived speciality chemicals through phenalkamines. Phenalkamines are made by Mannich reaction between cardanol, formaldehyde, and amines such as ethylenediamine and diethylenetriamine\textsuperscript{3a} The amine becomes attached to the phenol via a methylene bridge. Cardolite developed phenalkamines in the 1970s and was found to be a cheap alternative to polyamide curing agents for the durable epoxy coatings used on concrete floors. But phenalkamines made the coatings too dark for use in flooring. Soon thereafter, Louisville, Ky. USA based Devoe Coatings was working on alternatives to polyamide curing agents in marine paints, Stonis relates. The polyamides wouldn’t cure below 50°F, creating a barrier for painting year- round at shipyards. Isocyantes would cure at lower
temperatures, but they had to be mixed in the field at perfect ratios to the other epoxy components and were sensitive to humidity, leading to failures in the coatings. Phenalkamines can cure epoxies at 35°F and are more forgiving than isocyanates for blending into epoxies.

In 2004, Cardolite Company opened a second plant, in Zhihai, China, close to the massive Chinese, South Korean, and Japanese shipyards. Today, coatings components-phenalkamines and cardolite NC-513, a monoglycidal ether of cardanol used as an epoxy diluents – make up 60% of cardolite’s annual production of about 60,000 metric tones of CNSL, derivatives. They also represent about 80% of the firm’s sales, with the friction particles making up the balance. Cashewthane of Palmer company\(^3\) is added to wood coatings, such as those applied to gymnasium floors, and to light industrial primers. Cashewthane-based formulations, in contrast, don’t sacrifice the drying time or hardness as the cashewthane is toward the light industrial primer market, there is a demand for CNSL-based surfactants. Ethoxylating cardanol create a surfactant used as pigment dispersant for water-based inks. Palmer is looking at ultraviolet-light-curable coatings and other coatings additives by developing a water-based alkyd emulsion system based on cardanol\(^3\).

### 1.1.3 Biological Properties of anacardic acid;

Antimicrobial activity of anacardic acids has been examined against number of bacterial and yeast strains.\(^4\) it is found that sensitivity of gram- negative bacteria and protozoan *Gyrodinium cohni* increased with unsaturation of alkyl chain in anacardic acids. Various analogues of anacardic acid have been synthesized with differing alkyl chain length and their antimicrobial activity has been examined.\(^5\) Antitumor activity is exhibited by anacardic acid, cardol, and cadanol isolated from cashew apple and nuts.\(^6\) All CNSL phenols exhibited antitumor activity against BT-20 breast carcinoma cells and heleplithelial cervix carcinoma cells. In all cases triene showed highest activity. Anacardic acid monoene isolated from *Ginkgo biloba* (*anacardiaceae L.*) also shown antitumor principles.\(^7\) they have been tested against sarcoma 180 ascites in mice at dose of 40mg/kg body weight.
Enzyme inhibitory properties have been mainly attributed to anacardic acids. It has been found that saturated anacardic acid 10' Z-monoene isolated from *Pelargonium xhortorum* flowers are potato lipoxygenase and prostaglandin synthase inhibitors. Anacardic acid monoene had IC50 of 6 and 27µm towards lipoxygease and prostaglandin synthase respectively. Saturated anacardic acid is nearly inhibitory as monoene. Dimethyl derivative of monoene is a poor inhibitor of both enzymes indicating free phenolic group is required for optimum activity. A similar inhibition study against lipoxygenase isolated from potato and soyabean provided an interesting result. The mono and trienes of anacardic acid are potent inhibitors of lipoxygenase, where as diene of anacardic acid resembles arachidinoic acid, which is also a substrate of lipoxygenase. Kubo et al have studied molluscicidal activity of CNSL constituents against *Biomphalaria glabratus*, a snail vector causing schistosomiasis, which is one of the major health problems in the tropics. Inhibitory studies against mushroom tyrosinase have shown that, diene and triene of anacardic acid are competitive inhibitors. Anacardic acid is also found to act as a potentiator of antimicrobial activity. In this study they observed, combination of the antimicrobial compound with a potentiator (anacardic acid) are able to inhibit the growth of certain microorganisms using much lower concentrations of the antimicrobial compound. In an investigation on anti-obesity and fat-reducing agents, Nakatsu et al reported anacardic acid is a good anti-obesity agent. They also reported that, anacardic acid showed no toxicity at a 300mg/kg dose when administered to mice over a period of four weeks. Recently Hatano et al reported that anacardic acid in combination with organic zinc compounds can be used for treatment of coccidiosis in animals. Anacardic acid is also reported to possess mutagenic and carcinogenic activity. Anacardic acid was extensively derivatized to obtain drug like compounds, which are reported to have improved bio-availability. Kanojia et al reported 6-oxo isosteres of anacardic acids as potent inhibitors of bacterial histidine protein kinase.

1.1.4 Isolation of anacardic acid from CNSL

In view of biological and industrial applications of anacardic acid it is necessary to have an efficient method for the separation of anacardic acid. Chromotographic methods are
laborious, time consuming, expensive and not viable for large scale isolation. Separation by fractional distillation is ruled out as anacardic acid is thermo liable and is readily converted to cardanol via decarboxylation. The conventional chemical method of separation of acidic compounds from non-acidic components using carbonates and bicarbonates cannot be applied to CNSL constituents, because the corresponding salts transformed tend to give emulsions due to the hydrophobic nature of CNSL constituents.

There are methods attempted to make salts of anacardic acid with lead hydroxide, sodium hydroxide, later the free acid was generated by treatment with sulfuric acid or hydrochloric acid, followed by extraction with ethylacetate/ hexane. However anacardic acid obtained by these methods is not pure and the yields are low.

To overcome the drawbacks during the isolation of anacardic acid an American company has developed a process for separating acid constituents from toxic phenols. In this process, separation of anacardic acid was achieved by adding calcium hydroxide to a solution of CNSL in isopropyl alcohol and the precipitated calcium anacardate was separated by filtration. The free acid was regenerated by treatment with an inorganic acid such as sulfuric acid or hydrochloric acid. Although this method is considered efficient; there was no mention of either the yield or purity of product. Apart from these methods anacardic acid was isolated in small quantity by HPLC. Mono ene (1b), diene (1c) and triene (1d) of anacardic acid were separated by fractional crystallization between 0 and -80°C using acetone methanol as solvents and by silver nitrate impregnated chromatographic methods. GLC methods for the separation and identification of anacardic acid were unsuccessful.

In more recent efforts, a method has been found to be more efficient to isolate all the major phenolic components of CNSL in to a group of ene mixtures. In this method, the advantage was taken of (a) the difference in acidity of anacardic acid, cardanol and cardols, (b) the tendency of anacardic acid to form a stable salt with alkaline earth metal salt and (c) dihydric phenols forming a complex with amines and their solubility difference in polar and non polar solvents.
In this method the commercially available, solvent extracted CNSL was dissolved in 5% aqueous methanol and powdered calcium hydroxide was added. The solution was heated to 50°C for 3hrs. After completion of the reaction, precipitated calcium anacardate was filtered and washed with methanol. Anacardic acid was regenerated from calcium anacardate by treatment with hydrochloric acid followed by extraction with ethylacetate.

**1.1.5 Synthetic derivatives of Saturated anacardic acid and their applications**

Anacardic acid or its synthones were used to make drug analogues such as sildenafil (a potent phosphodiesterase-5 inhibitor)\(^3\) and 1,4-dihydropyridines (T-type & L-type calcium channel blockers)\(^3\) Its benzimidazole and benzoazole derivatives were explored as COX-1 and COX-2 inhibitors\(^3\)

Quaternary nitrogen compound (5) was synthesized from tetrahydro anacardic acid by mannich reaction\(^3\) This compound was found to have germicidal activity and its structure activity relationship indicated that protection of phenolic group by ether linkage enhanced the activity of quaternaries.

![Chemical structures](image)

Compound (6) and (7) have been synthesized\(^3\) from tetrahydro anacardic acid and studied for their antiallergenic reaction against poison ivy. Sodium anacardate was found to have bactericidal action\(^3\) B. Narayaswamy Et al\(^3\) reported the synthesis of Isonicotinyl hydrazones of anacardic acid. The unsaturated side chain in anacardic acid(1) and its 4-nitro derivative were converted into C\(_8\) – aldehydes and then coupled with isoniazide (an anti – TB drug) to obtain N-isonicotinyl-N’-8-[(2’-carbohydroxy-3’-hydroxy) phenyl] octanal hydrazone (11) N-isonicotinyl-N’-8-[(2’-carbohydroxy-3’-hydroxy-6-nitro) phenyl] octanal hydrazone (12). These isonicotinylhydrazones of anacardic aldehydes showed potent antimycobacterial activity against *Mycobacterium*
*smegmatis mc²*155. The synergistic studies of (11, 12) with isoniazide showed more inhibitory activities than isoniazid alone.

Scheme 1.1; Reagents; (i) HNO₃/CH₃COOH, 65°C; (ii) HCO₃H, 40°C, aq. HCOOH; (iii) NaIO₄; (iv) isoniazide, methanol, 80°C.

Recently it has been reported³⁶ that anacardic acid specifically inhibits HAT activity of p300 and pCAF and amide derivative of anacardic acid (CTPB, 13) has been reported to possess enhancement in p300 HAT activity.
More recently, several analogues of CTPB have been synthesized and elucidated their mechanism of HAT activation, which suggests that, CTPB and its analogues bind to p300 predominantly to the amide group of α-helix and β-sheets and affect the structure of the enzyme. However all these benzamide compounds derived from anacardic acid were reported to be non-cell permeable and are modulators of Histone acetyltransferase p300 activity.

1.2 IMPORTANCE OF THE PRESENT WORK

Natural products continue to be a fertile ground for chemical and biological enquiry and serve as invaluable source of drugs as well as lead molecules for drug synthesis. At present more than 60% of drugs approved for the treatment of cancer are from the natural origin or modeled on natural products scaffolds.

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. Isoniazid, rifampin, pyrazinamide, and ethambutol are the front-line agents that are recommended by World Health Organization (WHO) for the treatment of tuberculosis (TB). The problems with the current TB treatment regimen are complex and include a prolonged standard course regimen of 6 months, which often results in patient non-compliance, the emergence of extensively drug-resistant tuberculosis strains (XDRTB)

The aim of present work is to see, if the abundantly available anacardic acid can be used as synthon for generating derivatives and identify as anti-mycobacterial compounds for
their anti-mycobacterial activity. This was achieved by (a) Alkylation of hydroxyl and carboxylic acid groups of anacardic acid (b) Hydrolysis of ester to acid (c) converting acid to acid chloride and then coupled with substituted amines. The synthesized compounds were tested for anti-mycobacterial activity.

1.3 Results and discussion;

1.3.1 Chemistry

The ene mixture of anacardic acid (1a-d) was isolated from CNSL by a reported method. When calcium hydroxide was added to the natural CNSL it becomes 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 axcid was prepared from ene mixture (1a-d) using hydrogen and Pd/C (Scheme 1.2)

Scheme 1.2

Saturated anacardic acid (1a) was modified into several synthones (16, 19, 20, 21, 24, 25, 29, 30 and 31) as described in scheme 1.3
Scheme 1.3; Synthesis of compounds 16, 19, 20, 21, 24, 25, 29, 30 and 31. Reagents and conditions; (b) dimethyl sulfate, K₂CO₃, acetone, <20°C; (c) LAH, THF, reflux; (d) PCC, MDC, 20°C; (e) dimethyl sulfate, K₂CO₃, acetone, reflux; (f) LAH, THF, reflux; (g) SOCl₂, MDC, 40°C; (h) PCC, MDC, 20°C; (i) DMSO, t-BuOK, 40°C, 2h; (j) diethyl sulfate, K₂CO₃, acetone, reflux; (k) LAH, THF, reflux; (l) SOCl₂,MDC, 40°C; (m) PCC, MDC, 20°C; (n) DMSO, t-BuOK, 40°C, 2h; (o) i-PrBr, K₂CO₃, acetone, reflux; (p) LAH, THF, reflux; (q) ) SOCl₂, MDC, 40°C; (r) PCC, MDC, 20°C; (s) DMSO, t-BuOK, 40°C, 2h.
Compound **1a** was esterified using dimethyl sulfate to get methyl 2-hydroxy-6-pentadecylbenzoate **14**. This on reduction with LAH gave 2-hydroxy-6-pentadecylbenzyl alcohol **15**. Oxidation of **15** using pyridinium chlorochromate (PCC) yielded compound **16**. Similarly, O-alkylation and esterification of carboxylic acid group of **1a** using dimethyl sulfate, diethyl sulfate and isopropyl bromide obtained compounds **17, 22** and **27** respectively. Reduction followed by oxidation of these compounds obtained synthones **20, 25** and **30**. Compounds **19, 24** and **29** were obtained by the treatment of compounds **18, 23** and **28** with thionyl chloride. The synthones **21, 26** and **31** were obtained by the ester hydrolysis of compounds **17, 22** and **27** respectively. The Isonicotinyl hydrazone derivative compounds **32-38** were prepared from corresponding aldehydes (scheme 1.4) by refluxing with isoniazid to obtain isonicotinoylhydrazones of anacardic acid (**32-35**). Reduction of the compounds **33-35** obtained another set of isoniazide derivatives **36-38** (scheme 1.4).

**Scheme 1.4:** Synthesis of compounds 32 – 38. Reagents and conditions; (a) MeOH, isoniazide, reflux. (b) MeOH, NaBH₄, 25°C.
Scheme 1.5; Synthesis of compounds 39 – 44. Reagents and conditions; (a) Pyrazine – 2-carboxylic acid, K₂CO₃, DMF, 85°C; (b) N-methylpiperazine, aq. NaOH, MDC, TBAB, 40°C.

Also synthesized pyrazine carboxylic acid and N-methyl piperazine derivatives of anacardic acid, by reacting 2-alkoxy-6-pentadecylbenzyl chloride with piperazine-2-carboxylic acid and N-methyl piperazine (39–44, Scheme 1.5). Furthermore, D-cycloserine derivatives of anacardic acid (45, 46) were prepared by reacting corresponding acid chlorides (21, 26) with cycloserine (Scheme 1.6). 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.

Scheme 1.6; Synthesis of compounds 45-46. Reagents and conditions; (a) SOCl₂, Hexane, Reflux, 2h; (b) MDC-DMF, TEA, D-Cycloserine, 40°C, 1h
Compound **APHK-1** was synthesized from **26**, this on treatment with thionyl chloride gave acid chloride and then coupled with ammonia. (Scheme 1.7)

![Scheme 1.7](image)

**Scheme 1.7**: synthesis of compound **APHK – 1**, (a) Hexane, SOCl₂, two drops of DMF, reflux then to ammonia in toluene.

Compound **APHK-2** was synthesized from **17**, reduction of ester with LAH/THF, followed by treatment with PBr₃ gave bromo compound **47**, which on treatment with hydroxyl ethyl piperazine gave **APHK-2**. (scheme 1.8)

![Scheme 1.8](image)

**Scheme 1.8**: reagents and conditions; (a) LAH in THF, PBr₃ (b) N-hydroxy ethylamino piperazine

Title compound **APHK-3** was synthesized from **14**, condensation reaction of monoester with hydroxyl ethyl amino ethyl amine gave **APHK-3** (scheme 1.9)
Scheme 1.9; reagents and conditions; (a) hydroxyethylaminoethylamine, 120°C,

1.3.2 Biological activity;

MIC values for compounds were determined against *M. smegmatis* mc²155 cells which were grown to saturation in Youman-Karlson (YK) broth medium³⁸ at 37°C.

Antimycobacterial activity of the compounds was assayed by the broth dilution method. Stock solutions (10mg/ml) of the compounds were prepared in methanol and serially diluted using YK culture broth. To all serially diluted solutions, 0.5ml of suitably diluted inoculums was added (10⁶ cfu) and incubated at 37°C for 24 hours. The lowest concentrations of the compound that inhibited growth of the organism was taken as minimum inhibitory concentration (MIC), Ethambutol which is a anti-tuberculosis drug was taken as reference compound.
## Tabular Chart of compounds and their MIC<sub>50</sub> values

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<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg)</th>
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<tr>
<td>Ethambutol</td>
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<tr>
<td>APHK-1</td>
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<td>140.92</td>
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<td>APHK-3</td>
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Conclusion;

Saturated anacardic acid was prepared from the mixture (1a-d) obtained from cashew nut shell liquid (CNSL) using hydrogen and Pd/C and it was used to make isoniazide derivatives (32-38), pyrazine analogues (39-41) and N-methypiperazine analogues (42-44), D-cycloserine analogues (45, 46), APHK-1, APHK-2, and APHK-3. All these anacardic acid analogues were tested against *M. smegmatis* mc² 155 for anti-mycobacterial activity taking anacardic acid and Ethambutol (TB drug) as standards. APHK-3 showed good anti-mycobacterial activity compared to anacardic acid.
1.4 Experimental section;

1.4.1 General 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 200MHz on a Brukar A G Spectrometer. All the chemical shift values are reported in $\delta$ units and down field from TMS as internal standard. Mass spectra were recorded using GC MS-qp2010s (Direct probe) and on Q-TOF micro™ 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.

1.4.2 Solvent extracted CNSL

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.

1.4.3 Isolation of anacardic acid from natural CNSL

Commercially available solvent extracted CNSL (100g) was dissolved in 5% aqueous methanol (600ml). To the methanolic solution, activated charcoal (20g) 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 (50g) was added in portions under stirring. After complete addition of calcium hydroxide, the temperature of the reaction mixture was raised to 50°C and stirred for 3h. 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 (200ml) and the cake was dried under vacuum at 45-50°C and stirred for 2h (dry weight 110g). The calcium anacardate was suspended in distilled water (440ml) and 11 NHCl (60ml) was added and stirred for one hour. The resultant solution was extracted with ethyl acetate (2X150ml). the combined organic layers were washed with distilled water (2X100ml), dried over anhydrous sodium sulfate and concentrated under reduced
pressure to yield ene mixture of anacardic acid (60g). the identity of the compound was confirmed by HPLC and in comparison with standard samples.39

1.4.4 Preparation of saturated anacardic acid (1a)

Ene mixture of anacardic acid (30g) was dissolved in methanol (120ml). 5% Pd/c (0.75g) was added slowly and this solution was transferred into hydrogenation flask. Hydrogenation was carried out with 2.5Kg/cm² pressure for 2h, 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°C); Yield=27g, MP; 90-91°C (lit. Mp; 90-92°C).32 IR (KBr); 3140, 2917, 1650, 1655, 1604, 1466, 1308, 1206, 894, 815, 757 cm⁻¹; ¹H NMR (200 MHz, CDCl₃); 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).

1.4.5 Methyl 2-hydroxy-6-pentadecylbenzoate (14).

To a stirred solution of saturated anacardic acid 1a (10g, 0.028 mol) and powdered potassium carbonate (17.5g, 0.125 mol) in acetone (75 ml) was added dimethyl sulfate (3.62g, 0.028 mol) in portions with stirring at 10°C. After the addition of dimethyl sulfate, the temperature of the reaction mixture was raised to 15-20°C and maintained for 4h. After the completion of the reaction, the solvent was evaporated under reduced pressure. To the residue obtained was added distilled ethylacetate (50 ml) and the material was extracted into ethyl acetate (100 ml) washed with water (2X100 ml), finally dried over sodium sulfate and concentrated organic solvent to obtain crude mass (9g). The crude material was recrystallized from hexane to get title compound 14. Yield; 7.5g; mp; 40-41°C (lit mp 40-41°C)32; GC-MS (M/Z); 362 (M⁺).

1.4.6. 2-hydroxy-6-pentadecylbenzylalcohol (15);

To a stirred solution of compound 14 (7.5g, 0.022 mol) in THF (40 ml) was added LAH (0.75g, 0.019 mol) slowly in portions at RT. The reaction mass was refluxed for about 2h. It was then cooled to 10°C. 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 (2X50 ml) and finally dried over anhydrous Na₂SO₄. The organic layer was concentrated and the residue was recrystallized in hexane to obtain title compound 15. Yield: 5g, MP: 63-65°C (Lit mp 63-64°C). 32; GC-MS (M/Z): 334(M⁺).

1.4.7. 2-hydroxy-6-pentadecylbenzaldehyde (16);

To a stirred solution of compound 15 (5g, 0.015 mol) and MDC (50 ml) was added pyridinium chlorochromate (PCC) (6.4g, 0.03 mol) in portions at 20°C. After the complete addition of PCC, the reaction mixture was stirred for about 1h. 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 16. Yield: 4.5g; GC-MS (m/z): 332 (M⁺).

1.4.8. Methyl 2-methoxy-6-pentadecylbenzoate (17);

To a stirred solution of tetrahydroanacardic acid 1a (20g, 0.057 mol) and powdered potassium carbonate (32g, 0.232 mol) in acetone (120 ml) was added dimethyl sulfate (14.48g, 0.112 mol) in portions with stirring at room temperature. After the addition of dimethy sulfate, the reaction mixture was refluxed for about 3h. The reaction mixture was cooled to room temperature and inorganics 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 sulfate. The organic layer was concentrated to obtain title compound 17. Yield: 20g, mp: 37-38°C (lit mp: 37-38°C). 32; GC-MS (M/Z): 376 (M⁺).

1.4.9. 2-Methoxy-6-pentadecylbenzylalcohol (18);

Title compound was prepared in 80% yield from compound 17 and using the procedure described for compound 15. Mp: 57-58°C, (lit mp: 57-58°C). 32; GC-MS (m/z): 348 (M⁺).
1.4.10. 2-Methoxy-6-pentadecylbenzaldehyde (20);

Title compound was prepared in 90% yield from compound 18, and using the procedure described for compound 16. GC-MS, (m/z); 346 (M+).

1.4.11. Preparation of ethyl-2-ethoxy-6-pentadecylbenzoate (22);

To a stirred solution of 1a (12g, 0.035 mol) in acetone (60ml) was anhydrous powdered potassium carbonate (14.4g, 0.104 mol). The diethyl sulfate (10.7g, 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 3h. the reaction mass was cooled to RT and then concentrated under reduced pressure. Water (100ml) was added to the reaction mixture and extracted with ethyl acetate (80ml). The organic layer was evaporated to afford product 22 as viscous liquid. Yield: 12.8 gms, 92% (theoretical yield), IR (KBr); 2920, 1730, 1260 cm\(^{-1}\) GC-MS (m/z); 404 (M+).

1.4.12. 2-Ethoxy-pentadecylbenzylalcohol (23);

Title compound was prepared in 85% yield from compound 22 and using the procedure described for compound 15. Mp; 45-46\(^{\circ}\)c, (lit mp; 45-46\(^{\circ}\)c). GC-MS (m/z); 362 (M+).

1.4.13. 2-Ethoxy-6-pentadecylbenzaldehyde (25);

Title compound was prepared in 90% yield from compound 23, and using the procedure described for compound 16. GC-MS, (m/z); 360 (M+).

1.4.14. Isopropyl-2-isopropoxy-6-pentadecylbenzoate (27);

To a stirred solution of 1a (100g, 0.29 mol) in methyl isobutyl ketone (700 ml), potassium carbonate (130g, 0.94 mol) and tetrabutylammoniumhydrogen sulfate (2g), was added isopropyl bromide (90ml, 0.96 mol). The reaction mass was refluxed for about 24h, cooled to RT and added water (500 ml) & 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+).

1.4.15. 2-Isopropyloxy-6-pentadecylbenzylalcohol (28);
Title compound was prepared in 85% yield from compound 27, and using the procedure described for compound 15 as brown color liquid; GC-MS (m/z); 376 (M⁺).

1.4.16. 2-Isopropyloxy-6-pentadecylbenzaldehyde (30);

Title compound was prepared in 90% yield from compound 26, and using the procedure described for compound 16 as brown liquid; GC-MS (m/z); 374 (M⁺)

1.4.17. General procedure for the preparation of final compounds (32-35);

To a stirred solution of benzaldehyde (16, 20, 25, 30) (1 mmole) and methanol (10 ml) was added isoniazide (1 mmol). The reaction mixture was refluxed for about 1h. Reaction mixture was cooled to room temperature and filtered the solid to get title compounds in yield 90%

1.4.17a. N’-[(1E)-(2-Hydroxy-6-pentadecylphenyl) methylene] isonicotinohydrazide (32);

Using the starting materials 16 & isoniazid and general procedure described in 1.4.17., the title compound was obtained as cream color solid in 90% yield; mp. 174-176°C; 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-D₆, 200 M Hz); δ 0.82 (m, 3H), 1.22 (brs, 24H), 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⁺).

1.4.17b. N’-[(1E)-(2-Methoxy-6-pentadecylphenyl) methylene] isonicotinohydrazide (33);

Using the starting materials 20 & isoniazid and general procedure described in 1.4.17., the title compound was obtained as white solid in 90% yield; mp. 122-124°C; 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-D₆, 200 M Hz); 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); ¹³C NMR (DMSO-D₆,
200 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+).

1.4.17C. N’-[(1E)-(2-ethoxy-6-pentadecylphenyl) methylene] isonicotinohydrazide (34);

Using the starting materials 25 & isoniazid and general procedure described in 1.4.17., the title compound was obtained as white solid in 90% yield; mp. 106-108°C; 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-D₆, 200 M Hz); 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); ¹³C NMR (DMSO-D₆, 200 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⁺).

1.4.17d. N’-[(1E)-(2-isopropoxy-6-pentadecylphenyl) methylene] isonicotinohydrazide (35);

Using the starting materials 30 & isoniazid and general procedure described in 1.4.17., the title compound was obtained as white solid in 90% yield; mp. 81-83°C; 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-D₆, 200 M Hz); 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); ¹³C NMR (DMSO-D₆, 200 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⁺).

1.4.18 General procedure for the preparation of final compounds (36-38);

To a stirred solution of imine compound (33-35) (1 mmol) in methanol (5 ml) was added sodium borohydride (1 mmol) at 15-20 °C. the reaction mixture was stirred for about 0.5h. 10% aq. HCl (20 ml) was added and the material was extracted into ethyl acetate (20 ml).
Organic layer was washed with water (2x10 ml) and dried over sodium sulfate. Organic solvent was concentrated to obtain title compounds in 80% yield.

1.4.18a. N’-(2-methoxy-6-pentadecylbenzyl)isonicotinohydrazide (36);

Using the starting materials 33 & general procedure described in 1.4.18., the title compound was obtained as cream color solid in 80% yield; mp. 86-88°C; 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 (CDCl₃, 200 M Hz); 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⁺).

1.4.18b. N’-(2-ethoxy-6-pentadecylbenzyl)isonicotinohydrazide (37);

Using the starting materials 34 & general procedure described in 1.4.18., 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 (CDCl₃, 200 M Hz); 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⁺).

1.4.18c. N’-(2-isopropoxy-6-pentadecylbenzyl)isonicotinohydrazide (38);

Using the starting materials 35 & general procedure described in 1.4.18., 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 (CDCl₃, 200 M Hz); 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⁺).

1.4.19 General procedure for the preparation of final compounds (39-41);

To a stirred solution of benzyl alcohol (18, 23, 28) (6 mmol) and MDC (20 ml) was added thionyl chloride (19 mmol). The reaction mixture was stirred at 35-40°C for about
3h. The reaction mixture was cooled to 10°C and ice-water (20 ml) was added. The organic layer was separated and washed with water (2x20 ml), finally dried over sodium sulfate. The organic solvent was concentrated under reduced pressure to obtain corresponding benzyl chlorides (19, 24, 29). The benzyl chlorides obtained were dissolved in DMF (10 ml) and to this reaction mass was added powdered potassium carbonate (12 mmol) and pyrazine-2-carboxylic acid (6 mmol). The reaction mixture was heated to 80-90°C and stirred for about 3h. 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 (2x10 ml) and dried over sodium sulfate. 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%.

1.4.19a. (2-methoxy-6-pentadecylbenzyl) pyrazine-2-carboxylate (39);

Using the starting materials 18 & general procedure described in 1.4.19., the title compound was obtained as white solid in 70% yield; mp. 72-73°C; 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 (CDCl₃, 200 M Hz); δ 0.84-0.91 (m, 3H), 1.24 (bbrs, 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 = 7.6 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); ¹³C NMR (CDCl₃, 200 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, 144.92, 145.33, 146.70, 147.78, 159.37, 164.47; GC-MS (m/z); 430 (M⁺).

1.4.19b. (2-ethoxy-6-pentadecylbenzyl) pyrazine-2-carboxylate (40);

Using the starting materials 23 & general procedure described in 1.4.19., the title compound was obtained as cream color solid in 70% yield; mp. 48-50°C; 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 (CDCl₃, 200 M Hz); δ 0.84-0.90 (m, 3H), 1.25 (bbrs, 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); 13C NMR (CDCl3, 200 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+).

**1.4.19c. (2-isopropoxy-6-pentadecylbenzyl)pyrazine-2-carboxylate (41);**

Using the starting materials 28 & general procedure described in 1.4.19., the title compound was obtained as light brown solid in 70% yield; mp. 44-45°C; 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 (CDCl3, 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 = 8.2 & 7.6 Hz, 1H), 8.72 (s, 2H), 9.24 (s, 1H); 13C NMR (CDCl3, 200 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⁺).

**1.4.20. General procedure for the preparation of final compounds (42-44);**

To a stirred solution of substituted benzyl alcohol (18, 23, 28) (6 mmol) and MDC (20 ml) was added thionyl chloride (19 mmol). The reaction mixture was stirred at 35-40°C for about 3h. The reaction mixture was cooled to 10°C and ice-water (20 ml) was added. The organic layer was separated and washed with water (2x20 ml), finally dried over sodium sulfate. The organic solvent was concentrated under reduced pressure to obtain corresponding benzyl chlorides (19, 24, 29). The benzyl chlorides obtained were dissolved in MDC (10 ml) and to this reaction mass were added N-methyl piperazine (6 mmol), aq. Sodium hydroxide (12 mmol 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 (2x10 ml) and dried over sodium sulfate. 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%.

1.4.20a. 1-(2-methoxy-6-pentadecylbenzyl)-4-methylpiperazine (42);

Using the starting materials 18 & general procedure described in 1.4.20., 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; ¹H NMR (CDCl₃, 200 M Hz); 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); ¹³C NMR (CDCl₃, 200 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⁺).

1.4.20b. 1-(2-ethoxy-6-pentadecylbenzyl)-4-methylpiperazine (43);

Using the starting materials 23 & general procedure described in 1.4.20., 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; ¹H NMR (CDCl₃, 200 M Hz); 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); ¹³C NMR (CDCl₃, 200 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⁺).

1.4.20c. 1-(2-isopropoxy-6-pentadecylbenzyl)-4-methylpiperazine (44);

Using the starting materials 28 & general procedure described in 1.4.20., the title compound was obtained as brown color liquid in 65% yield; IR (KBr); 2920, 2850, 2792, 1581, 1461, 1370, 1253, 1118, 1010, 964, 870, 810, 736, cm⁻¹; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 200 MHz); δ 14.52, 22.60, 23.10, 29.77, 30.12, 30.48, 32.15,
1.4.21. General procedure for the preparation of final compounds (45-46);

To a stirred solution of 2-alkoxy-6-pentadecylbenzoic acid (21, 26) (5 mmol) 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 2h. 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 mmol) and triethylamine (10 mmol) in DMF (5 vol), by keeping the temperature of the reaction mixture at 20-25°C. After the complete addition of acid chloride, the reaction mixture was allowed to stir at 40°C for about 1h. 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 sulfate, 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%.

1.4.20a. 2-methoxy- N-(3-oxoisoxazolidin-4-yl)-6-pentadecylbenzamide (45);

Using 21, D-cycloserine as starting materials and general procedure described in 1.4.20., the title compound 45 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 200 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⁺).

1.4.20b. 2-ethoxy- N-(3-oxoisoxazolidin-4-yl)-6-pentadecylbenzamide (46);
Using 26, D-cycloserine as starting materials and general procedure described in 1.4.20., the title compound 46 was obtained as off-white solid in 90% yield; IR (KBr); 3356, 3257, 3061, 2918, 1712, 1654, 1595, 1581, 1469, 1392, 1303, 1257, 1197, 1116, 1078, 1057, 920 cm⁻¹; ¹H NMR (CDCl₃, 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⁺).

1.4.21 Preparation of 2-ethoxy-6-pentadecylbenzoic acid (26);

To a stirred solution of 22 (10g, 24.7 mmol) in DMSO (50ml) was added potassium tert-butoxide (3g, 24.7 mmol) at RT. The reaction mass was stirred for about 2h at RT and heated to 40°C, stirred for another 2h. 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 26 as brown solid. 6.5g, Yield= 70%; Mp; 60-62°C. IR (KBr); 2916, 2846, 1705, 1585, 1461, 1396, 1265, 1118, 1076, cm⁻¹; ¹H NMR (CDCL₃, 200 MHz); δ 0.88 (t, J=6.0 Hz, 3H), 1.25 (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⁺).

1.4.22 Preparation of APHK-1;

To a stirred solution of 26 (5 mmol) 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 2h. 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 temperature of the reaction mass at 15-20°C and stirred for 2h at 25-30°C. Filter off white colour solid, ¹H NMR (CDCl₃, 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) (calcd. for C₂₄H₄₁NO₂.Na, 398.3035).

1.4.23 Preparation of 2-methoxy-6-pentadecylbenzylbromide (47);
Ester 17 (5 mmol) is added to LAH(20 mmol) in THF at 25-30°C, stir for 1 hr and check TLC for the absence of starting material, then add ethyl acetate stir for one hr, 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°C, then added PBr₃ slowly at 15-20°C, stir for 1 hr. to give bromo compound 47.

1.4.24 Preparation of APHK-2;

To bromo compound 47 (5 mmol) in chloroform, added 1-hydroxyl ethyl piperazine at 25-30°C, stirred for 2 hr. to give APHK-2 as off white solid. ¹H NMR (CDCl₃, 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 (cald for C₂₉ H₅₂O₂N₂461.4107),

1.4.12 Preparation of APHK-3;

Mono ester 14 (5 mmol) and hydroxyl ethyl amino ethylamine (6 mmol), heat to 120°C for 2 hr, cool, add acetone filter, gave off white solid, APHK-3 ¹H NMR (CDCl₃, 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⁺),
1.5 Reference;


19. Survey of cashew nut shell liquid. The Regional Research. Laboratory. Hyderabad, 1, **1985**.


22. General Foods Corporation, USA, Indian Patent, **1946**, 34671.


