Synthesis and Antibacterial Activity of Anacardic Acid Derivatives

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Abstract: New anacardic acid derivatives (**6a -6u**) were prepared from commercially available anacardic acid and tested for Gram positive and Gram negative activities. Most compounds were found to be active compared to ampicillin.

Keywords: Anacardic acid derivatives, Cashew Nut Shell Liquid, Antibacterial activity, Synthesis, Gram positive bacteria, Gram negative bacteria.

1. INTRODUCTION

The emergence of drug resistant strains in clinical applications [1-3] especially to Gram positive bacteria [4-5] has created a problem of global proportions [6-7]. This phenomenon has led to a resurgence of interest in creating novel antibacterial agents distinct from existing classes of compounds.

Anacardic acid (pentadecyl salicylic acid, Fig. **1**) is a phenolic constituent present in Cashew Nut Shell Liquid (CSNL); (*Anacardium occidentale L.*) and exhibits antimicrobial properties [8-9], which have led to the preparation of various analogues [10-11]. This report describes the synthesis, spectroscopic identification and antibacterial activity of some novel anacardic acid derivatives (**6a-6u**) against *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Staphylococcus aureus* bacterial strains.

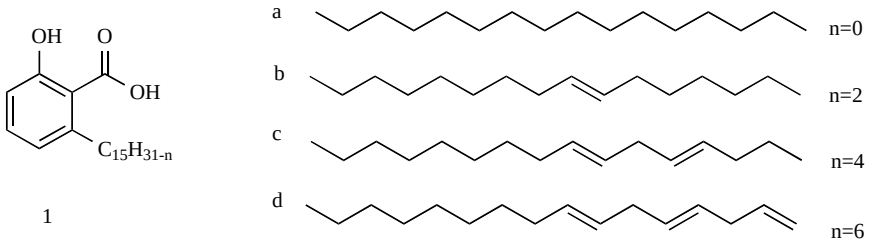

Fig. (1). The anacardic acid mixture.

2. SYNTHESIS, RESULTS AND DISCUSSION

2.1. Synthesis and Evaluation

The anacardic acid mixture (Fig. **1**, **1a–d)** was isolated [12] from commercially available CNSL as a mixture of monoene, diene and triene located at (8'), (8', 11') and (8', 11', 14') isomers of the C15 alkyl chain, respectively. Hydrogenation of the ene mixture of anacardic acid [13] resulted in the formation of the saturated anacardic acid which was converted to the dialkylated compound by reaction with dimethylsulfate in acetonitrile. The dialkylated anacardic acid was reduced to alcohol by treatment with $LiAlH_4$ in tetrahydrofuran and then protected with methanesulphonyl chloride in dichloromethane. The resultant mesylated compound was then coupled with various amines in presence of triethylamine in acetonitrile to obtain derivatives of anacardic acid (**6a-6u)** and no dialkylated products were observed (Scheme **1**). Compounds **6a – 6u** were tested against two Gram positive strains viz., i) *Escherichia coli, and ii) Pseudomonas aeruginosa,* and two Gram negative strains *viz., i). Streptococcus pyogenes, and ii) Staphylococcus aureus* using agar well diffusion method according to the literature protocol [14]. The anti-bacterial activity of the analogues was compared with standard drug ampicillin (Table **1**).

2. RESULTS AND DISCUSSION

Based on the test results it is evident that several synthesized anacardic acid analogues possess moderate to good activity against the Gram +ve and Gram –ve bacteria. Of all the compounds prepared entities **6b**, **6c, 6e, 6g, 6h, 6j, 6l, 6m, 6o, 6p, 6s** and **6u** display good to excellent activity while the remaining compounds showed moderate activity against *Staphylococcus aureus.* In case of *Streptococcus pyogenes* compounds **6d**, **6k**, **6l**, **6r**, **6t** showed moderate activity while the remaining compounds showed good activity. In case of inhibition of *Pseudomonas aeruginosa* compounds **6d, 6e, 6f, 6j, 6l, 6o** and **6u** showed good to excellent

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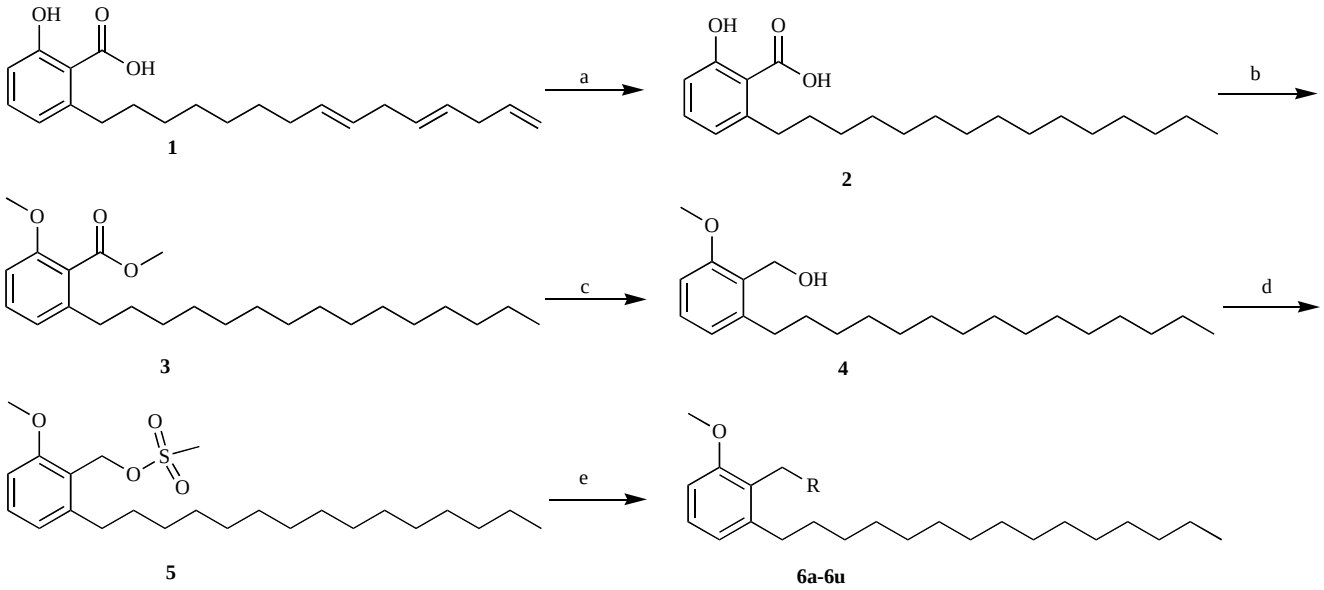
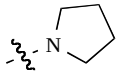
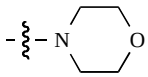
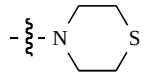
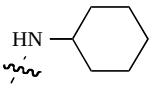
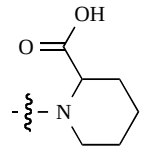
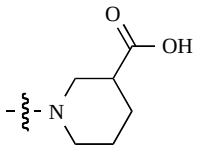
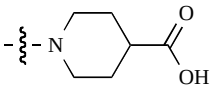


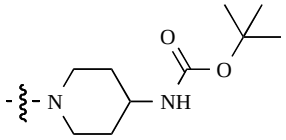
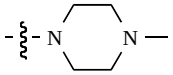
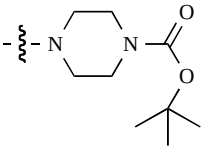
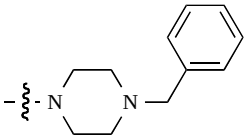
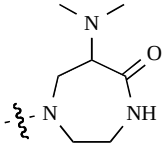
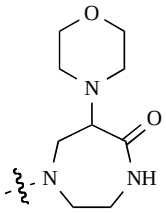
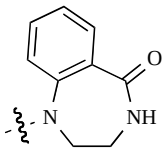
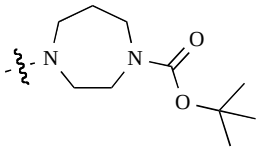
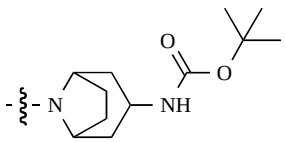
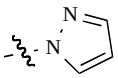
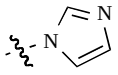
Scheme 1. Synthesis of anacardic acid derivatives **6a-6u**.

Experimental conditions: a) 10% Pd/C, EtOH, H_2, 50 psi, rt, 2h; b) Dimethyl sulfate, K_2CO_3, Acetonitrile, 90 °C, 24h; c) $LiAlH_4$,THF, 0 °C–rt,18h; d) Methanesulfonyl chloride, triethylamine, dichloromethane, 0 °C-rt, 3h; e) amines, triethylamine, acetonitrile, 85 °C, 3-18h

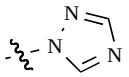
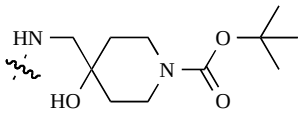
Table 1. Results of Antibacterial Bioassay of Compounds 6a-6u (Concentration Used 250 µg/mL of DMSO) Zones of inhibition of compounds 6a-6u

		Name of the Bacteria			
Compound no.	**R**	***E. coli***	***P. aeruginosa***	***S. aureus***	***S. pyogenes***
6a		19	17	16	18
6b		19	18	17	19
6c		20	18	18	20
6d		22	19	16	16
6e		19	20	19	18
6f		18	19	16	17
6g		16	17	18	18
6h		20	18	19	19

(Table 1). Contd…..

Name of the Bacteria					
Compound no.	**R**	***E. coli***	***P. aeruginosa***	***S. aureus***	***S. pyogenes***
6i		21	19	16	18
6j		19	19	19	21
6k		21	15	15	16
6l		19	20	18	16
6m		20	17	17	19
6n		20	15	16	19
6o		17	21	17	19
6p		17	18	17	19
6q		17	18	15	21
6r		18	16	16	17
6s		16	18	18	18

(Table 1). Contd…..

Name of the Bacteria					
Compound no.	**R**	***E. coli***	***P. aeruginosa***	***S. aureus***	***S. pyogenes***
6t		14	15	16	16
6u		20	20	18	18
SD* ampicillin	SD* ampicillin	20	20	18	19

activity. In case of inhibition of *Escherichia coli* compounds **6c, 6d, 6h, 6i, 6k, 6m, 6n,** and **6u** showed good activity with a zone of inhibition 20, 22, 20, 21, 21, 20, 20, 20 mm. The most active antibacterial agent against *Escherichia coli* was found to be compound **6d** having thiomorpholine, compound **6i** having 4-amino boc protected piperidine and compound **6k** having N-Boc protected piperizine residue as R, while all the other compounds in the series exhibited moderate to good activity. These results indicate that compound **6a, 6b, 6c** and the remaining compounds in the series might find less resistance to pass the cell wall in comparison to compounds **6d, 6i and 6k.** The activity depends to some extent on the R substituent, however all the compounds show antibacterial activity. So other functionalities in the molecule will contribute to the activity as well**.** It may be suggested that the anacardic acid derivative with a suitable R may lead to a good antibacterial agent for all the *Escherichia coli*, *Pseudomonas aeruginosa, Streptococcus pyogenes* and *Staphylococcus aureus* bacterial strains.

3. GENERAL EXPERIMENT

Melting points were determined in open glass capillaries on a Mel-temp apparatus and are uncorrected.

Thin-layer chromatography (TLC) was performed on E.Merk AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-360 spectrometer (400MHz). All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS.

3.1. Antibacterial Bioassay

Anacardic acid analogues (**6a – 6u**) were dissolved in dimethyl sulphoxide at 250 µg/mL concentration. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4. After 18h the exponentially growing cultures of the six bacteria in nutrient broth at 37 ^{o}C were diluted in sterile broth. From each of these diluted cultures, 1mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^6 cell/ml. The plates were set at room temperature and later dried at 37 °C for 20h. Paper discs (6mm, punched from whatmann no 41 paper) were ultraviolet sterilized and used for the assays. Discs were soaked in different concentrations of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. All the samples were taken in triplicates. The plates were incubated at 37 °C in an inverted fashion. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

3.2. Experimental Section

2-hydroxy-6-pentadecyl-benzoic acid (2)

An ethanol solution (500 mL) of **1** (100 g, 0.28 mol) was hydrogenated in a 1L Parr apparatus at 50 psi in the presence of 10 % Pd/C (10 g, 10 %) under argon for 2 h. The reaction mixture was filtered through celite and concentrated to obtain **2** which was recrystallized in pet ether (Yield: 70 g, 68.8%; white solid); M.p: 85-86 °C; IR (KBr): ν_{max} 3071, 3002, 2918, 2851, 1655, 1450, 1246, 1214 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, *J* = 6.8 Hz), 1.27 (bs, 24H), 1.57-1.63 (m, 2H), 2.98 (t, 2H, *J* = 8.0 Hz), 6.78 (d, 1H, *J* = 7.6 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 7.37 (t, 1H, *J* = 8.0 Hz), 11.02 (bs, 1H); EI MS: m/z (rel.abund.%) 349 (M^+, 100)

2-Methoxy-6-pentadecyl-benzoic acid methyl ester (3)

An acetonitrile (200 mL) solution of **2** (20 g, 0.57 mol), K_2CO_3 (40.8 g, 0.28 mol) and dimethyl sulphate (21.76 mL, 0.22 mol) was refluxed for 24 h. The reaction mixture was filtered and the filtrate was distilled. The residue was dissolved in ethyl acetate and washed with water (2x200 mL), brine solution (175 mL), dried over anhydrous sodium sulphate, filtered and concentrated to obtain **3** (Yield: 18.5 g, 85.5%, pale yellow solid); M.p: 36-37 °C; IR (KBr): ν_{max} 3004, 2921, 2852, 1732, 1589, 1266, 1105 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (bs, 24H), 1.53-1.60 (m, 2H), 2.53 (t, 2H, *J* = 8.0 Hz), 3.81 (s, 3H), 3.90 (s, 3H), 6.75 (d, 1H, *J* = 8.4 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 7.25 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 377 (M^+, 100).

2-Methoxy-6-pentadecyl-phenyl-methanol (4)

To a suspension of $LiAlH_4$ (3.03 g, 0.08 mol) dry tetrahydrofuran (150 mL) was added a pre-mixed of **3** (20 g, 0.05 mol) in tetrahydrofuran (100 mL) drop wise over a period of 40 min at 0 °C and was to slowly brought to room temeprature, and stirred for 18 h. The reaction mixture was quenched

with brine solution (40 mL) at 0 °C diluted with ethyl acetate, filtered (200 mL) and washed with ethyl acetate (100 mL), the filtrate was washed with brine solution (200 mL) dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to obtain **4** (Yield: 15 g, 81%, off-white solid); M.p: 60-62 °C; IR (KBr): ν_{max} 3386, 3073, 2917,2847, 1465,1263, 1093 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, *J* = 7.2 Hz), 1.27 (bs, 24H), 1.53-1.58 (m, 2H), 2.37 (t, 1H, *J* = 6.4 Hz), 2.68 (t, 2H, *J* = 6.4 Hz), 3.87 (s, 3H), 4.75 (d, 2H, *J* = 6.4 Hz) 6.77 (d, 1H, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 7.6 Hz), 7.20 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 349 (M^+, 100).

Methanesulfonic acid 2-methoxy-6-pentadecyl-benzyl ester (5)

To a solution of **4** (15 g, 0.04 mol) in dichloromethane was added triethyl amine (13.92 mL, 0.09 mol) followed by methanesulfonyl chloride (4.2 mL, 0.05 mol) at 0 °C over a period of 15 min. The content was stirred at room temperature for 3 h. The reaction mixture was washed with water (150 mL), brine solution (200 mL) dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to obtain **5** (Yield: 17g, 92.59%, off-white solid).

Representative procedure for the synthesis of amines (6)

To a acetonitrile solution containing **5** (500 mg, 1.17 mmol) was added triethylamine (3.52 mmol) and the appropriate amine (1.17 mmol). The contents were heated at 85 °C for 3h-18 h. The reaction mixture was distilled and the crude compounds obtained were dissolved in ethyl acetate, washed with water, brine solution dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to obtain the crude amines which were purified by column chromatography.

2-methoxy-6-pentadecylphenylmethanamine (6a)

White coloured solid; Yield: 320 mg, 78.8%; M.p: 55-56 °C; IR (KBr): ν_{max} 3400, 3066, 2924, 1583, 1464,1259 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, *J* = 7.2 Hz), 1.26 (brs, 24H), 1.51-1.57 (m, 2H), 1.76 (bs, 2H), 2.65(t,2H, *J* = 7.6 Hz), 3.84 (s, 5H), 6.74 (d, 1H, *J* = 8.0 Hz),6.79 (d, 1H, *J* = 7.6 Hz), 7.15 (t, 1H, *J* = 7.6 Hz); EI MS: m/z (rel.abund.%) 348 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)pyrrolidine (6b)

Pale brown liquid; Yield: 325 mg, 69.1%; IR (neat): ν_{max} 3013, 2921, 2848, 1589, 1473, 1273, 1092 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (bs, 24H), 1.50-1.53 (m, 2H), 2.05-2.16 (m, 4H), 2.67 (t, 2H, *J* = 8.0 Hz), 2.94 (bs, 2H), 3.74 (bs, 2H), 3.89 (s, 3H), 4.33 (s, 2H), 6.79 (d, 1H, *J* = 8.4 Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 7.32 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 402 (M^+, 100).

4-(2-methoxy-6-pentadecylbenzyl)morpholine (6c)

Pale yellow liquid; Yield: 366 mg, 75%; IR (neat): ν_{max} 3071, 2922, 2849, 1584, 1467, 1261, 1115 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (bs, 24H), 1.58-1.64 (m, 2H), 2.44 (t, 4H, *J* = 4.8 Hz), 2.65 (t, 2H, *J* = 8.0 Hz), 3.54 (s, 2H), 3.63 (t, 4H, *J* = 4.8 Hz), 3.78 (s, 3H), 6.70 (d, 1H, *J* = 8.4 Hz), 6.81 (d, 1H, *J* = 8.0 Hz), 7.16 (t, 1H, *J* = 7.6 Hz); EI MS: m/z (rel.abund.%) 418 (M^+, 100).

4-(2-methoxy-6-pentadecylbenzyl)thiomorpholine (6d)

White coloured solid; Yield: 295 mg, 58.1%; M.p: 50-51 °C; IR (neat): ν_{max} 3066, 2922, 2853, 1585, 1462, 1257 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.26 (brs, 24H), 1.56-1.60 (m, 2H), 2.58-2.71 (m, 10H), 3.53 (s, 2H), 3.78 (s, 3H), 6.70 (d, 1H, *J* = 8.4 Hz), 6.81 (d, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 434 (M^+, 100).

N-(2-methoxy-6-pentadecylbenzyl)cyclohexanamine (6e)

Light yellow liquid, Yield: 260 mg, 51.6%; IR (neat): ν_{max} 2923, 2853, 1585, 1459, 1254, 1089 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.0 Hz), 1.12-1.40 (m, 29H), 1.52-1.61 (m, 4H), 1.72-1.75 (m, 2H), 1.89-1.92 (m, 2H), 2.45 (m, 1H), 2.64 (t, 2H, *J* = 8.0 Hz), 3.78 (s, 2H), 3.81 (s, 3H), 6.70 (d, 1H, *J* = 8.4 Hz), 6.77 (d, 1H, *J* = 7.6 Hz), 7.12 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 430 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)piperidine-2-carboxylic acid (6f)

Light yellow liquid; Yield: 389 mg, 72.3%; IR (neat): ν_{max} 3400, 2923, 2853, 1585, 1463, 1266 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.21-1.42 (m, 28H), 1.51-1.55 (m, 2H), 2.74 (t, 2H, *J* = 8.0 Hz), 3.61-3.66 (m, 5H), 3.88 (s, 3H), 4.63 (s, 2H), 6.82 (d, 1H, *J* = 8.4 Hz), 6.95 (d, 1H, *J* = 8.0 Hz), 7.39 (t, 1H, *J* = 8.0 Hz); ESIMS(m/z): EI MS: m/z (rel.abund.%) 458 (M^-, 100).

1-(2-methoxy-6-pentadecylbenzyl)piperidine-3-carboxylic acid (6g)

Light yellow liquid; Yield: 410 mg, 76%; IR (neat): ν_{max} 3428, 2926, 2856, 1720, 1588, 1462, 1263cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.23-1.41 (m, 28H), 1.50-1.55 (m, 2H), 2.74 (t, 2H, *J* = 8.0 Hz), 3.60-3.61 (m, 5H), 3.88 (s, 3H), 4.61 (s, 2H), 6.82 (d, 1H, *J* = 7.6 Hz), 6.95 (d, 1H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 460 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)piperidine-4-carboxylic acid (6h)

Light yellow liquid; Yield: 380 mg, 70.6%; IR (neat): ν_{max} 3397, 2923, 2854, 1462, 1263 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.24-1.41 (m, 28H), 1.53-1.55 (m, 2H), 2.75 (t, 2H, *J* = 7.6 Hz), 3.61-3.66 (m, 5H), 3.88 (s, 3H), 4.62 (s, 2H), 6.82 (d, 1H, *J* = 8.4 Hz), 6.95 (d, 1H, *J* = 7.6 Hz), 7.26-7.29 (m, 1H); EI MS: m/z (rel.abund.%) 458 (M^-, 100).

tert-butyl 1-(2-methoxy-6-pentadecylbenzyl)piperidin-4-ylcarbamate (6i)

Brown coloured semi solid; Yield: 435 mg, 70%; IR (neat): ν_{max} 3339, 3079, 2925, 2854, 1706, 1462, 1256, 1172 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 7.2 Hz), 1.25 (bs, 24H), 1.43 (s, 9H), 1.50-1.59 (m, 2H), 1.53 (brs, 2H), 1.85 (bs, 2H), 2.20 (bs, 2H), 2.65- 2.82 (m, 4H), 3.49 (bs, 2H), 3.79 (s, 3H), 4.42 (bs, 1H), 6.71 (d, 1H, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 7.2 Hz), 7.16-7.18 (m, 1H); EI MS: m/z (rel.abund.%) 531 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)-4-methylpiperazine (6j)

Pale brown liquid; Yield: 340 mg, 67.4%; IR (neat): ν_{max} 3068, 2924, 2852, 1585, 1460, 1258 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.25-1.36 (bs, 24H), 1.55-1.63 (m, 2H), 2.25 (s, 3H), 2.36-2.57 (m, 8H), 2.68 (t, 2H, *J* = 8.0 Hz), 3.54 (s, 2H), 3.78 (s, 3H), 6.70 (d, 1H, *J* = 8.7 Hz), 6.80 (d, 1H, *J* = 9.6Hz), 7.15 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 431 (M^+, 100).

tert-butyl 4-(2-methoxy-6-pentadecylbenzyl)piperazine-1-carboxylate (6k)

Pale yellow liquid; Yield: 427 mg, 70.6%; IR (neat): ν_{max} 3070, 2924, 2855, 1698, 1463, 1249, 1172, 1124, 1085cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (brs, 24H), 1.45 (s, 9H), 1.55-1.61 (m, 2H), 2.38 (bs, 4H), 2.68 (t,2H, *J* = 7.6 Hz), 3.34 (bs, 4H), 3.53 (s, 2H), 3.78 (s, 3H), 6.71 (d, 1H, *J* =8.4 Hz),6.82 (d, 1H, *J* = 7.6 Hz), 7.17 (t, 1H, *J* = 7.6 Hz); EI MS: m/z (rel.abund.%) 517 (M^+, 100).

1-Benzyl-4-(2-methoxy-6-pentadecylbenzyl)piperazine (6l)

Light yellow liquid; Yield: 410 mg, 69.1%; IR (neat): ν_{max} 3028, 2923, 2853, 1458, 1340, 1259, 1084, 738 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.25 (brs, 24H), 1.56-1.60 (m, 2H), 2.48 (bs, 8H), 2.67 (t, 2H, *J* = 8.0 Hz), 3.47 (s, 2H), 3.53 (s, 2H), 3.76 (s, 3H), 6.91 (d, 1H, *J* = 8.4 Hz), 6.80 (d, 1H, *J* = 7.6 Hz), 7.15 (t, 1H, *J* = 7.6 Hz), 7.22-7.30 (m, 5H); EI MS: m/z (rel.abund.%) 507 (M^+, 100).

6-(dimethylamino)-1-(2-methoxy-6-pentadecylbenzyl)-1,4-diazepan-5-one (6m)

Pale brown coloured solid; Yield: 368 mg, 64.5%; M.p: 82-83 °C; IR (KBr): ν_{max} 3185, 3065, 2919, 1679, 1466, 1317, 1261 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (bs, 24H), 1.55-1.63 (m, 2H), 2.28 (s, 6H), 2.54 (brs, 2H), 2.65- 2.77 (m, 4H), 3.05-3.15 (m, 2H), 3.55-3.65 (m, 3H), 3.787 (s, 3H), 5.73 (bs, 1H), 6.71 (d, 1H, *J* = 8.4 Hz), 6.82 (d, 1H, *J* = 7.6 Hz), 7.18 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 488 (M^+, 100).

tert-butyl 1-(2-methoxy-6-pentadecylbenzyl)-6-morpholino-1,4-diazepan-5-one (6n)

Cream coloured solid; Yield: 348 mg, 56.1%; M.p: 80-81 °C; IR (KBr): ν_{max} 3232, 2924, 2853, 1672, 1462, 1348, 1257, 1117 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 7.2 Hz), 1.25 (bs, 24H), 1.53-1.59 (m, 2H), 2.21-3.12 (m, 12H), 3.50-3.53 (m, 2H), 3.63-3.66 (m, 5H), 3.77 (s, 3H), 5.88 (s, 1H), 6.72 (d, 1H, *J* = 8.4 Hz), 6.80 (d, 1H, *J* = 7.2 Hz), 7.18 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 530 (M^+, 100).

1-(2-methoxy-pentadecylbenzyl)-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (6o)

Light yellow liquid; Yield: 375 mg, 65%; IR (neat): ν_{max} 3402, 2923, 2853, 1659,1463, 1256, 1089 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 7.2 Hz), 1.25 (m, 24H), 1.41-1.49 (m, 2H), 2.54 (t, 2H, *J* = 8.0 Hz), 3.11 (t, 2H, *J* = 6.0 Hz), 3.23 (t, 2H, *J* = 6.0 Hz), 3.81 (s, 2H), 4.38 (s, 3H), 6.09 (t, 1H, *J* = 6.0 Hz), 6.73 (d, 1H, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 7.2 Hz), 7.01 (t, 1H, *J* = 7.8 Hz), 7.15-7.21 (m, 2H), 7.42 (t, 1H, *J* = 7.2 Hz), 7.68 (d, 1H, *J* = 7.6 Hz); EI MS: m/z (rel.abund.%) 493 (M^+, 100).

tert-butyl 4-(2-methoxy-6-pentadecylbenzyl)-1,4-diazepane-1-carboxylate (6p)

Yellow liquid; Yield: 360 mg, 57.8%; IR (neat): ν_{max} 2925, 2855, 1695, 1467, 1251, 1168 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.25 (bs, 24H), 1.45 (s, 9H), 1.51-1.61 (m, 2H), 1.76-1.84 (m, 2H), 2.61 (bs, 2H), 2.71 (t, 2H, *J* = 7.6 Hz), 3.32-3.45 (m, 6H), 3.62 (s, 2H), 3.78 (s, 3H), 6.71 (d, 1H, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 7.6 Hz); EI MS: m/z (rel.abund.%) 531(M^+, 100).

tert-butyl 8-(2-methoxy-6-pentadecylbenzyl)-8-azabicyclo [3,2,1]octan-3-ylcarbamate (6q)

Brown coloured solid; Yield: 429 mg, 65.9%; M.p: 50-51 °C; IR (KBr): ν_{max} 3350, 2925, 2855, 1709, 1463, 1250, 1171 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 7.2 Hz), 1.21-1.46 (m, 35H), 1.59-1.75 (m, 6H), 2.04-2.09 (m, 2H), 2.76 (t, 2H, *J* = 8Hz), 3.14 (s, 2H), 3.54 (s, 2H), 3.77 (s, 3H), 4.24-4.26 (m, 1H), 6.69 (d, 1H, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 7.8 Hz), 7.15 (t, 1H, *J* = 8.0 Hz); EI MS: m/z (rel.abund.%) 557 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)-1H-pyrazole (6r)

Off white solid; Yield: 283 mg, 60.7%; M.p: 58-59 °C; IR (KBr): ν_{max} 3009, 2918, 2846, 1465, 1263, 1088 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.0 Hz), 1.25 (brs, 24H), 1.39-1.46 (m, 2H), 2.71 (t, 2H, *J* = 7.2 Hz), 3.83 (s, 3H), 5.40 (s, 2H), 6.14 (s, 1H), 6.78 (d, 1H, *J* = 8.0 Hz), 6.84 (d, 1H, *J* = 7.6 Hz), 7.22-7.27 (m, 2H), 7.47 (s, 1H); EI MS: m/z (rel.abund.%) 399 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)-1H-imidazole (6s)

Light brown coloured solid; Yield: 266 mg, 57.1%; M.p: 45-46 °C; IR (KBr): ν_{max} 3107, 2922, 2854, 1588, 1460, 1265, 1080 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (brs, 24H), 1.40-1.49 (m, 2H), 2.64 (t, 2H, *J* = 8.0 Hz), 3.82 (s, 3H), 5.15 (s, 2H), 6.76-6.87 (m, 3H), 6.97 (s, 1H), 7.23-7.27 (m, 1H), 7.46 (s, 1H); EI MS: m/z (rel.abund.%) 399 (M^+, 100).

1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,4-triazole (6t)

Off white solid; Yield: 349 mg, 74.7%; M.p: 65-66 °C; IR (KBr): ν_{max} 3000, 2918, 2850, 1589, 1468, 1264 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.24 (brs, 24H), 1.46-1.52 (m, 2H), 2.74 (t, 2H, *J* = 8.0 Hz), 3.83 (s, 3H), 5.39 (s, 2H), 6.78 (d, 1H, *J* = 8.4 Hz), 6.86 (d, 1H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 7.89 (s, 1H), 7.92 (s, 1H); EI MS: m/z (rel.abund.%) 400 (M^-, 100).

tert-butyl-4-hydroxy-4-((2-methoxy-6-pentadecylbenzyl-amino)methyl)piperidine-1-carboxylate (6u)

Yellow liquid; Yield: 320 mg, 48.7%; IR (neat): ν_{max} 3445, 2925, 2854, 1691, 1465, 1365, 1088 cm^{-1}; H^1-NMR (400 MHz, $CDCl_3$) δ: 0.880 (t, 3H, *J* = 7.2 Hz), 1.21-1.61 (m, 39H), 2.54 (s, 2H), 2.64 (t, 2H, *J* = 8.0 Hz), 3.13-3.19 (m, 2H), 3.82 (bs, 7H), 6.73 (d, 1H, *J* = 8.0 Hz), 6.80 (d, 1H, *J* = 7.2 Hz), 7.16 (t, 1H, *J* = 8.4 Hz); EI MS: m/z (rel.abund.%) 561 (M^+, 100).

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