Synthesis and Antibacterial Activity of Sulfonamide Derivatives of Anacardicacid Mixture Isolated from a Natural Product Cashew Nut Shell Liquid (CNSL)

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Abstract: Synthesis and antibacterial activity of some novel sulfonamide derivatives of anacardic acid were (**8a-8l**) prepared from commercially available anacardic acid mixture (**1a–d**) isolated from a natural product Cashew Nut Shell Liquid (CNSL).Compounds (**8a-8l**) were tested for Gram positive and Gram negative bacterial cultures. Most of the compounds were showed active compared with standard drug ampicilline.

Keywords: Anacardic acid, anti-bacterial activity, sulfonamide derivatives, synthesis.

INTRODUCTION

Anacardic acid mixture (**1a–d**) isolated from a natural product Cashew Nut Shell Liquid (CNSL) which is a by-product of cashew nut industry and these are salicylic acid derivatives with a nonisoprenoid alk(en)yl side chain [1]. Anacardic acid and its derivatives exhibits biological activities like antimicrobial activity [2, 3] and soybean lipoxygenase-1 inhibitory activity [4, 5]. G.C.Reddy *et al.* reported the synthesis of benzamide derivatives of anacardic acid [6], sildenafil analogs [7], dihydropyridine analogs [8] as calcium channel blockers, isonicotinoylhydrazones for antimycobacterial activity [9] starting from anacardic acid. Kubo *et al.* reported the separation of anacardic acid into monoene (15:1), diene (15:2) and triene (15:3) 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 [10]. Recently, a few anacardic acid derivatives exhibited various activities like affecting the structure of the enzyme [11], anacardic acid is a specific activator of kinase activity of Aurora Kinase A [12], suppresses 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].

The emergence of drug resistant strains in clinical applications [16-18] especially to Gram positive bacteria [19, 20] has created a problem of global proportions [21, 22]. This phenomenon has led in creating novel antibacterial agents distinct from existing classes of compounds. Anacardic acid (pentadecyl salicylic acid) is a phenolic constituent present in Cashew Nut Shell Liquid (CNSL); (*Anacardium occidentale L.*) and exhibits antimicrobial properties [2, 3] which have led to the preparation of various analogs [23, 24]. In the present work we wish to report to synthesize novel cell permeable sulfonamide compounds from abundantly and cheaply available anacardic acid which was a major constituent of Cashew Nut Shell Liquid (CNSL) natural source to evaluate their biological activity by various antibacterial strains. This report describes the synthesis, spectroscopic identification and antibacterial activity of some novel anacardic acid derivatives against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes* bacterial strains.

RESULTS AND DISCUSSION

Here, we described the synthesis of various biologically active novel sulfonamides derivatives using anacardic acid mixture as starting material and various reagents in the given below conditions (Scheme **1**).

The anacardic acid mixture (**1a–d)** was isolated from commercially available CNSL by a reported method [25]. Accordingly, CNSL was treated with calcium hydroxide, during which anacardic acid present in CNSL becomes calcium anacardate, which was isolated and hydrolyzed with dil. hydrochloric acid to generate anacardic acid ene mixture, which was a mixture of monoene, diene and triene located at (8'), (8', 11') and (8', 11', 14') of the C15 alkyl chain respectively. Saturated anacardic acid was obtained by

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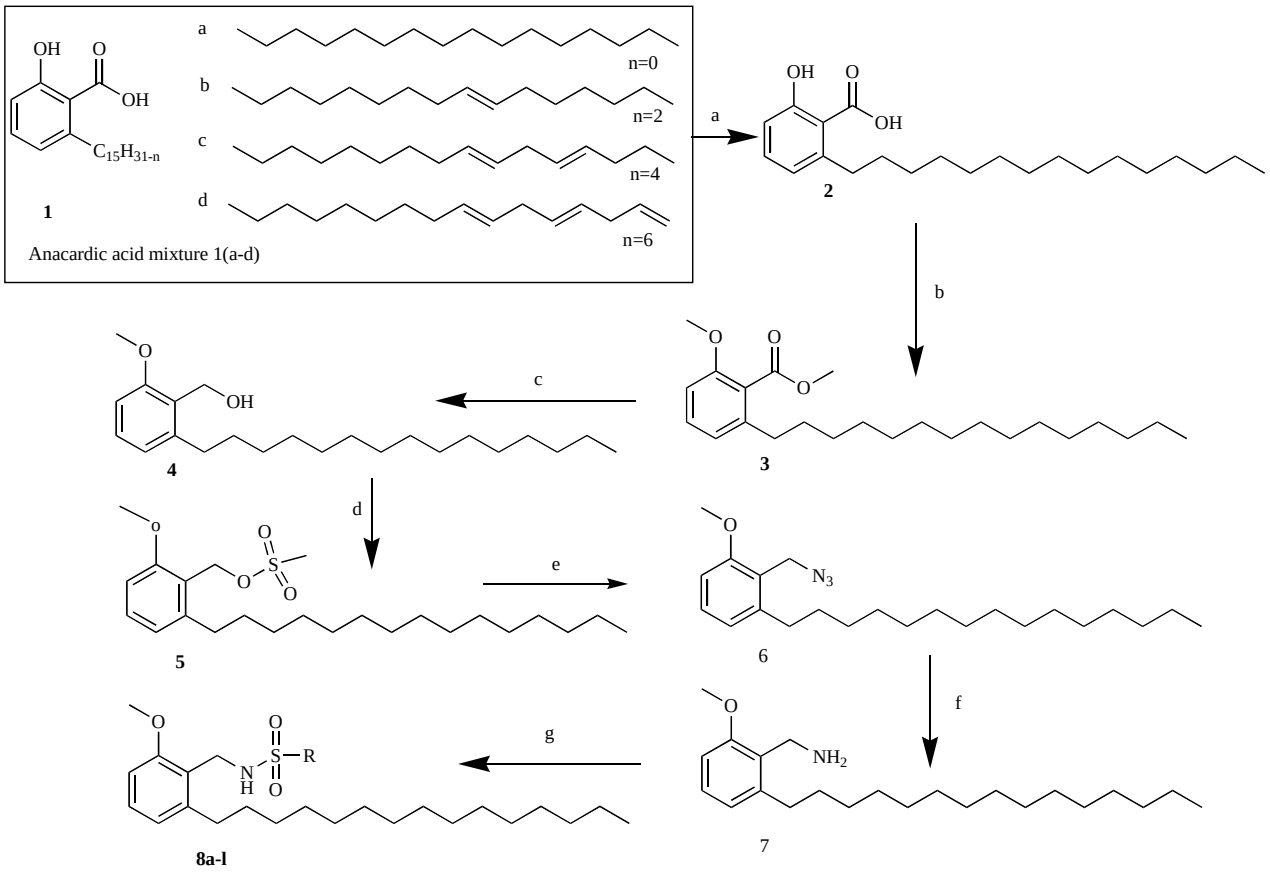


Scheme 1. Synthesis of various biologically active sulfonamides from anacardic acid mixture.

Reagents: a) 10% Pd/C, EtOH, 50psi, RT, 2h; b) Dimethyl sulfate, K_2CO_3, Acetonitrile, 90°C, 24h; c) LAH, THF, 0°C –RT, 18h; d) Methane sulphonyl chloride, Et_3N, DCM, 0°C-rt, 3h; e) NaN_3, DMF; f) 10% Pd/C, 50 psi, 2h; g) Different sulphonyl chlorides, TEA, DCM.

hydrogenation of the ene mixture of anacardic acid[7] and was further converted to dialkylated compound by reacting with dimethylsulfate in acetonitrile. Dialkylated anacardic acid was reduced to alcohol by treatment with lithium aluminium hydride in tetrahydrofuran and then protected with methane sulphonyl chloride in dichloromethane. Resultant mesylated compound was reacted with sodium azide followed by reduction with Pd/C under H_2 pressure to obtained amine coupled with various sulphonyl chloride in the presence of triethylamine in DCM to obtain compounds (**8a-8l**, Scheme **1**) of sulfonamide derivatives were purified by column chromatography to yield title compounds. The structure of sulfonamide derivatives **8a-8l** was determined by using different spectroscopic techniques ^{1}H NMR, IR, Mass. The resulting compounds are screened for their antibacterial activity.

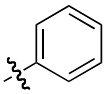
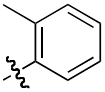
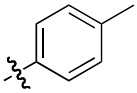
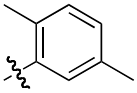
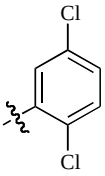
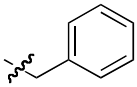
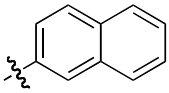
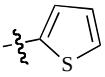
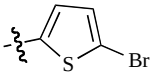
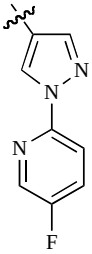
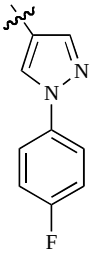
Biological Activity

The sulfonamide derivatives **8a-8l** were screened for their antibacterial activity [26] against some of the pathogenic bacteria viz. *E.coli* (MTCC443), *P.aeruginosa* (MTCC424), *S.aureus,* (MTCC96) and *S.pyogenes* (MTCC443) using agar well diffusion method according to the literature protocol [26]. The anti-bacterial activity of the analogs was compared with standard drug ampicilline and the results of investigation have been presented in Table **1** and observed that the most of compounds showed high biological activity. Based on the test results it is evident that several of the synthesized anacardic acid analogs possess moderate to good activity against the Gram +ve and Gram –ve bacteria. Of all the compounds prepared entities **8a**, **8k**, **8l** of *E. coli* MTCC443, **8a**, **8g**, **8h**, **8k**, **8l** of *P. aeruginosa* MTCC424, **8f** of *S. aureus* MTCC96 and **8g**, **8h** of *S. pyogenes* MTCC442 display good to excellent activity, while the remaining compounds showed moderate activity. The most active antibacterial agent against *Escherichia coli* found to be compound **8k** and **8l** having *N*-containing compound and other compounds in the series exhibited moderate to good activity. 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 against all the Escherichia *coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes* bacterial strains.

CONCLUSION

In summary, the present study describes a convenient and efficient protocol for the synthesis of sulfonamide derivatives by using anacardic acid mixture using various

Table 1. Antibacterial activity of sulfonamide derivatives of anacardic acid

Compound No.	R	Name of the Bacteria (Conc. 250 µg/ml) & Inhibition Zone in mm			
		E. coli **MTCC443**	***P. aeruginosa*** **MTCC424**	***S. aureus*** **MTCC96**	***S. pygenes*** **MTCC442**
8a		22	21	16	16
8b		19	17	18	16
8c		15	15	15	17
8d		16	18	16	16
8e		17	20	16	17
8f		15	15	19	18
8g		16	21	16	19
8h		17	22	15	19
8i		19	18	16	18
8j		17	19	17	18
8k		21	21	16	16
8l		22	22	15	15
SD*	SD* ampliciline (Conc. 250 µg/ml)	20	20	18	19

reagents and different conditions. We believe that this procedure is convenient, economic and a user-friendly process for the synthesis of these various sulphonamide compounds from anacardic acid mixture. All compounds structures are supported by physico chemical and IR, NMR, Mass spectral data. Sulphonamide derivatives were screened for their antibacterial activity against few bacterial strains and observed that some of the compounds have shown more biological activity than the standards used.

EXPERIMENTAL SECTION

All chemicals and solvents were obtained from Aldrich and Spectrochem., India and used without further purification. Column chromatographic separations were carried out on silica gel 60-120 mesh size. Melting points were determined in open glass capillaries on a Mel-temp apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm−1. The ^{1}H and^{13}C NMR spectra of samples were recorded on a Varian EM-360, NMR spectrometer using TMS as an internal standard in $CDCl_3$. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat b at 70 eV with an emission current of 100μA.

General Procedure: Synthesis of 2-hydroxy-6-pentadecyl-benzoic Acid (2)

A solution of compound **1** (100 gm, 287.35 mmol) in ethanol (500 mL) was taken into a 1L Parr-hydrogenation vessel and added a suspension of 10 % Pd/C (10g, 10%) in 70 mL of ethanol under argon atmosphere and applied H_2-pressure (50 psi) for 2h. Reaction mixture was filtered through celite bed and concentrated the filtrate under reduced pressure to obtain compound recrystallized in pet ether to get 2-hydroxy-6-pentadecyl-benzoic acid (**2**) as white color solid (70g); (Yield:70 g, 68.8%; white solid); M.p: 85-86 °C; IR (KBr): ν_{max} 3010, 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 Hz), 6.78 (d, 1H, *J* = 7.6 Hz), 6.88 (d, 1H, *J* = 8.4 Hz), 7.37 (t, 1H, *J* = 8 Hz), 11.02 (bs, 1H); EI MS: m/z (rel.abund.%) 349 (M^+, 100)

Synthesis of 2-Methoxy-6-pentadecyl-benzoic Acid Methyl Ester (3)

A solution of compound **2** (20g, 57.471 m.mol) in ACN (200 mL) was added K_2CO_3 (40.8 g, 287.35 m.mol) and DMS (21.76 mL, 229.88 m.mol). The content was heated to reflux for 24h. Reaction mixture was filtered and distilled off filtrate, obtained residue was re dissolved in ethyl acetate and washed with water (2x200 mL), brine solution (175 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to obtain 2-Methoxy-6-pentadecyl-benzoic acid methyl ester**(3)** as pale yellow solid 18.5g; Yield: 85.5%; M.p: 36-37°C; IR (KBr): ν_{max} 3004, 2921, 2852, 1732, 1589, 1460, 1266, 1105, 1067, 954, 747 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 Hz), 3.81 (s, 3H), 3.90 (s, 3H), 6.75 (d, 1H, *J* = 8.4 Hz), 6.82 (d, 1H, *J* = 8 Hz), 7.25 (t, 1H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.07, 22.66, 29.32, 29.38, 29.48, 29.51, 29.61, 29.65, 31.12, 31.88, 33.45, 52.04, 55.80, 108.30, 121.45, 123.44, 130.17, 141.35, 156.20, 168.88; EI MS: m/z (rel.abund.%) 377 (M^+, 100).

Synthesis of 2-Methoxy-6-pentadecyl-phenyl) - Methanol (4)

A suspension of $LiAlH_4$ (3.03g, 79.787 m.mol) in Dry THF (150 mL) was added compound **3** (20g, 53.19 m.mol) in THF (100 mL) drop wise over a period of 40 min at 0°C. The content was slowly, stirred at room temp., for 18h. Reaction mixture was quenched with saturated brine solution (40 mL) at 0°C diluted with ethyl acetate filtered (200 mL) and washed with ethyl acetate (100 mL), filtrate was washed with brine solution (200 mL) dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to obtain 2-Methoxy-6-pentadecyl-phenyl)- methanol (**4**) (15gm) as off white solid; Yield: 81%; M.p: 60-62°C; IR (KBr): ν_{max} 3386, 3073, 2917, 2847, 1589, 1465, 1318, 1263, 1197, 1093, 1001, 739 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 Hz), 6.82 (d, 1H, *J* = 7.6 Hz), 7.20 (t, 1H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.07, 22.66, 29.32, 29.46, 29.57, 29.61, 29.65, 31.88, 32.10, 33.19, 55.37, 57.30, 108.01, 122.28, 126.83, 128.45, 142.62, 158.22; EI MS: m/z (rel.abund.%) 349 (M^+, 100).

Synthesis of Methanesulfonic Acid 2-methoxy-6-pentadecyl-benzyl Ester (5)

To a solution of compound **4** (15g, 45.181m.mol) in DCM was added TEA (13.92 mL, 99.398 m.mol) followed by mesyl chloride (4.2 mL, 54.21 m.mol) at 0°C over a period of 15 min. The content was stirred at room temp., for 3h. Reaction mixture was washed with water (150 mL), brine solution (200 mL) dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to obtain methanesulfonic acid 2-methoxy-6-pentadecyl-benzyl ester(**5**) (17g, 92.59%) as off-white color solid.

Synthesis of 2-(azidomethyl)-1-methoxy-3-pentadecyl-benzene (6)

To a solution of compound **5** (7.5g, 17.605 mmol) in DMF (30 mL) was added sodium azide (1.49g, 22.887 mmol), the content was heated at 100°C for 2h. Reaction mixture was cooled to room temp., and poured into cool water (150 mL) solid compound was precipitated filtered and dried to get Azide (**6**) (6.2g, 94.4%) as white color solid; IR (KBr): ν_{max} 3087, 3013, 2924, 2854, 2096, 1589, 1463, 1316, 1262, 1089, 782, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.25 (bs, 24H), 1.52-1.56 (m, 2H), 2.63 (t, 1H, *J* = 7.6 Hz), 3.85 (s, 3H), 4.42 (s, 2H) 6.78 (d, 1H, *J* = 8 Hz), 6.83 (d, 1H, *J* = 8 Hz), 7.24-7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.09, 22.67, 29.35, 29.48, 29.56, 29.66, 31.56, 31.91, 32.98, 45.14, 55.49, 108.11, 121.55, 121.97, 129.27, 143.70, 158.28; ESIMS(m/z): 331 (M-N3) $(M+H)^+$.

Synthesis of 2-methoxy-6-pentadecyl-benzyl Amine (7)

A solution of compound **6** (1.5g, 4.021 mmol) in ethanol (30 mL) was taken into a 500 mL Parr-hydrogenation vessel and added a suspension of 10 % Pd/C (250 mg, 10%) in 20 mL of ethanol under argon atmosphere and applied H_2-pressure (60 psi) for 2h. Reaction mixture was filtered through celite bed and concentrated the filtrate under reduced pressure to obtain 2-methoxy-6-pentadecyl-benzyl amine (**7**) (1.1g, 78.8%) as a off-white solid. M.p. 55-56 °C, IR (neat): ν_{max} 3400, 3066, 2924, 2853, 1583, 1464, 1439, 1374, 1259, 1149, 1121, 1079, 879, 787, 742 cm^{-1}; ^1H NMR (CDCl3, 400 MHz): 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 Hz),6.79 (d, 1H, *J* = 7.6 Hz), 7.15 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06, 22.64, 29.31, 29.49, 29.57, 29.61, 31.88, 32.14, 33.14, 37.54, 55.24, 107.96, 122.02, 127.33, 129.76, 141.62, 157.87; MS(m/z): 348 $(M+H)^+$.

Synthesis of Sulphonamides (8)

A solution of amine **7** (1.0eq) in dry DCM was added TEA (2.2 eq) followed by sulphonyl chloride (1.1 eq) at 0°C. The contents were slowly bringing it to r.t and stirred for 2h. Reaction mixture was diluted with DCM and washed with water and brine solution dried and distilled off to obtain crude compound **8** which was purified by column.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)methanesulfonamide (8a)

Using **7** and methane sulfonyl chloride as starting materials, the title compound **8a** was obtained as a white color solid (59.8%); MP: 77-78 °C; IR (DCM film): ν_{max} 3287, 3020, 2918, 2849, 1588, 1467, 1512, 1322, 1268, 1224, 1144, 1096, 1046, 1002, 871, 773, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, *J*=6.8 Hz), 1.25 (brs, 24H), 1.52-1.56 (m, 2H), 2.72 (t, 2H, *J*=7.2 Hz), 2.77 (s, 3H), 3.85 (s, 3H), 4.35 (d, 1H, *J*=6), 4.87 (bs, 1H), 6.76 (d, 1H, *J*=8.4 Hz), 6.82 (d, 1H, *J*=7.2 Hz), 7.22 (t, 1H, *J*=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.09, 22.66, 29.33, 29.49, 29.53, 29.57, 29.65, 31.84, 31.89, 33.06, 39.22, 40.45, 55.49, 108.07, 122.40, 122.77, 128.95, 142.85, 157.90; ESIMS(m/z): 424 $(M-H)^+$.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)benzenesulfonamide (8b)

Using **7** and benzene sulfonyl chloride as starting materials, the title compound **8b** was obtained as a light brown solid (90.2%); M.p.: 68-69°C; IR (KBr pellet): ν_{max} 3286, 3079, 2921, 2851, 1587, 1464, 1418, 1344, 1310, 1269, 1156, 1089, 1044, 921 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, J=6.8 Hz), 1.25 (brs, 24H), 1.39-1.44 (m,2H), 2.518 (t, 2H, *J*=8 Hz), 3.69 (s, 3H), 4.17 (d, 2H, *J*=6.4 Hz), 4.99 (t, 1H), 6.602 (d, 1H, *J*=8 Hz), 6.69 (d, 1H, *J*=8 Hz), 7.11 (t, 1H, *J*=8 Hz), 7.44 (t, 2H, *J*=7.8 Hz), 7.50-7.52 (m, 1H), 7.79-7.81 (m, 2H); ESIMS(m/z): 486 $(M-H)^+$.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)-2-methylbenzenesulfonamide (8c)

Using **7** and 2-methyl benzene sulfonyl chloride as starting materials, the title compound **8c** was obtained as a yellow liquid (78.5%); IR (DCM film): ν_{max} 3305, 3062, 2962, 2853, 1589, 1465, 1407, 1328, 1265, 1216, 1162, 1054, 991, 905, 758, 695cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.9 (t, 3H, *J*=7.2 Hz), 1.27 (brs, 24H), 1.32-1.402 (m,2H), 2.45 (t, 2H, *J*=7.6 Hz),2.58 (s, 3H), 3.77 (s, 3H), 4.14 (d, 2H, *J* = 6.4 Hz), 5.11 (t, 1H, *J* = 6 Hz), 6.65-6.71 (m, 2H), 7.14 (t, 1H, *J* = 7.6Hz), 7.23-7.30 (m,2H), 7.40-7.44 (m,1H), 8.01 (d, 1H, *J* = 7.6Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12, 19.94, 22.69, 29.37, 29.45, 29.50, 29.61, 29.67, 29.70, 31.60, 31.93, 33.00, 38.94, 55.28, 107.74, 122.14, 122.18, 125.93, 128.72, 129.63, 132.20, 132.49, 137.00, 137.88, 142.87, 157.77. ESIMS(m/z): 500 $(M-H)^+$.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)-4-methylbenzenesulfonamide (8d)

Using **7** and para toluene sulfonyl chloride as starting materials, the title compound **8d** was obtained as a light brown solid (96.9%); M.p. 79-80 °C; IR (KBr pellet): ν_{max} 3293, 2920, 2851, 1591, 1468, 1424, 1329, 1261, 1157, 1091, 1049, 816, 787cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J*=7.2 Hz), 1.26 (brs, 24H), 1.39-1.49 (m,2H), 2.40 (s, 3H), 2.51 (t, 2H, *J*=8 Hz), 3.71 (s, 3H), 4.13 (d, 2H, *J*=6Hz) 4.93 (t, 1H), 6.61 (d, 1H, *J*=8 Hz), 6.71 (d, 1H, *J*=7.6Hz), 7.12 (t, 1H, *J*=7.6 Hz), 7.23-7.26 (m,2H), 7.70 (d, 2H, *J*=7.6 Hz); ESIMS(m/z): 500 $(M-H)^+$.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)-2,5-dimethylbenzenesulfonamide (8e)

Using **7** and 2,5 dimethyl benzenesulfonyl chloride as starting materials, the title compound **8e** was obtained as a light yellow semi solid (96.6%); IR (DCM film): ν_{max} 3241, 3050, 2924, 2854, 1588, 1406, 1324, 1265, 1218, 1154, 1083, 1056, 901, 820, 781cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.9 (t, 3H, *J*=6.8 Hz), 1.27 (brs, 24H), 1.32-1.41 (m,2H), 2.35 (s, 3H) , 2.46 (t, 2H, *J*=7.2 Hz),2.52 (s, 3H), 3.77 (s, 3H), 4.14 (d, 2H, *J*=6.4 Hz), 5.11 (t, 1H, *J*=6 Hz), 6.65 (d, 2H, *J*=8 Hz), 6.69 (d, 2H, *J*=7.6 Hz), 7.10-7.21 (m, 2H), 7.78 (s, 1H); ESIMS(m/z): 514 $(M-H)^+$.

Synthesis of 2,5-dichloro-N-(2-methoxy-6-pentadecylbenzyl)benzenesulfonamide (8f)

Using **7** and 2,5-dichloro-benzene sulfonyl chloride as starting materials, the title compound **8f** was obtained as a off white solid (87.3%); M.p. 66-77°C; IR (KBr pellet): ν_{max} 3338, 3286, 3087, 3007, 2920, 2850, 1589, 1464, 1405, 1341, 1262, 1164, 1096, 1035, 982, 891 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J*=6.4 Hz), 1.25 (brs, 24H), 1.38-1.42 (m,2H), 2.53 (t, 2H, *J*=8 Hz), 3.76 (s, 3H), 4.26 (d, 2H, *J*=6.4 Hz), 5.90 (t, 1H, *J*=8 Hz), 6.54 (d, 1H, *J*=8.4 Hz), 6.57 (d, 1H, *J*=8Hz), 7.01 (t, 1H, *J*=7.6 Hz), 7.152 (d, 1H, *J*=8.4 Hz), 7.25-7.27 (m,1H), 7.92 (s,1H); ESIMS(m/z): 554 $(M-H)^+$. 556 (chloro isotope).

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)-1-phenylmethanesulfonamide (8g)

Using **7** and phenylmethanesulfonyl chloride as starting materials, the title compound **8g** was obtained as a light brown solid (64.6%); M.p.58-59 °C; IR (KBr pellet): ν_{max} 3285, 3078, 3023, 2919, 2851, 1588, 1466, 1407, 1322, 1268, 1226, 1152, 1081, 1052, 992, 835, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J*=6.8 Hz), 1.25 (brs, 24H), 1.51-1.547 (m,2H), 2.72 (t, 2H, *J*=7.2 Hz), 3.74 (s, 3H), 4.1 (s, 2H), 4.33 (d, 2H, *J*=6 Hz), 4.82 (t, 1H), 6.74 (d,

1H, *J*=8.4 Hz), 6.84 (d, 1H, *J*=7.6 Hz), 7.10 (d, 2H, *J*=6.4 Hz), 7.22-7.4 (m,4H); ESIMS(m/z): 500 $(M-H)^+$.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)naphthalene-2-sulfonamide (8h)

Using **7** and Naphthalene-2-sulfonyl chloride as starting materials, the title compound **8h** was obtained as an light brown solid (75.4%); M.p.60-61°C; IR (KBr pellet): ν_{max} 3299, 3056, 3014, 2921, 2850, 1589, 1507, 1467, 1405, 1343, 1318, 1269, 1160, 1123, 1072, 1034, 913, 864, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J*=6.8 Hz), 1.19 (bs, 24H), 1.30-1.41 (m, 2H), 2.48 (t, 2H, *J*=8 Hz), 3.64 (s, 3H), 4.20 (d, 2H, *J*=6 Hz), 5.07 (t, 1H, *J*=7.6 Hz), 6.54 (d, 1H, *J*=8.4 Hz), 6.61 (d, 1H, *J*=7.6 Hz), 7.02(t, 1H, *J*=8Hz), 7.57-7.65 (m,2H), 7.73-7.76 (m,1H), 7.86-7.92 (m, 3H), 8.37 (s, 1H); ESIMS(m/z): 536 $(M-H)^+$.

Synthesis of N-(2-methoxy-6-pentadecylbenzyl)thiophene-2-sulfonamide (8i)

Using **7** and thiophene-2-sulfonyl chloride as starting materials, the title compound **8i** was obtained as an off white solid (51.6%); M.p.67-68°C; IR (KBr pellet): ν_{max} 3273, 3100, 2920, 2848, 1585, 1543, 1466, 1410, 1338, 1267, 1230, 1159, 1090, 1023, 920, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J*=6.8 Hz), 1.25 (brs, 24H), 1.40-1.42 (m,2H), 2.58 (t, 2H, *J*=5.6 Hz), 3.73 (s, 3H), 4.24 (d, 2H, *J*=5.6 Hz), 5.06 (t, 1H, *J*=7.2 Hz), 6.65 (d, 1H, *J*=8.4 Hz), 6.74 (d, 1H, *J*=7.2Hz), 7.02 (t, 1H, *J*=4.4 Hz), 7.14 (t, 1H, *J*=8 Hz), 7.52-7.54 (m,2H); ESIMS(m/z): 492 $(M-H)^+$.

Synthesis of 5-bromo-N-(2-methoxy-6-pentadecylbenzyl) thiophene-2-sulfonamide (8j)

Using **7** and 5-bromo-thiophene-2-sulfonyl chloride as starting materials, the title compound **8j** was obtained as an off white solid (68.9%); M.p.71-72°C; IR (KBr pellet): ν_{max} 3291, 3111, 2920, 2850, 1589, 1517, 1467, 1407, 1323, 1267, 1155, 1082, 1051, 964, 921, 797cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J*=6.8 Hz), 1.26 (brs, 24H), 1.43-1.49 (m,2H), 2.59 (t, 2H, *J*=7.6 Hz), 3.75 (s, 3H), 4.25 (d, 2H, *J*=6 Hz), 5.10 (t, 1H), 6.69 (d, 1H, *J*=8.4 Hz), 6.75 (d, 1H, *J*=7.6Hz), 6.96 (d, 1H, *J*=4.4 Hz), 7.16 (t, 1H, *J*=8 Hz), 7.24 (d, 1H, *J*=4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10, 22.67, 29.34, 29.48, 29.53, 29.59, 29.64, 29.67, 31.64, 31.90, 33.08, 39.51, 55.38, 107.86, 119.44, 121.51, 122.22, 128.95, 129.95, 132.00, 142.08, 143.04, 157.78; ESIMS(m/z): 570 $(M-H)^+$. 572 (bromo isotope).

Synthesis of 1-(5-fluoropyridin-2-yl)-N-(2-methoxy-6-pentadecylbenzyl) -1H-pyrazole-4-sulfonamide (8k)

Using **7** and 1-(5-fluoropyridin-2yl)-*1H*-pyrazole-4-sulfonyl chloride as starting materials, the title compound **8k** was obtained as an off white solid (Yield = 90.9%); M.p. 103-104°C; IR (DCM film): ν_{max} 3285, 3145, 3072, 2924, 2854, 1590, 1524, 1478, 1331, 1263, 1234, 1179, 1143, 1091, 1043, 954, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, *J* =6.4 Hz), 1.25 (brs, 24H), 1.41-1.57 (m,2H), 2.62 (t, 2H, *J* = 7.6 Hz), 3.75 (s, 3H), 4.27 (d, 2H, *J* =6 Hz), 5.07 (t, 1H, *J* =6 Hz), 6.62(d, 1H, *J* = 8.4 Hz), 6.70 (d, 1H, *J* =7.6 Hz), 7.1 (t, 1H, *J* =8 Hz), 7.56-7.59 (m, 1H), 7.61 (d, 1H, *J* =2.8 Hz), 7.95-7.98 (m, 1H), 8.29 (d, 1H, *J* =2.8Hz), 8.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.08, 22.66, 29.33, 29.46, 29.52, 29.58, 29.63, 29.66, 30.89, 31.64, 31.89, 33.07, 39.34, 55.37,107.82, 113.87, 113.93, 121.80, 122.16, 124.79, 125.91, 126.11, 128.59, 128.79, 135.89, 136.15, 140.05, 143.01, 146.54, 157.30, 157.73, 159.84; ESIMS(m/z): 573 $(M-H)^+$.

Synthesis of 1-(4-fluorophenyl)-N-(2-methoxy-6-pentadecylbenzyl) -1H-pyrazole-4-sulfonamide (8l)

Using **7** and 1-(4-fluorophenyl)-*1H*-pyrazole-4-sulfonyl chloride as starting materials, the title compound **8l** was obtained as an off white solid (Yield = 54.5%); M.p. 118-119°C; IR (KBr): ν_{max} 3257, 3134, 3079, 2921, 2851, 1651, 1591, 1524, 1470, 1422, 1320, 1241, 1175, 1145, 1087, 1045, 999, 952cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, 3H, *J* =6.8 Hz), 1.24 (brs, 24H), 1.43-1.47 (m,2H), 2.62 (t, 2H, *J* =7.6 Hz), 3.75 (s, 3H), 4.29 (d, 2H, *J*=6 Hz), 5.14 (t, 1H, *J*=6.4 Hz), 6.59-6.73(m, 2H), 7.06-7.20 (m, 3H), 7.54-7.57 (m, 2H), 7.81 (s, 1H), 7.95 (s, 1H); ESIMS(m/z): 572 $(M+H)^+$.

Antibacterial Bioassay

Sulfonamide derivatives of Anacardic acid (**8a – 8l**) were dissolved in dimethyl sulphoxide at 250 µg/mL concentration. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5g), NaCl (10 g), final pH 7.4. After 18 h the exponentially growing cultures of the six bacteria in nutrient broth at 37°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 concentration 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.

CONFLICT OF INTEREST

Declared none.

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