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Synthesis, Characterization and Antimicrobial Evaluation of (*E*)-N'-[(1-(2-methoxy-6-pentadecylbenzyl)-1*H*-1,2,3-triazol-4-yl]-methylene)benzohydrazide Derivatives

N. RAMBABU[1,2,*], P.K. DUBEY[1], B. RAM[3] and B. BALRAM[3]

[1]Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad-500 072, India
[2]Syngene International Ltd, Biocon Park, Plot No. 2 & 3, Bommasandra IV Phase, Banglore-560 099, India
[3]Green Evolution Laboratories, Wangapally Village, Nalgonda-500 085, India

*Corresponding author: E-mail: rambabun2013@gmail.com

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Anacardic acid (pentadecyl salicylic acid) is a phenolic constituent present in cashew nut shell liquid (*Anacardium occidentale* L.) and exhibits antimicrobial properties. The present paper describes the synthesis, characterization and antimicrobial evaluation of hydrazone derivatives of anacardic acid (**9a-l**) linked with 1,2,3-triazole ring. All the newly synthesized compounds were determined by ^{1}H NMR, mass and IR spectroscopy. Compounds **9d**, **9e**, **9h**, **9i** and **9j** exhibited strong antifungal activity against the tested fungal strains *viz.*, *A. niger* and *C. albicans*.

Keywords: Anacardic acid, Antibacterial, Antifungal, Hydrazone, 1,2,3-Triazole.

INTRODUCTION

The triazole nucleus is one of the most significant and well known azole which is widespread and important feature of a variety of natural products and medicinal agents [1]. Triazole derivatives are known to exhibit various pharmacological properties such as antiviral [2], antimicrobial [3,4], anticonvulsant [5], anticancer [6,7], antitubercular [8], antiinflamatory and analgesic [9].

Hydrazones are of great interest to researchers because of their diverse biological and clinical applications. They have been reported to exhibit antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular and antitumor activities [10-12].

Anacardic acid (pentadecyl salicylic acid) is a phenolic constituent present in cashew nut shell liquid (CNSL); (*Anacardium occidentale* L.) and exhibits antimicrobial properties [13-19], soybean lipoxygenase-1 inhibitory activity [20,21]. Reddy *et al.* [22] reported the synthesis of benzamide derivatives of anacardic acid. Furthermore, the following anacardic analogs *viz.*, dihydropyridine analogues [23], sildenafil analogues [24], isonicotinoylhydrazones for antimycobacterial activity [25], as calcium channel blockers, were appeared to possess prominent medicinal importance. Furthermore, anacardic acid exhibited, various activities like, is a specific activator of kinase activity of Aurora Kinase A [26], suppresses expression of nuclear factor-kB regulated gene products leading to potentiation of apoptosis [27] inhibitor of the HAT activity of recombinant Plasmodium falciparum GCN5 [28] and as modulators of histone acetyltransferases [29]. Cooper *et al.* [30] reported the antibacterial activities of anacardic acid derivatives and Dekker *et al.* [31,32] reported the anacardic acid derived salicylates as inhibitors or activatiors of lipoxygenases.

Resistance to antibacterial agents is a major problem since last three decades [33,34]. This emerging resistance has resulted in the development of a wide variety of antibiotics. In addition, primary and opportunistic fungal infections continue to increase rapidly because of the increased number of immune compromised patients (AIDS, cancer and transplants). Several reviews have appeared illustrating the problems encountered by today's infectious disease clinicians [29]. The present paper describes herein the synthesis, characterization and antimicrobial evaluation of hydrazone derivatives of anacardic acid (**9a-l**) linked with 1,2,3-triazole ring.

EXPERIMENTAL

The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. All reagents used were commercial and laboratory grade, melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on potassium bromide disks on a Perkin-Elmer 383

spectrophotometer. ^{1}H NMR spectra were obtained on Varian 400 MHz instrument with TMS as internal Standard and chemical shifts are expressed in ppm solvent used in $CDCl_3$ & DMSO-d_6 and mass spectrum on a Hewelett Packard mass spectrometer operating at 70 ev, purity of the compounds were checked by TLC, which is performed with E. Merck pre coated silica gel plates (60 F-254) with iodine as a developing agent. Acme, India silica gel, 60-120 mesh for column chromatography is used. All compounds were purified by column chromatography using ethylacetate in hexane.

Synthesis of 2-hydroxy-6-pentadecylbenzoic acid (2): An ethanolic solution (50 mL) of anacardic acid ene mixture (**1**) (10 g, 29.16 mmol) was hydrogenated in a 1 L Parr-apparatus at 50 psi of H_2 pressure in presence of 10 % Pd/C (1 g, 10 %) for 2 h. The reaction mixture was filtered through celite and the filtrate concentrated under reduced pressure to obtain **2**, which was recrystallized in petroleum ether to obtain the pure 2-hydroxy-6-pentadecylbenzoic acid **2**. White solid; Yield: 7 g, 68.8 %; m.p.: 85-86 °C; IR (KBr, ν_{max}, cm^{-1}): 3002, 2918, 2851, 1655, 1450, 1246, 1214; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.02 (brs, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 2.98 (t, *J* = 8.0 Hz, 2H), 1.57-1.63 (m, 2H), 1.27 (brs, 24H), 0.89 (t, *J* = 6.8 Hz, 3H); ESIMS: *m/z* 349 $(M+H)^+$.

Synthesis of methyl 2-methoxy-6-pentadecylbenzoate (3): To a solution of 2-hydroxy-6-pentadecylbenzoic acid (**2**) (5 g, 14.34 mmol) in dry CH_3CN (200 mL) was added dimethyl sulphate (5.44 mL, 57.36 mmol) followed by anhydrous K_2CO_3 (10.2 g, 71.70 mmol) and refluxed for 24 h. After the completion of the reaction, the reaction mixture was diluted with isopropyl acetate (150 mL) and water (200 mL). The organic layer was washed with water followed by brine solution (75 mL), dried over Na_2SO_4, filtered and concentrated to obtain methyl 2-methoxy-6-pentadecylbenzoate (**3**). Pale yellow solid; Yield: 18.5 g, 85.6 %; m.p.: 36-37 °C; IR (KBr, ν_{max}, cm^{-1}): 3004, 2921, 2852, 1732, 1589, 1460, 1266, 1105; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.53 (t, *J* = 8.0 Hz, 2H), 1.53-1.60 (m, 2H), 1.25 (brs, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 29.3, 29.3, 29.4, 29.5, 29.6, 29.6, 31.1, 31.8, 33.4, 52.0, 55.8, 108.3, 121.4, 123.4, 130.1, 141.3, 156.2, 168.8; ESIMS: *m/z* 377 $(M+H)^+$.

Synthesis of (2-methoxy-6-pentadecylphenyl)methanol (4): A stirred suspension of sodium borohydride (6 eq) and methyl 2-methoxy-6-pentadecylbenzoate (**3**) (4 g, 10.62 mmol) in anhydrous THF (30 mL) was heated under reflux for 20 min. To the above reaction contents, methanol (30 mL) was added slowly over a period of 30 min. The reaction was further refluxed for 1 h. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and quenched with a saturated solution of NH_4Cl (25 mL) for 1.5 h and diluted with isopropyl acetate. The organic layer was separated and the aqueous phase extracted with isopropyl acetate (2 × 25 mL). The organic extracts were combined and dried over Na_2SO_4 and concentrated under low pressure to give (2-methoxy-6-pentadecylphenyl)methanol (**4**). Off white solid; Yield: 3 g, 81 %; m.p.: 60-62 °C; IR (KBr, ν_{max}, cm^{-1}): 3367, 3004, 2924, 2853, 2781, 1689, 1596, 1577, 1472, 1457, 1438, 1409, 1377, 1268, 1180, 1169, 1119, 1080, 823, 788, 650, 474, 466, 418; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.75 (d, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 6.4 Hz, 1H), 1.53-1.58 (m, 2H), 1.27 (brs, 24H), 0.89 (t, *J* = 7.2 Hz, 3H, D_2O exchangeable OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 29.3, 29.4, 29.5, 29.6, 29.6, 31.8, 32.1, 33.1, 55.3, 57.3, 108.0, 122.2, 126.8, 128.4, 142.6, 158.2; ESIMS: *m/z* 349 $(M+H)^+$.

Synthesis of 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene (5): To a stirred solution of triphenyl phosphine (4.86 mmol) in dichloromethane (25 mL) was added tribromoisocyanuric acid (1.7 mmol). After 15 min, (2-methoxy-6-pentadecylphenyl)methanol (**4**) (2.43 mmol) was added and the suspension was stirred at room temperature for 3 h. The completion of the reaction was monitored by TLC. The cyanuric acid was filtered off and organic layer was washed with water (3 × 25 mL), the organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure to obtain 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene (**5**) as a reddish yellow syrupy liquid. IR (KBr, ν_{max}, cm^{-1}): 3418, 3020, 2949, 2919, 2849, 2717, 1841, 1683, 1593, 1583, 1509, 1468, 1456, 1437, 1421, 1400, 1385, 1349, 1317, 1279, 1234, 1198, 1160, 1135, 1092, 1031, 1010, 982, 873, 809, 774, 734, 721, 652, 567, 540; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.22 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.62 (s, 2H), 3.84 (s, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.60-1.54 (m, 2H), 1.30-1.18 (m, 24 H), 0.88 (t, *J* = 5.6 Hz, 3 H); ESIMS: *m/z* 331.4 $(M-HBr)^+$.

Synthesis of 2-(azidomethyl)-1-methoxy-3-pentadecylbenzene (6): To a stirred solution of compound **5** (1g, 2.43 mmol) in DMF was added sodium azide (165 mg, 2.55 mol) and heated to 90 °C for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water (10 mL) followed by ethyl acetate (10 mL). The organic layer was separated, washed with water followed by brine solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give pale yellow syrupy liquid. Yield: 0.8 g, 90 %. IR (KBr, ν_{max}, cm^{-1}): 3444, 2950, 2915, 2849, 2092, 1652, 1599, 1586, 1466, 1437, 1315, 1266, 1186, 1114, 1090, 1054, 864, 829, 783, 768, 754, 721, 669, 564, 493; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.41 (s, 2H), 3.84 (s, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.60-1.54 (m, 2H), 1.30-1.18 (m, 24 H), 0.88 (t, *J* = 5.6 Hz, 3 H); ESIMS: *m/z* 345.9 $(M-N_3)^+$.

Synthesis of 1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazole-4-carbaldehyde (7): To a stirred solution of 2-(azidomethyl)-1-methoxy-3-pentadecylbenzene (6) (0.8 g, 2.14 mmol) in acetonitrile (4 mL) was added propynaldehyde diethyl acetal (2.33 mmol) followed by CuI (10 mol %) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and added 2 N HCl (5 mL) and heated to 80 °C for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water, the precipitated yellow solids were filtered and dried to obtain 1-(2-methoxy-6-pentadecylbenzyl)-

1H-1,2,3-triazole-4-carbaldehyde (**7**). IR (KBr, ν_{max}, cm^{-1}): 3428, 3144, 3109, 2952, 2918, 2851, 1704, 1650, 1598, 1589, 1531, 1472, 1458, 1433, 1350, 1328, 1268, 1244, 1172, 1160, 1116, 1103, 1079, 1058, 1038, 1016, 836, 815, 801, 758, 685, 642, 573; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.02 (s, 1H), 8.82 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.61 (s, 2H), 3.80 (s, 3H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.42-1.38 (m, 2H), 1.30-1.18 (m, 24 H), 0.82 (t, *J* = 5.6 Hz, 3 H); ESIMS: *m/z* 428.1 $(M+H)^+$.

General procedure for the preparation of hydrazone derivatives (9a-l): To a stirred solution of AA-1,2,3-triazole aldehyde **7** (0.117 mmol) in ethanol was added corresponding benzohydrazides (**8a-l**) (0.122 mmol) and refluxed for 30 min. The reaction mixture was cooled to room temperature, filtered the precipitated solids and washed with petroleum ether, to obtain triazole hydrazide-hydrazone derivatives (**9a-m**) in quantitative yields.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]benzohydrazide (9a): White solid; m.p.: 112-113 °C; IR (KBr, ν_{max}, cm^{-1}): 3437, 3260, 3158, 3065, 3014, 2993, 2919, 2869, 2850, 1655, 1616, 1601, 1584, 1565, 1536, 1469, 1435, 1368, 1290, 1277, 1267, 1236, 1181, 1155, 1084, 1055, 957, 911, 823, 795, 716, 693, 681, 654, 572; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 2H), 3.83 (s, 3H), 2.72 (brs, 2H), 1.36 (brs, 2H), 1.20 (brs, 24 H), 0.84 (brs, 3H); ESI-MS: *m/z*, 546.1 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-4-methoxybenzohydrazide (9b): White solid; m.p.: 118-119 °C; IR (KBr, ν_{max}, cm^{-1}): 3443, 3252, 3167, 3012, 2954, 2917, 2850, 1648, 1608, 1586, 1561, 1533, 1509, 1472, 1439, 1373, 1361, 1328, 1293, 1267, 1260, 1228, 1185, 1153, 1121, 1110, 1082, 1072, 1060, 1046, 1027, 963, 954, 912, 842, 814, 765, 719, 687, 658, 626, 618, 503; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 8.50 (s, 1H), 8.13 (s, 1H), 7.86 (d, *J* = 9.2 Hz, 2H), 7.31 (s, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.62 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.72 (brs, 2H), 1.36 (brs, 2H), 1.19 (brs, 24 H), 0.84 (brs, 3H); ESI-MS: *m/z*, 576.1 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-4-chlorobenzohydrazide (9c): White solid; m.p.: 99-101 °C; IR (KBr, ν_{max}, cm^{-1}): 3417, 3253, 3167, 3072, 3012, 2991, 2952, 2920, 2870, 2850, 1653, 1616, 1590, 1563, 1536, 1484, 1467, 1434, 1367, 1297, 1265, 1237, 1180, 1155, 1094, 1085, 1065, 1053, 1013, 962, 910, 853, 823, 771, 757, 720, 703, 690, 666, 656, 623, 571, 534; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.31 (s, 1H), 6.93 (d, *J* = 6.4 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 2H), 3.83 (s, 3H), 2.72 (brs, 2H), 1.35 (brs, 2H), 1.18 (brs, 24 H), 0.84 (t, *J* = 5.6 Hz, 3H); ESI-MS: *m/z*, 580.0 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-4-hydroxybenzohydrazide (9d): White solid; m.p.: 126-128 °C; IR (KBr, ν_{max}, cm^{-1}): 3252, 3220, 3162, 3130, 3074, 3019, 2949, 2916, 2850, 2682, 2616, 1698, 1650, 1612, 1588, 1576, 1541, 1512, 1472, 1443, 1379, 1367, 1351, 1328, 1300, 1276, 1267, 1236, 1180, 1164, 1154, 1102, 1082, 1072, 1056, 967, 949, 917, 858, 835, 812, 789, 761, 715, 701, 662, 635, 623, 565, 515; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 10.12 (s, 1H), 8.47 (s, 1H), 8.11 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 8.4 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 2H), 5.62 (s, 2H), 3.83 (s, 3H), 2.71 (brs, 2H), 1.36 (brs, 2H), 1.19 (brs, 24 H), 0.84 (brs, 3H); ESI-MS: *m/z*, 562.1 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-3,4,5-trimethoxybenzohydrazide (9e): White solid; m.p.: 120-122 °C; IR (KBr, ν_{max}, cm^{-1}): 3440, 3260, 3108, 3090, 3065, 3002, 2922, 2851, 1649, 1614, 1583, 1556, 1525, 1503, 1470, 1461, 1437, 1413, 1376, 1363, 1335, 1268, 1235, 1183, 1133, 1088, 1063, 1002, 974, 849, 835, 809, 768, 756, 736, 714, 694, 654, 591, 564; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 7.20 (s, 2H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H), 2.72 (brs, 2H), 1.37 (brs, 2H), 1.20 (brs, 24 H), 0.84 (t, *J* = 5.6 Hz, 3H); ESI-MS: *m/z*, 636.1 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-2,5-dichlorobenzohydrazide (9f): White solid; m.p.: 122-123 °C; IR (KBr, ν_{max}, cm^{-1}): 3444, 3244, 3062, 2955, 2919, 2850, 1667, 1616, 1585, 1561, 1530, 1465, 1437, 1377, 1364, 1290, 1260, 1239, 1162, 1135, 1099, 1085, 1062, 977, 964, 934, 882, 829, 794, 780, 764, 719, 691, 666, 657, 599, 569, 547; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (* 11.96, s, 1H), 8.30 (* 8.09, s, 1H), 8.19 (* 7.78, s, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 7.54 (s, 1H), 7.33-7.25 (m, 1H), 6.94-6.82 (m, 2H), 5.61 (* 5.50, s, 2H), 3.83 (* 3.73, s, 3H), 2.74-2.67 (m, 2H), 1.36 (brs, 2H), 1.22 (brs, 24 H), 0.84 (t, *J* = 5.6 Hz, 3H); ESI-MS: *m/z*, 614.0 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-3,5-dichlorobenzohydrazide (9g): White solid; m.p.: 133-134 °C; IR (KBr, ν_{max}, cm^{-1}): 3432, 3236, 3178, 3115, 3076, 3020, 2994, 2953, 2920, 2849, 1661, 1583, 1566, 1534, 1469, 1434, 1417, 1375, 1360, 1348, 1327, 1298, 1286, 1270, 1261, 1240, 1229, 1170, 1114, 1098, 1084, 1075, 1045, 951, 945, 897, 866, 829, 817, 805, 771, 757, 748, 720, 712, 670, 655, 638, 566; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1H), 8.50 (s, 1H), 8.18 (s, 1H), 7.92 (s, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 2H), 3.83 (s, 3H), 2.72 (brs, 2H), 1.35 (brs, 2H), 1.18 (brs, 24 H), 0.84 (t, *J* = 5.6 Hz, 3H); ESI-MS: *m/z*, 614.0 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-3-nitrobenzohydrazide (9h): White solid; m.p.: 86-88 °C; IR (KBr, ν_{max}, cm^{-1}): 3436, 3233, 3170, 3074, 3044, 3015, 2954, 2920, 2870, 2851, 1665, 1655, 1619, 1586, 1567, 1531, 1470, 1439, 1353, 1328, 1298, 1266, 1227, 1159, 1122, 1081, 1060, 1046, 959, 912, 861, 823, 817, 764, 731, 719, 687, 672, 661, 650, 565; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 8.72 (s, 1H), 8.53 (s, 1H), 8.44 (d, *J* = 6.8 Hz, 1H), 8.34 (d, *J* = 6.0 Hz, 1H), 8.22 (s, 1H), 7.85 (s, 1H), 7.31 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 6.4 Hz, 1H), 5.61 (s, 2H), 3.84 (s, 3H), 2.72 (brs, 2H), 1.35 (brs, 2H), 1.18 (brs, 24 H), 0.84 (brs, 3H); ESI-MS: *m/z*, 591.1 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-4-fluorobenzohydrazide (9i): White solid; m.p.: 128-129 °C; IR (KBr, ν_{max}, cm^{-1}): 3432, 3255, 3166, 3074, 3015, 2991, 2950, 2920, 2869, 2850, 1655, 1616, 1602, 1586, 1565, 1537, 1506, 1469, 1435, 1366, 1307, 1288, 1275, 1265, 1234, 1179, 1159, 1099, 1085, 1066, 1053, 957, 912, 857, 826, 812, 771, 763, 720, 690, 662, 656, 625, 612, 571; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 7.96 (s, 2H), 7.36-7.31 (m, 4H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 4.0 Hz, 1H), 5.61 (s, 2H), 3.83 (s, 3H), 2.72 (brs, 2H), 1.35 (brs, 2H), 1.19 (brs, 24 H), 0.84 (brs, 3H); ESI-MS: *m/z*, 564.0 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-2,5-difluorobenzohydrazide (9j): White solid; m.p.: 94-96 °C; IR (KBr, ν_{max}, cm^{-1}): 3303, 3114, 3090, 3066, 3009, 2950, 2916, 2848, 1667, 1586, 1561, 1534, 1488, 1471, 1441, 1425, 1366, 1307, 1285, 1270, 1246, 1229, 1182, 1135, 1124, 1111, 1083, 1057, 1036, 964, 901, 860, 827, 814, 776, 763, 752, 719, 690, 655, 603, 579, 540; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (* 11.89, s, 1H), 8.36 (* 8.10, s, 1H), 8.19 (* 7.83, s, 1H), 7.51-7.42 (m, 2H), 7.33-7.25 (m, 2H), 6.99-6.82 (m, 2H), 5.61 (* 5.51, s, 2H), 3.83 (* 3.74, s, 3H), 2.74-2.67 (m, 2H), 1.35 (brs, 2H), 1.24 (brs, 24 H), 0.84 (t, *J* = 5.6 Hz, 3H); ESI-MS: *m/z*, 582.1 $(M+H)^+$.

(*E*)-N'-[{1-(2-Methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-3-chlorobenzohydrazide (9k): White solid; m.p.: 134-135 °C; IR (KBr, ν_{max}, cm^{-1}): 3441, 3208, 3072, 3051, 2953, 2920, 2869, 2850, 1654, 1615, 1586, 1561, 1532, 1469, 1436, 1365, 1307, 1289, 1266, 1231, 1172, 1115, 1084, 1072, 1049, 946, 889, 823, 805, 759, 737, 721, 689, 683, 655; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 8.48 (s, 1H), 8.20 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 6.4 Hz, 1H), 5.61 (s, 2H), 3.82 (s, 3H), 2.71 (brs, 2H), 1.37 (brs, 2H), 1.18 (brs, 24 H), 0.84 (brs, 3H); ESI-MS: *m/z*, 580.0 $(M+H)^+$.

(*E*)-N'-[{1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]-4-(methylsulfonyl)benzohydrazide (9l): White solid; m.p.: 131-132 °C; IR (KBr, ν_{max}, cm^{-1}): 3434, 3279, 3245, 3064, 3038, 3009, 2953, 2918, 2850, 1655, 1585, 1559, 1529, 1505, 1471, 1439, 1395, 1361, 1316, 1298, 1283, 1267, 1233, 1155, 1146, 1087, 1060, 1047, 964, 908, 855, 821, 786, 763, 752, 720, 688, 670, 565, 553, 521, 463; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 8.20 (s, 1H), 8.09 (d, *J* = 4.8 Hz, 4H), 7.31 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.72 (brs, 2H), 1.37 (brs, 2H), 1.20 (brs, 24 H), 0.84 (t, *J* = 5.6 Hz, 3H); ESI-MS: *m/z*, 624.1 $(M+H)^+$.

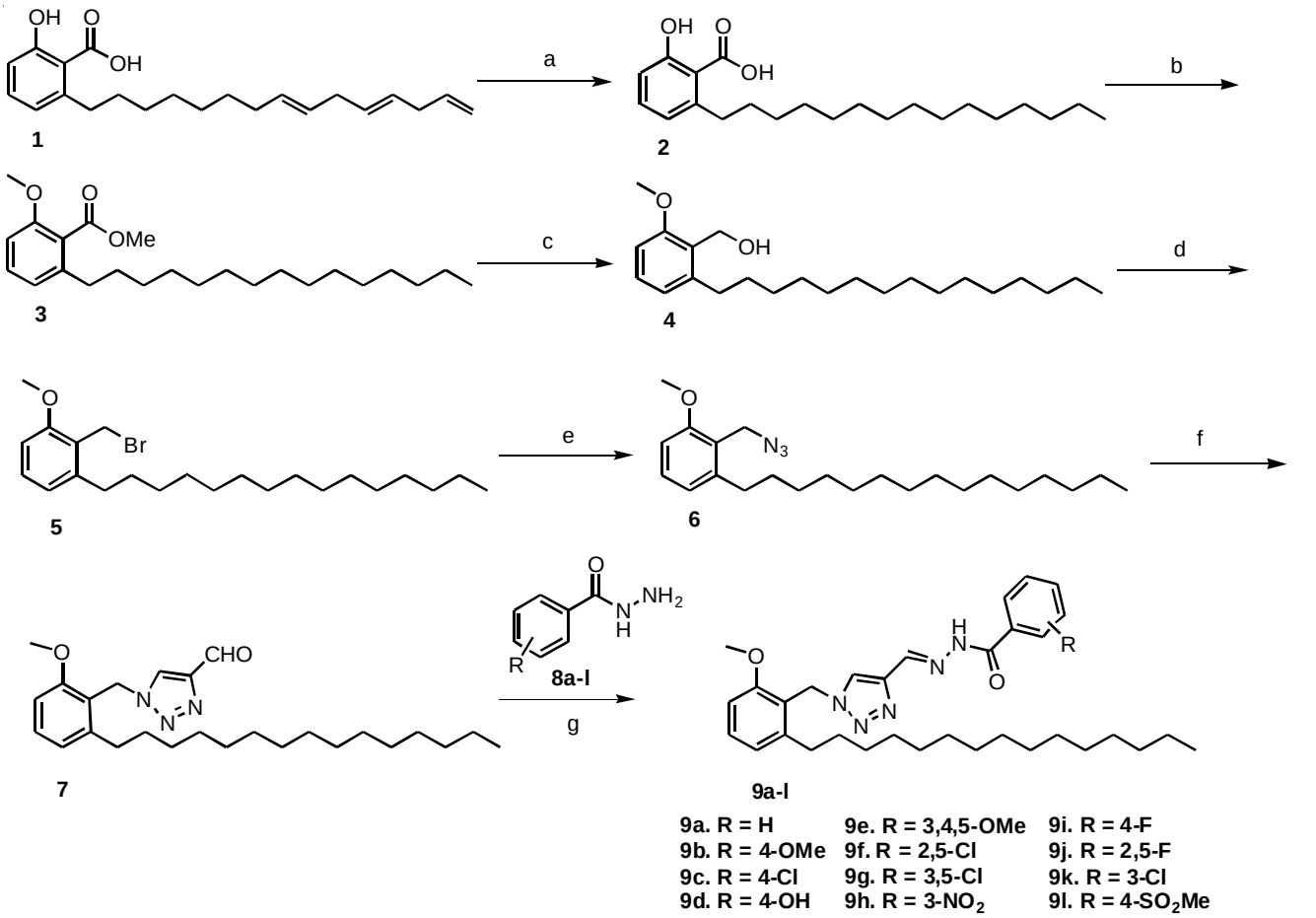
Antimicrobial screening

Antibacterial and antifungal assay: The antimicrobial activities of the synthesized triazole linked hydrazone derivatives of anacardic acid (**9a-l**) were determined by agar diffusion method [35]. The compounds were evaluated for antimicrobial activity against bacteria *viz. Escherichia coli* (MTCC 443), *Pseudomonas auriginosa* (MTCC 424), *Staphylococus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442) and antifungal activity against fungi *viz. Aspergillus niger* (MTCC 282), *Candida albicans* (MTCC 227). The antibiotic ampicillin and greseofulvin are used as reference antibacterial and antifungal substances, respectively under similar conditions for comparison. Dimethyl sulphoxide (1 %, DMSO) was used as control. The minimum inhibitory concentration (MIC) value was determined at a concentration of 25 µg/mL using dimethyl sulfoxide (DMSO) as solvent against bacteria as well as fungal strains. The culture strains of bacteria were maintained on nutrient agar slant at 37 ± 0.5 °C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85 %) of 10^5 cfu/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of target compound dilution ranging from 25 to 1000 µg/mL separately for each bacterial strain. All the plates were incubated at 37 ± 0.5 °C for 24 h.

For antifungal activity, all the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27 ± 0.2 °C for 24-48 h, till sporulation. Spore of strains were transferred in to 5 mL of sterile distilled water containing 1 % Tween-80 (to suspend the spore properly). The spores were counted by haemocytometer (10^6 CFU/mL). Sterile PDA plate was prepared containing 2 % agar; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27 ± 0.2 °C for 12 h. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL compound solution of concentrations 25 to 1000 µg/mL separately to get minimum inhibitory concentration value of hydrazone derivatives **9a-l**. The plates were kept in refrigerator for 20 min for diffusion and then incubated at 27 ± 0.2 °C for 24-28 h.

RESULTS AND DISCUSSION

The synthesis of (*E*)-N'-[{1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]benzohydrazide derivatives (**9a-l**) is illustrated in **Scheme-I**. Anacardic acid (**2**) was obtained by hydrogenation of anacardic ene mixture (**1**) according to the literature procedure [36-40]. Methylation of anacardic acid (**2**) was carried out using dimethyl sulphate in presence of potassium carbonate in acetonitrile to obtain methylated derivative (**3**) of ancardic acid. Reduction of compound **3** with $NaBH_4$ in presence of THF:MeOH [41] resulted in (2-methoxy-6-pentadecylphenyl)methanol (**4**). Bromination of carbinol **4** was carried out using tribromoisocyanuric acid in presence of triphenyl phosphine [42] in dichloro-methane to afford 2-(bromomethyl)-1-methoxy-3-pentadecyl-benzene (**5**). Bromide **5** was reacted with sodium azide in DMF at 90 °C to obtain azide **6**. Reaction of azide **6** with propynaldehyde diethal acetal in presence of CuI in acetonitrile at 3 h followed by the deprotection of acetal group in acidic medium (2 N HCl) resulted in the formation of the key intermediate 1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazole-4-carbaldehyde (**7**). Condensation of the triazole aldehyde **7** with different benzohydrazide **8a-l** in ethanol at reflux for 30 min resulted in the formation of (*E*)-N'-[{1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}-methylene]benzohydrazide derivatives (**9a-l**) in quantitative yields. All the synthesized hydrazone derivatives (**9a-l**) was characterized by ^{1}H NMR, mass and IR spectroscopic techniques. Mass spectral data of all the hydrazone derivatives (**9a-l**) and its associated intermediates are in agreement with the desired molecular formulae exhibiting (M+H) peaks. As a



Experimental conditions: a) 10 % Pd-C, EtOH, H_2, 50 psi, 2 h; b) Dimethyl sulphate, K_2CO_3, CH_3CN, reflux, 24 h; c) $NaBH_4$, THF:Methanol, reflux, 1 h; d) Tribromoisocyanuric acid, TPP, dichloromethane, r.t., 3 h; e) NaN_3, DMF, 90 °C, 1 h; f) i. propynaldehyde diethyl acetal, CuI, acetonitrile, reflux, 3 h, ii. 2N HCl, 80 °C, 12 h; g) Benzohydrazide **8a-l**, ethanol, 30 min

Scheme-I: Synthesis of novel triazole-hydrazone derivatives of anacardic acid **9a-l**

general representative example for hydrazone derivatives, the ^{1}H NMR assignment of (*E*)-N'-[{1-(2-methoxy-6-pentadecyl-benzyl)-1H-1,2,3-triazol-4-yl}methylene]-3,4,5-trimethoxy-benzohydrazide (**9f**) is exemplified here: the protons signals at 0.84 ppm (triplet, 3H), 1.30-1.18 ppm (multiplet, 24H), 1.37 ppm (brs, 2H) and 2.72 ppm (brs, 2H) resonating in the aliphatic region corresponds to the side chain of the anacardic acid moiety. The protons of the methoxy groups of **9f** appeared in the expected region. The characteristic methylene proton of **9f** appeared as singlet at 5.61 ppm. The characteristic proton signals resonating at 11.61ppm, 8.52 ppm and 8.19 ppm as singlets corresponds to -CO**NH**-, -N=**CH**-and triazole ring respectively. In the aromatic region, the protons resonating at 7.20 ppm as singlet corresponds to the 3,4,5-trimethoxy phenyl ring while the protons resonating at 7.31, 6.93 and 6.86 ppm as triplet and doublets represents the aromatic ring protons of anacardic acid. The IR spectra of the compounds **9a-l** indicated the following characteristic peaks: A strong characteristic bands in the region 1667-1649 cm^{-1} are due to the C=O stretching vibrations of amide functional group. The multiple peaks in the region 1614-1437 cm^{-1} are due to C=N and aromatic ring stretching vibrations. The peaks in the regions 1335-1235 cm^{-1} are due to (C-N) stretching vibrations. The N-H stretching vibrations of the compounds gave rise to broad bands in the region 3443-3418 cm^{-1}. The N=N stretching absorption for triazole compounds appeared nearly around 1400 cm^{-1} which was assigned within the same absorption region of the C=C stretching for all compounds.

Antibacterial and antifungal: The results of *in vitro* antibacterial and antifungal activities are summarized in Table-1. Compounds **9d**, **9e**, **9h**, **9i** and **9j** exhibited excellent antifungal activity against the tested fungal strains *viz., A. niger* and *C. albicans*. Compounds **9c**, **9f** and **9g** showed good activity and are lower than that of greseoflavin. The remaining compounds in the series showed moderate fungal activity.

On the basis of zone of inhibition (ZI) with reference to the standard drug ampicillin, the antibacterial activity of the compounds **9a-l** is measured as good, moderate and weak activity. In case of Gram-positive bacteria compounds **9c, 9e, 9g, 9h** and **9j** exhibited good antibacterial activity (ZI: 9-12 mm), compounds **9a, 9d** and **9f** showed moderate antibacterial activity (ZI: 6-8 mm), whereas compounds **9b, 9i, 9k and 9l** showed weak to nil antibacterial activity (ZI: 0-4 mm). Similar trends of antibacterial activity were observed in case of Gram-negative bacterial strain. Considering the results obtained from antifungal and antibacterial tests together, it is noteworthy to mention that tested compounds are more active towards fungi than bacteria.

TABLE-1
ANTIMICROBIAL ACTIVITY OF HYDRAZONE DERIVATIVES (**9a-l**)

Compound No.	Zone of inhibition (mm)					
	Gram-positivee bacteria		Gram-negative bacteria		Fungi	
	S. aureus MTCC 96	*S. pyogenes* MTCC 442	*E. coli* MTCC 443	*P. aeruginosa* MTCC 424	*A. niger* MTCC 282	*C. albicans* MTCC 227
9a	6	7	7	8	16	15
9b	4	3	5	6	13	12
9c	9	9	11	12	17	18
9d	8	8	9	9	26	24
9e	10	9	13	13	27	23
9f	7	7	10	9	19	19
9g	10	11	12	13	20	20
9h	11	11	14	14	25	24
9i	3	3	6	6	24	22
9j	11	12	11	11	26	24
9k	–	–	6	5	12	12
9l	–	–	4	6	14	15
SD*	13	14	15	15	–	–
SD**					23	21

SD*: Standard drug: Ampicillin (conc. 25 μg/mL^{-1}) was used as a standard drug for antibacterial activity.
SD**: Greseofulvin (conc. 25 μg/mL) was used as a standard drug for antifungal activity.

Conclusion

The present paper describes the synthesis, characterization and antimicrobial evaluation of (*E*)-N'-[{1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl}methylene]benzohydrazide derivatives **9a-l** derived from commercially available cashew nut shell liquid (*Anacardium occidentale* L.). The results of *in vitro* antibacterial and antifungal activities revealed that tested compounds are more active towards fungi than bacteria.

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