Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2016, 5 (4): 783-791

(International Peer Reviewed Journal)

Synthesis and Antibacterial Activity of Some Novel Hydrazone Derivatives of Anacardic acid Linked with 1, 4-Disubstituted 1,2,3-Triazole Ring.

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Accepted on 14th July 2016

ABSTRACT

*The synthesis of the hydrazone derivatives was accomplished in five steps from anacacrdic acid (as starting material) utilization greener solvents/green reagents. Some of the highlights of the synthesis involves (i) methylation reaction using dimethyl carbonate as greener reagent (ii) mild bromination reaction utilizing TCT /DMF complex / NaBr (iii) one pot click reaction using ionic liquid (iv) synthesis of hydrazone derivatives under solvent free conditions. The structures of newly synthesized derivatives 7**a-g** were determined by spectroscopic techniques like ^{1}H NMR, mass and IR spectral data. Antibacterial activity screening results revealed that hydrazone derivatives **7a**, **7b** and **7e** with R = 4-OMe, 3, 4, 5-OMe and 2,5-F exhibited good antibacterial activity against Gram positive (viz., S.aureus and B. subtilus) and Gram negative strains (viz., E.Coli and P.Aeruginosa).*

Keywords: Anacardic acid, Click reaction, Green conditions, 1, 2, 3-Triazole ring, Antibacterial activity.

INTRODUCTION

1,2,3-Triazoles are important five-membered nitrogen heterocycles, involved in a wide range of industrial applications such as agrochemicals, corrosion inhibitions, dyes, optical brighteners and biologically active agents [1]. The compounds are in general prepared through the coupling reaction between alkynes and azides to form a mixture of 1, 4-substituted- and 1,5- substituted-1,2,3-triazoles at high temperature [2]. The copper (I)-catalyzed Huisgen cycloaddition reaction of azides and terminal alkynes has emerged as a novel alternative, and received much attention since its discovery. 1,2,3-Triazole derivatives have been shown to exhibit a wide range of diverse, interesting biological properties such as anti-HIV [3] antimalarial [4], antiepileptic [5], antialergic [6], antileishmanial [7], anticancer [8,9], anti-inflammatory [10], antitubercular [11, 12], antidiabetic [13], antifungal [14-16], antiviral [17, 18] and antibacterial [19, 20].
Anacardic acid (pentadecyl salicylic acid) is a phenolic constituent present in CNSL; (Anacardium occidentale L.) which is a by-product of cashew nut industry and these are salicylic acid derivatives with a non-isoprenoid alk (en)yl side chain [21]. Anacardic acid derivatives exhibit biological activities like soybean lipoxygenase-1 inhibitory activity [22, 23] and antimicrobial activity [24, 25, 26-30].

Hydrazones possessing an azomethine -NHN=CH- proton. Hydrazones constitute an important class of compounds for development of novel drugs. A number of hydrazone derivatives have been reported to various biological activities like analgesic, anti-inflammatory, antihypertensive, anticonvulsant, antimicrobial, anti-tubercular, antitumor, antimalarial and antiproliferative activities [31].

The worldwide rise of antimicrobial resistance, combined with the rapid rate of microbial evolution, and the slower development of novel antibiotics, accents the crucial need for novel therapeutics. Development of new antimicrobial or antipathogenic agents that act upon new microbial targets is a necessity [32]. Although there has been a unyielding increase in resistance to antimicrobial agents between important bacterial pathogens throughout the world, it is well known that the number of new antimicrobial agents being brought to the market had a consistent decline in the past decades.

In the present study, we aimed to synthesize new compounds containing, anacacrdic acid ring linked with 1, 2, 3-Triazole ring and a hydrazone moiety in the same structure, using green conditions and also a click chemistry approach to achieve the above said compounds. The newly synthesized compounds have been characterized by various spectroscopic techniques *viz.*, ^{1}H NMR, mass and IR data. These compounds were further evaluated for antimicrobial studies.

MATERIALS AND METHODS

Chemicals and solvents were purchased from Sigma-Aldrich and Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellets with Perkin-Elmer Spectrum GX FTIR instrument and only diagnostic and/or intense peaks were reported. ^{1}H NMR spectra were recorded in DMSO- d_6 with Varian Mercury plus 400 MHz instrument. Signals due to the residual protonated solvent (^{1}H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity was indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) correspond to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under nitrogen atmosphere.

Synthesis of Methyl (2-methoxy-6-pentadecyl) benzoate (2): In a sealed tube vessel, was added 2-hydroxy-6-pentadecylbenzoic **1** (10g, 28.70 mmol), 2-methyl tetrahydrofuran (60 mL), dimethylcarbonate (5.17g, 57.40 mmol) followed by DBU (0.44g, 2.90 mmol) and the cap was screwed tightly. The reaction mixture was heated to 140^{o}C for 17 h. After cooling, the reaction contents was diluted with cyclopentyl methyl ether (25 mL), washed with 10% solution of sodium bicarbonate solution (3 X 15 mL), washed with 1M HCl (3 X 25 mL) and with water (3 X 25 mL), dried over sodium sulphate, filtered and concentrated to afford methyl 2-methoxy-6-pentadecylbenzoate **3.** Pale yellow solid; Yield: 9.0 g, 84%; M.p.: 36-37°C; IR (KBr): ν_{max} 3004, 2921, 2852, 1732, 1589, 1460, 1266, 1105 cm^{-1}; ^{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 $(M+H)^+$.

Preparation of (2-Methoxy-6-pentadecylphenyl) methanol (3): To a stirred suspension of methyl 2-methoxy-6-pentadecylbenzoate **2** (5.0 g, 13.28 m.mol) in 2-Methyl THF (75 mL) was added sodium borohydride (2g, 52.86 mmol) and heated under reflux for 1h. The above reaction mixture was, diluted with methanol (75 mL) and was further refluxed for 1 h. The reaction mixture was cooled to room temperature and quenched with a saturated solution of NH_4Cl (50 mL) for 2 h and diluted with

isopropylacetate. The organic extracts was washed with water followed by brine solution, dried over Na_2SO_4 and concentrated under reduced pressure to obtain (2-methoxy-6-pentadecylphenyl) methanol **3.** Off white solid; Yield: 3 g, 81 %; M.p.: 60-62°C; IR (KBr): v_{max} 3367, 3004, 2924, 2853, 2781, 1689, 1596, 1577, 1472, 1457, 1438, 1409, 1377, 1268, 1180, 1169, 1119, 1080, 823, 788, 650, 474, 466, 418 cm^{-1}; ^1H 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 $(M+H)^+$.

Preparation of 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene (4): A pre-mixed mixture of 2,4,6-Trichloro-[1,3,5]-triazine (2.64 g, 14.32 mmol) in DMF (2.7 mL) was maintained at 25 °C. After the formation of a white solid, cyclopentyl methyl ether (50 mL) was added, followed by NaBr (2.94 g, 28.58 mmol). The mixture was stirred for 16 h and in sequence 2-methoxy-6-pentadecylphenyl) methanol **3** (5.0 g, 14.34 mmol) was added. The mixture was then stirred at room temperature, until the completion of the reaction (monitored TLC, 45 min). To the reaction mixture water (30 mL) was added and the organic phase washed with saturated solution of sodium carbonate (2 X 15 mL), followed by 1 N HCl and brine. The organic layer were dried over sodium sulphate and was concentrated under reduced pressure to obtain 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene **4.** Pale yellow oily liquid; Yield: 88%; B.P.: 198°C; IR (KBr): v_{max} 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 cm^{-1}; ^1H 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 $(M- HBr)^+$.

Preparation of 4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1, 2, 3-triazol-4-yl)benzaldehyde (5): 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene **4** (0.62 g, 1.46 mmol), 4-ethynylbenzaldehyde (192 mg, 1.46 mmol) and NaN_3 (115 mg, 1.77 mmol) were placed in a round-bottomed flask (25 mL). To the above reaction mixture was added, sequentially, sodium carbonate (310 mg, 2.92 mmol), CuI (15 mol %) followed by [bmim][BF_4]/H_2O 1:1 and stirred for at room temperature for 6 h and then extracted with diethyl ether (3 X 25 mL). The combined organic extracts were washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified via silica gel column chromatography (60-120 mesh, eluant: MeOH; Chloroform / 1: 4). Ionic liquid was recovered by extracting with dichloromethane and can be reused for the same reactions. Pale yellow solid; M.p.: 102-103 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 8.48 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 5.59 (s, 2H), 3.82 (s, 3H), 2.71 (t, J = 7.2 Hz, 2H), 1.21-118 (m, 26H), 0.84 (t, J = 6.4 Hz, 3H); ESI-MS: m/z, 504.3 $(M+H)^+$.

General procedure for the preparation of hydrazone derivatives (7a-g): A mixture of 4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzaldehyde **5** (0.117 mmol), corresponding benzo hydrazides **6a-g** (0.122 mmol) in ethanol (0.1 mL) was grinded in mortar-pestle for 2-3 min. After completion of the reaction (checked by T.L.C), the precipitated solids were filtered and washed with cyclopentyl methyl ether to obtain the corresponding hydrazone derivatives **7a-g** in quantitative yields.

(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)-4-methoxy benzohydrazide (7a): Off-white solid; M.p.: 131-133^oC; IR (KBr): υ_{max} 3668.9, 3444.2, 3286.1, 3150.2, 3073.0, 3001.7, 2953.4, 2918.7, 2851.2, 1907.3, 1658.5, 1605.4, 1586.2, 1553.4, 1509.0, 1471.4, 1437.7, 1417.4, 1374.0, 1349.0, 1308.5, 1289.2, 1273.8, 1253.5, 1223.6, 1183.1, 1144.5, 1108.9, 1084.8, 1065.5, 1044.3, 1032.7, 971.9, 950.7, 919.9, 840.8, 824.4, 807.1, 760.8, 729.0, 720.3, 693.3, 649.9, 635.4, 615.2, 535.1, 507.2, 455.1 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.72 (s, 1H), 8.44 (s, 1H), 8.33 (s, 1H), 7.90 (t, J = 7.2 Hz, 2H), 7.73-7.68 (m, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.0

Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 5.60 (s, 2H), 3.84 (s, 6H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.33-1.14 (brm, 26H), 0.81 (t, *J* = 6.8 Hz, 3H); ESI-MS: m/z, 652.4 $(M+H)^+$.

(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)-3,4,5-trimethoxybenzohydrazide (7b): Off-white solid; M.p.: 117-118 ^oC; IR (KBr): υ_{max} 3849.2, 3433.6, 3228.3, 2916.8, 2849.3, 1698.0, 1648.8, 1602.6, 1585.2, 1540.8, 1503.2, 1465.6, 1436.7, 1414.5, 1361.5, 1333.5, 1307.5, 1267.0, 1235.2, 1181.2, 1128.2, 1085.7, 1001.8, 974.8, 945.9, 839.8, 807.1, 769.5, 723.2, 687.5, 570.8, 537.1, 514.9, 502.4, 492.7 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.70 (s, 1H), 8.45 (s, 1H), 8.36 (s, 1H), 7.93 (t, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.22 (s, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.58 (s, 2H), 3.83 (s, 6H), 3.84 (s, 3H), 3.71 (s, 3H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.33-1.12 (brm, 26H), 0.80 (t, *J* = 6.6 Hz, 3H); ESI-MS: m/z, 712.4 $(M+H)^+$.

(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)-4-chlorobenzohydrazide (7c): Pale yellow solid; M.p.: 122-123 ^oC; IR (KBr): υ_{max} 3898.4, 3731.6, 3440.4, 3289.0, 3153.0, 3077.8, 3007.4, 2918.7, 2851.2, 1661.4, 1602.6, 1588.1, 1570.7, 1555.3, 1485.9, 1471.4, 1438.6, 1417.4, 1397.2, 1379.8, 1364.4, 1350.9, 1306.5, 1294.0, 1273.8, 1228.4, 1192.8, 1183.1, 1143.6, 1109.8, 1093.4, 1085.7, 1062.6, 1047.2, 1014.4, 972.9, 950.7, 918.9, 839.8, 805.1, 752.1, 729.0, 721.2, 686.5, 634.5, 613.3, 576.6, 532.3, 483.1 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 3H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.60 (s, 2H), 3.84 (s, 3H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.33-1.13 (m, 26H), 0.81 (t, *J* = 6.6 Hz, 3H); ESI-MS: m/z, 656.3 $(M+H)^+$.

(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)-3-nitrobenzohydrazide (7d): Yellow solid; M.p.: 100-101^oC; IR (KBr): υ_{max} 3442.3, 3316.0, 3232.1, 3070.1, 2919.7, 2849.3, 1731.8, 1656.6, 1613.2, 1601.6, 1585, 1546.6, 1529.3, 1495.5, 1469, 1439.6, 1413.6, 1348.0, 1295.0, 1268.0, 1225.5, 1179.3, 1156.1, 1111.8, 1083.8, 1057.8, 1019.2, 974.8, 951.7, 915.1, 844.7, 829.2, 793.6, 768.5, 718.4, 690.4, 462.8 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 8.74 (s, 1H), 8.50-8.3 (m, 4H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.29 (t, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 2H), 3.84 (s, 6H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.34-1.12 (brm, 26H), 0.80 (t, *J* = 7.2 Hz, 3H); ESI-MS: m/z, 667.4 $(M+H)^+$.

(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)-2,5-difluorobenzohydrazide (7e): Yellow solid; M.p.: 130-131^oC; IR (KBr): υ_{max} 3849.2, 3731.6, 3305.4, 3099.0, 3076.9, 3009.4, 2915.8, 2848.3, 1655.6, 1603.5, 1587.1, 1544.7, 1489.7, 1470.5, 1457.0, 1441.5, 1424.2, 1363.4, 1339.3, 1323.9, 1306.5, 1272.8, 1223.6, 1181.2, 1151.3, 1125.3, 1109.8, 1085.7, 1062.6, 1045.2, 977.7, 964.2, 943.0, 906.4, 871.7, 836.0, 828.3, 809.0, 776.2, 769.5, 753.1, 721.2, 697.1, 686.5, 653.8, 606.5, 572.8, 540.0, 469.6 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.99 (* 11.81, s, 1H), 8.32 (s, 1H), 8.25 (* 8.06, s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.81 (* 7.75, d, *J* = 8.0 Hz, 2H), 7.50-7.29 (m, 5H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 5.59 (* 5.56, s, 2H), 3.84 (* 3.83, s, 3H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.36-1.15 (m, 26H), 0.81 (t, *J* = 7.2 Hz, 3H); ESI-MS: m/z, 657.8 $(M+H)^+$.

(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)benzohydrazide (7f): Off-white solid; M.p.: 108-109^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 7.86 (t, *J* = 7.2 Hz, 2H), 7.72-7.64 (m, 7H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 5.60 (s, 2H), 3.86 (s, 3H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.33-1.14 (brm, 26H), 0.83 (t, *J* = 6.8 Hz, 3H); ESI-MS: m/z, 622.4 $(M+H)^+$.

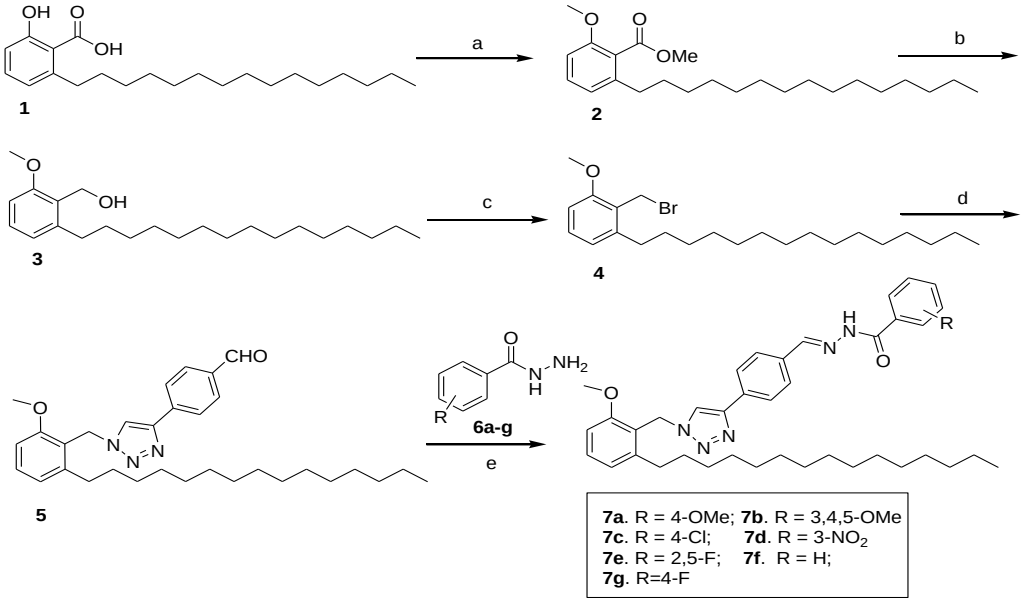
(*E*)-N'-(4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1,2,3-triazol-4-yl)benzylidene)-4-fluorobenzohydrazide (7g): Pale yellow solid; M.p.: 128-129^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H), 8.48 (s, 1H), 8.36 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 3H), 7.78-7.72 (m, 3H), 7.60 (d, *J* = 7.6 Hz, 2H),

7.30 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 5.58 (s, 2H), 3.85 (s, 3H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.33-1.12 (m, 26H), 0.82 (t, *J* = 6.6 Hz, 3H); ESI-MS: m/z, 640.4 $(M+H)^+$.

Antibacterial Bioassay: The synthesized derivatives were tested against Gram negative strains (*i) Escherichia coli* (MTCC 2692) and *(ii) Pseudomonas aeruginosa* (MTCC 2453) and Gram positive strains of (iii) *Staphylococcus aureus* (MTCC 902) and (*iv) Bacillus subtilus* (MTCC 441) using agar well diffusion method according to the literature protocol [33, 34]. The compounds were dissolved in dimethylsulphoxide at 10, 20, 30 μg mL^{-1} concentration, however showed appreciable zone of inhibition at 30 μg mL^{-1} and Streptomycin was used as the reference antibacterial drug. Antibacterial activity of the compounds was determined by zones showing complete inhibition (mm). No zone of inhibition was observed at 10, 20 μg mL^{-1} concentration. Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicate.

RESULTS AND DISCUSSION

The synthesis of novel hydrazone derivatives of anacacrdic acid linked with 1,4-disubstituted triazoles is illustrated in **scheme-1**. The synthesis of the hydrazone derivatives was accomplished in five synthetic steps from anacacrdic acid utilizing greener solvents/green reagents. The starting material anacacrdic acid **1** was isolated from CNSL liquid as per the reported literature methods [35]. Phenolic and carboxylic acid methylation of anacacrdic acid **1** was achieved in presence of dimethyl carbonate, 1,8-diaza bicyclo[5.4.0]undec-7-ene (DBU) in 2-Me THF in sealed tube at 140 ^oC for 17h produced methyl (2-methoxy-6-pentadecyl)benzoate **2** in 84%. Dimethyl carbonate is a green reagent and generates methanol and CO2 as by-products after reaction. The methylating activity of DMC has been widely studied in recent years.[36]. Sodium borohydride reduction of 2-methoxy-6-pentadecylbenzoate **2** in presence of 2-Me THF [37] at reflux for 1h yielded (2-Methoxy-6-pentadecylphenyl)methanol **3** in 81%. 2-Methyl tetrahydro furan (2-MeTHF) which is derived from renewable resources such as corncobs and bagasse was used as a choice of solvent for the reduction of ester to alcohol; 2-MeTHF offers both economical and environmentally friendly advantages over tetrahydrofuran. Bromination of (2-Methoxy-6-penta decylphenyl)methanol **3** was accomplished in presence of 2,4,6-Trichloro-[1,3,5]-triazine in DMF followed by the addition of sodium bromide at ambient temperature for 16h to obtain 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene **4** in 88% yield. The bromination procedure adapted [38] is operationally simple and allows a rapid and high-yielding conversion of alcohols to the corresponding bromides under very mild conditions. The method seems to be more convenient with respect to other reports and can be used as a valid alternative to other methods, so avoiding tedious purifications or the use of more toxic reagents. A one pot conversion of 2-(bromomethyl)-1-methoxy-3-pentadecylbenzene **4 to** 4-(1-(2-methoxy-6-pentadecylbenzyl)-1H-1, 2, 3-triazol-4-yl) benzaldehyde **5** was performed using the 'click chemistry approach" [39]. Reaction of bromide **4** with NaN_3, 4-ethynylbenzaldehyde [40] CuI in presence of room temperature ionic liquid (RTIL's) as solvent (ex: [bmim][BF4]/H2O (1:1)) at room temperature for 6 h resulted in the formation of 1,4-disubstituted-1,2,3-triazole-aldehyde **5** in quantitative yield. RTILs are used as a green recyclable alternative to conventional solvent. Room temperature ionic liquids are environmentally benign solvents due to their unique chemical and physical properties, and have proved to be especially useful in the case of catalytic reactions [41-43]. Condensation of 1, 4-disubstituted-1,2,3-triazole-aldehyde **5** with benzohydrazides **6a-6j** in equimolar ratio was done under solvent free conditions using minimum quantity of ethanol, the contents were grinded in mortar and pestle for 2-3 min to afford the corresponding hydrazone derivatives of anacardic acid linked with 1,4-disubstituted triazoles **7a-7j**. The advantage of the reaction is, it is carried out under solvent free condition, short reaction time and has a minimum environmental impact. The structures of newly synthesized derivatives 7**a-j** were determined by spectroscopic techniques like ^1H NMR, mass and IR spectral data.



Scheme-1: Synthesis of Novel Anacardic acid Derivatives Bearing 1,4-disubstituted 1,2,3-Ttriazoles

Experimental conditions: (a) dimethyl carbonate, DBU, 2-Me THF, 140^{o}C, sealed tube; (b) NaBH4, 2-MeTHF, reflux, 1h; (c) 2,4,6-Trichloro-[1,3,5]-triazine, DMF, NaBr, cyclopentyl methyl ether, 25^{o}C, 16h; (d) NaN_3, 4-ethynylbenzaldehyde, CuI, [bmim] $[BF_4]/H_2O$ (1:1), r.t., 6h; (e) Benzohydrazides, ethanol, grinding, 2-3min.

Antibacterial activity: The results of the antibacterial activity of the newly synthesized compounds **7a-g** is complied in **table -1**. It is observed from **table-1**, that hydrazone derivatives **7a**, **7b and 7e** with R = 4-OMe, 3,4,5-OMe and 2,5 -F exhibited good antibacterial activity (zone of inhibition; 23-38 mm) against the Gram positive (*viz., S.aureus and B.subtilus*) and Gram negative strains (*viz., E.coli and P.aeruginosa*), while the hydrazone derivatives **7d** and **7f** with R = NO_2, and H showed moderate antibacterial activity (zone of inhibition: 18-28 mm) and the remaining hydrazone derivatives *viz.*, **7c** and **7g** R = 4-Cl and 4-F did not project any antibacterial activity. In general, a further structural modification of the 'R' in the main scaffold may evolve a potential antibacterial drug.

Table-1: Antibacterial Activity of Compounds 7a-g

Compound No[a]	**R**	*Gram negative*		*Gram positive*	
		E.coli MTCC 2692	*P.aeruginosa MTCC 2453*	*S.aureus MTCC 902*	*B.subtilus MTCC 441*
		Zones of Inhibition of compounds 7a –j in mm			
7a	4-OMe	**28**	**23**	**34**	**37**
7b	3,4,5-OMe	**30**	**25**	**37**	**38**
7c	4-Cl	-	-	-	-
7d	3-NO_2	**26**	**18**	**24**	**26**
7e	2,5-F	**29**	**24**	**36**	**34**
7f	H	**26**	**18**	**28**	**26**
7g	4-F	-	-	-	-
[b]**Standard Drug**	-	31	25	38	40

a: Concentration used 30 µg/mL of DMSO; *b: Streptomycin (30 µg/mL of DMSO)*

APPLICATIONS

The newly synthesized hydrazone derivatives **7a-g** was found to display good to moderate antibacterial activity and the probability of these compounds becoming an active pharmacophore is high. Therefore a further structural activity studies and evaluation towards various biological activities is the future scope of the work.

CONCLUSIONS

In conclusion, the present paper describes the synthesis of some novel hydrazone derivatives (linked with anacacrdic acid and triazole ring) **7a-g** and evaluated for antibacterial activity. Among these newly synthesized hydrazone derivatives compounds **7a**, **7b** and **7e** with R = 4-OMe, 3,4,5-OMe and 2,5-F exhibited good antibacterial activity (zone of inhibition; 23-38 mm) against the Gram positive (*S.aureus and B. subtilus*) and Gram negative strains (*E.coli* and *P.aeruginosa*).

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