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Synthesis of novel Quinoline Carboxylic acids from Anacardic acid

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ABSTRACT

The anacardic acid is having mild anti-bacterial activity due to its long alkyl chain. Quinolines are well known as anti-bacterial agents. The synthesis novel quinoline carboxylic acids from anacardic acid were reported here.

Keywords: CSNL, CSNL, Anacardic acid, Quinoline carboxylic acids.

INTRODUCTION

Quinolines are well known compounds in synthetic chemistry as well medicinal chemistry and served the mankind in several forms, majorly as antibiotic drugs. Quinolines were discovered and several varieties have been synthesized from decades to treat several diseases and infections. However, the increased resistance of microbials to the existing quinolines is an alarming problem now. The increased resistance of microbials to known quinolines is constantly demanding to generate novel quinolines to meet the requirements.

Cashew Nut Shell Liquid (CSNL) is abundantly and cheaply available natural product from cashew nut industry. CSNL contains several natural products like ene-mixture of anacardic acid, cardal and cardanol etc. The ene-mixture of anacardic acid (**1a-1c**) can be reduced to afford anacardic acid, which is having long alkyl chain at C-6 position with salicylic acid moiety[1, 2]. After through investigation, literature on anacardic acid has revealed that anacardic acid is having mild anti-bacterial activity due to its long alkyl-chain Fig.1[3]. Earlier several researchers have carried out their research on anacardic acid to generate different lead compounds for different therapeutic purposes[4 to 16]. In our previous communication, we have reported the synthesis of benzyl amine analogues of anacardic acid as potent anti-bacterial agents [17].

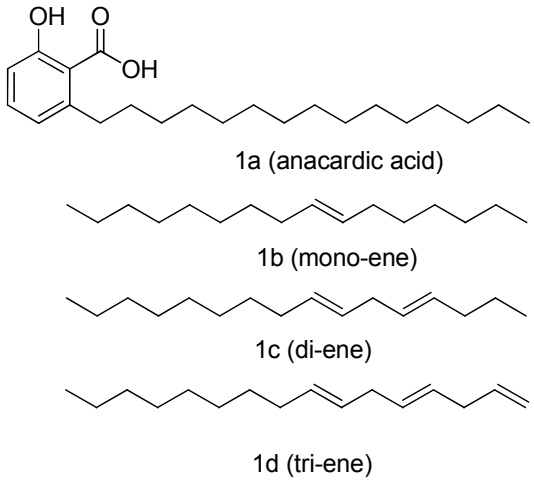


Fig. 1 Anacardic acid and its ene-mixture

Several reports were proved that quinolines are well known anti-bacterial agents. The synthesis of quinoline carboxylic acids from anacardic acid was not reported so far, which encouraged us to synthesize quinoline carboxylic acids from Anacardic acid and the structures were as depicted in Fig.2.

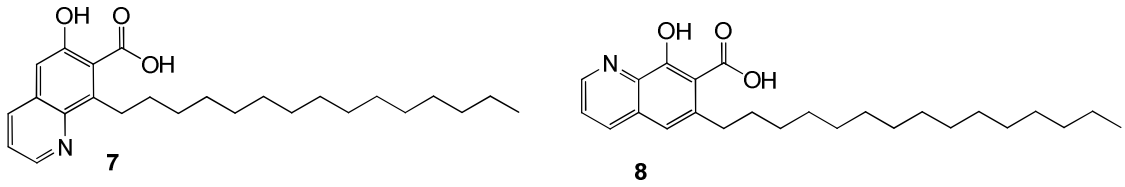


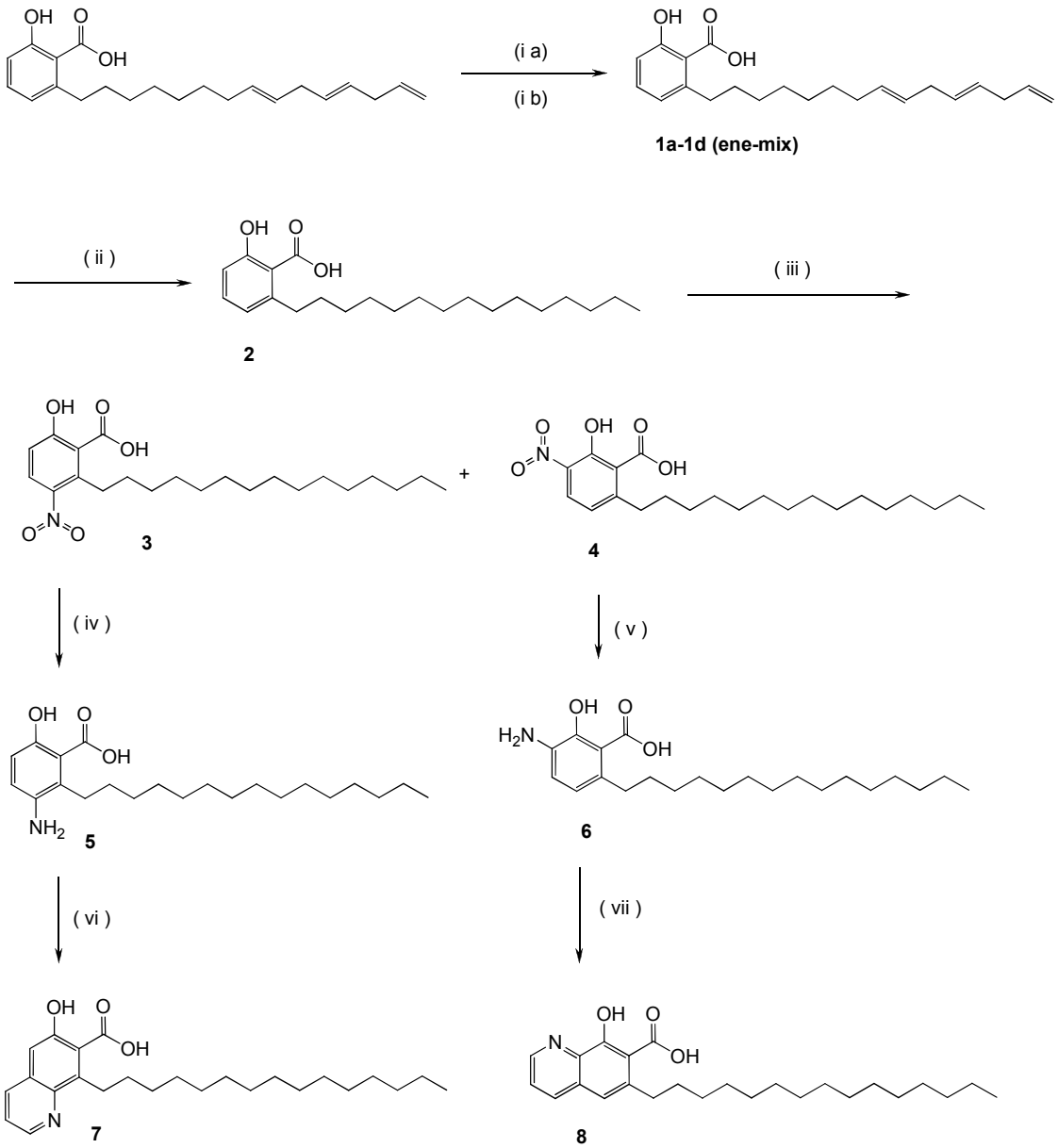
Fig. 2. Quinoline carboxylic acids from Anacardic acid

MATERIALS AND METHODS

General procedure:

The reagents and solvents used in this study were of analytical grade and were used without further purification. Melting points were determined in open capillaries and are uncorrected. Thin-layer chromatography (TLC) was applied for the purity determination of substrates, products and reaction monitoring using silica gel GF254 plates and spots were detected using iodine chamber or U.V lamp at 254nm. The products were characterized by IR, ^{1}H NMR (400 MHz), Mass analysis. IR were recorded on FT-IR Perkin Elmer spectrometer and the ^{1}H NMR spectra on a Varian EM-360 spectrometer (400 MHz). TMS was used as an internal standard. The mass spectra were recorded on Agilent ion trap MS. All the yields refer to isolated pure compounds. The compounds were purified by column chromatography packed with silica gel or preparative HPLC method. All compounds named as IUPAC by Chemdraw 11.0 computer program. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet, dd = doublet of doublet.

Scheme-1



Reagents: *(ia) $Ca(OH)_2$, MeOH:H_2O(5:1), 60 °C, 3 h, (i b) 6 N HCl, (ii) 10% Pd/C, H_2, EtOH, 60 psi, r.t, 2 h; (iii) Fuming. HNO_3, AcOH, 65 °C, 3h (iv) & (v) 10% Pd/C, H_2, EtOH, 50 psi, r.t, 2 h; (vi) & (vii) Glycerol, Nitrobenzene, H_3BO_3, Conc.H_2SO_4, 135 °C, 24 h.*

Commercially available CSNL was treated with $Ca(OH)_2$ in a mixture of methanol and water (6:1) at 65 °C for 3 hrs under vigorous stirring. The reaction mixture was cooled to room temperature, filtered, washed with ethyl acetate to remove the other impurities like Cardanol, Cardol etc. The calcium salt of anacardic acid was treated 6 N HCl and extracted with ethyl acetate to give ene-mixture anacardic acid as semi-pure product (compound **1**). The compound **1** was reduced with Pd/C in ethanol under 60 psi of hydrogen pressure for 3 hrs to give anacardic acid (**2**).

The compound **2** was treated with nitric acid in acetic acid at 65 °C for 3 h to give 6-Hydroxy-3-nitro-2-pentadecyl-benzoicacid (**3**, major isomer) and 2-Hydroxy-3-nitro-6-pentadecyl-benzoic acid (**4**, as minor isomer). Both the compounds **3** & **4** were reduced with Pd/C in ethanol under hydrogen pressure separately to give 3-amino-6-Hydroxy -2-pentadecyl-benzoic acid (**5**) and 3-amino-2-Hydroxy -6-pentadecyl-benzoic acid (**6**) respectively. Compound **5** was treated with glycerol, Nitrobenzene, Boric acid and Conc. Sulphuric acid at 130 °C for 24 h to give 6-hydroxy-8-pentadecyl-quinoline-7-carboxylic acid (**7**). In a similar procedure compound **6** was converted to compound **8** (i,e) 8-hydroxy-6-pentadecyl-quinoline-7-carboxylic acid (**8**) with moderate yields as depicted in Scheme-**1**.

Experimental:

2-Hydroxy -6-pentadeca-8,11, 14-trienyl-benoic acid (as ene-mixture, 1): To a solution of MeOH (6 vol) and H_2O (1 vol) containing commercial grade CSNL (100 g), was added $Ca(OH)_2$ (50 g) and the contents were heated to 60 °C for 3h. The precipitated solid was filtered and the wet cake was washed with MeOH (1 vol) to remove the Cardol and Cardanol. The brown colored precipitate was then suspended in water, pH was adjusted to 2.0 range using 6 N HCl solution under vigorous stirring and extracted with ethyl acetate (3 x 200 mL). The combined organics were washed with H_2O, brine solution, dried over anhydrous Na_2SO_4, concentrated to dryness to afford the anacardic acid ene-mixture as dark-brown colored viscous oil (60 g, crude), which was used as such in the next step without further purification.

Preparation of 2-hydroxy -6-pentadecyl-benzoic acid (anacardic acid, 2): To a solution of ethanol (700 mL) containing the ene-mixture (**1a-1d**) (60 g, crude) 10% Pd/C (6 g) was slowly added under inert atmosphere into a hydrogenation flask. Hydrogenation was carried out under 60 psi of hydrogen pressure for 2 h. Filtered the contents through a pad of celite to remove the catalyst, collected the clear filtrate, concentrated under reduced pressure to afford the crude anacardic acid (**2**), which was recrystallized from petroleum ether (40–60 °C); Yield: 36 g ; m.p. 85-86 °C; IR (KBr, $cm^{-}1$): 3071, 3002, 2917, 1655, 1450, 1246, 1214, 894, 815, 757 ; ^{1}H NMR (400 MHz, $CDCl_3$): ð 11.02 (bs, 1H), 7.36 (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), 1.27-1.20 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H), Mass: m/z 349 $(M+H)^+$.

6-Hydroxy-3-nitro-2-pentadecyl-benzoicacid (3) and 2-Hydroxy-3-nitro-6-pentadecyl-benzoic acid (4): To a solution of compound **2** (36 g, 103 mmol) in glacial acetic acid (144 mL) was added the fuming nitric acid (65%) (20.4 mL, 310 mmol) at 65 °C slowly over a period of 30 min. The contents were heated to 65 °C for 4 hrs. After completion of the reaction, the reaction mass was slowly poured into ice-cold water under vigorous stirring and extracted with ethyl acetate (3 x 250 mL). The combined organic layer was washed with 5% aqueous $NaHCO_3$ solution, brine solution, dried over anhydrous sodium sulphate and concentrated to dryness to afford the crude compound (mixture of compound **3** & **4**) as black syrupy mass. The crude product was passed through silica gel (60-120 mesh) packed column to remove all the non-polar and polar impurities and the compound was eluted with 10-30% ethyl acetate/pet ether by gradient method to afford the mixture of compound **3** and **4** (20 g) as brown colored solid. The mixture of compound **3** and **4** was separated by preparative HPLC method to afford the pure 6-Hydroxy-3-nitro-2-pentadecyl-benzoicacid (**3**) and 2-Hydroxy-3-nitro-6-pentadecyl-benzoic acid (**4**) as brown coloured solids. Compound **3:** brown coloured solid, (15 g, 37%); m.p. 58-61 °C;

IR (KBr, cm-1): 3438, 2917, 2848, 1707, 1688, 1600, 1526, 1465, 1284, 899, 723; ^{1}H NMR (400 MHz, $CDCl_3$): ð 12 (bs, 2H), 7.94 (t, *J*= 9.2 Hz, 1H), 6.90 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1H), 2.76-2.73 (m, 1H), 2.67-2.63(m, 1H), 1.58-1.45 (m, 2H), 1.35-1.20 (m, 24H), 0.85 (t, *J* = 6.6 Hz, 3H); Mass: m/z 392 $(M-H)^+$. Compound **4:** brown coloured solid, (4.1 g, 10%); m.p. 67-70 °C; IR (KBr, cm-1): 3240, 2918, 2850, 1715, 1598, 1472, 1444, 1328, 1284, 1140, 899, 743; ^{1}H NMR (400 MHz, $CDCl_3$): ð 12 (bs, 2H), 7.95 (d, *J*= 8.8 Hz, 1H), 6.90 (d, *J*= 9.2 Hz, 1H), 2.65 (t, *J* = 8.0 Hz, 7.8 Hz), 1.59-1.50 (m, 2H), 1.32-1.20 (bs, 24H), 0.85 (t, *J* = 7.0 Hz, 3H), Mass: m/z 392 $(M-H)^+$.

3-amino-6-Hydroxy -2-pentadecyl-benzoic acid (5): To a suspension of Pd/C (10%, 1.5 g) in ethanol was added the solution of compound **3** (15 g, 38 mmol) under inert atmosphere. The contents were hydrogenated over Parr hydrogenator under 60 psi of hydrogen pressure at room temperature 3 h. Filtered, collected the clear filtrate, adjusted the pH to 3.0 range using ethanolic HCl solution, concentrated under reduced pressure to afford compound **5** as brown coloured thick mass. The crude product was washed with n-Hexane, filtered and dried further to afford the title compound **5** as pale brown colored solid (9 g, 65%). m.p. 184-189 °C; IR (KBr, cm-1): 3448, 2918, 2849, 1660, 1617, 1470, 1436, 1243, 1162, 850, 738; ^{1}H NMR (400 MHz, DMSO-d_6): ð 10 (bs, 4H), 7.30 (d, *J*= 8.4 Hz, 1H), 6.78 (d, *J*= 8.4 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.55-1.45 (m, 2H), 1.32-1.20 (bs, 23H), 0.85 (t, *J* = 6.8 Hz, 3H); Mass: m/z 362 $(M-H)^+$.

3-amino-2-Hydroxy -6-pentadecyl-benzoic acid (6): To a suspension of Pd/C (10%) in ethanol was added the solution of compound **4** (4 g, 11.01 mmol) under inert atmosphere. The contents were hydrogenated over Parr hydrogenator under 60 psi of hydrogen pressure at room temperature 3 h. Filtered, collected the clear filtrate, adjusted the pH to 3.0 range using ethanolic HCl solution, concentrated under reduced pressure to afford the crude compound **6** as brown coloured thick mass. The crude product was washed with n-Hexane, filtered and dried further to afford the title compound (2.1 g, 57%). m.p. 160 °C (decomposed); IR (Neat, cm-1): 3434, 2919, 2848, 2635, 1652, 1614, 1409, 1229, 1160, 848, 722; ^{1}H NMR (400 MHz, DMSO-d_6): ð 10 (bs, 4H), 7.56 (d, *J*= 8.4 Hz, 1H), 6.89 (d, *J*= 8.0 Hz, 1H), 2.76 (t, *J* = 8.0 Hz, 2H), 1.51-1.41 (m, 2H), 1.33-1.19 (bs, 24H), 0.87 (t, *J* = 6.6 Hz, 3H); Mass: m/z 362 $(M-H)^+$.

6-Hydroxy -8-pentadecyl-quinoline-7-carboxylic acid (7): To a solution of compound **5** (1.0 g, 2.75 mmol) in Conc. Sulphuric acid (1.04 g, 10.61 mmol) was added Glycerol (1.01 g, 11 mmol), Boric acid (0.1 g, 1.612 mmol) and Nitro benzene (0.24 g, 1.94 mmol) at room temperature and the contents were heated to 130 °C for 24 hrs. The reaction mixture was cooled to room temperature, poured into ice-cold water (50 mL) and the aqueous layer was basified to pH 9.0 range using 20% aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified with 1 N HCl solution, concentrated to 1/3rd volume, cooled to 5-10 °C, filtered the precipitated solid and dried further. The crude product was purified by silica gel (100-200 mesh) column chromatography using Methanol/Chloroform (1-5% by gradient method) to afford 6-Hydroxy -8-pentadecyl-quinoline-7-carboxylic acid (**7**) (200 mg, 18%) as brown coloured solid; m.p. 185-188 °C; IR (KBr): 3070, 3000, 2914, 1660, 1454, 1248, 1210, 899, 820, 759 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): ð 11.02 (bs, D_2O exchangeable, 1H), 8.92 (bs, 1H), 8.72 (d, *J*= 7.6 Hz, 1H), 7.81 (t, *J* = 6.4 Hz, 1H), 7.33 (s, 1H), 6.7 (bs, D_2O exchangeable, 1H), 3.37-3.05 (m, 2H), 1.57-1.63 (m, 2H), 1.27 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); Mass: m/z 400 $(M+H)^+$.

8-Hydroxy -6-pentadecyl-quinoline-7-carboxylic acid (8): To a solution of compound **6** (1.0 g, 2.75 mmol) in Conc. Sulphuric acid (1.04 g, 10.61 mmol) was added Glycerol (1.01 g, 11 mmol), Boric acid (0.1 g, 1.612 mmol) and Nitro benzene (0.24 g, 1.94 mmol) at room temperature and the contents were heated to 130 °C for 24 hrs. The reaction mixture was cooled to room temperature, poured into ice-cold water (50 mL) and the aqueous layer was basified to pH 9.0 range using 20% aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer was acidified with 1 N HCl solution, concentrated to 1/3rd volume, cooled to 5-10 °C, filtered the precipitated solid and dried further. The crude product was purified by silica gel (100-200 mesh) column chromatography using Methanol/Chloroform (1-5% by gradient method) to afford 8-Hydroxy -6-pentadecyl-quinoline-7-carboxylic acid (**8**) (100 mg, 9%) as dark brown coloured solid; m.p. 170-174 °C; IR (KBr): 3090, 3020, 2925, 1665, 1452, 1240, 1205, 887, 810, 720 cm^{-}1; ^{1}H NMR (400 MHz, $CDCl_3$): ð 11.2 (bs, D_2O exchangeable, 1H), 9.0 (bs, 1H), 8.50 (d, *J*= 7.6 Hz, 1H), 7.89 (t, *J* = 6.4 Hz, 1H), 7.40 (s, 1H), 6.9 (bs, D_2O exchangeable, 1H), 2.75-2.55 (m, 2H), 1.63-1.57 (m, 2H), 1.27 (m, 24H), 0.89 (t, *J* = 6.6 Hz, 3H); Mass: m/z 400 $(M+H)^+$.

RESULTS AND DISCUSSION

So far, the synthesis of quinoline carboxylic acids from anacardic acid was not reported earlier, hence we wish to report the synthesis of novel quinoline carboxylic acids from anacardic acid, which is a very cheaply available natural product from cashew nut shell industry.

CONCLUSION

Due to mild anti-bacterial activity of anacardic acid, we became interested to synthesize novel quinoline carboxylic acids to meet the current demand for novel anti-bacterial agents.

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