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Synthesis and Antibacterial Activity of Urea and Thiourea Derivatives at C-8 Alkyl Chain of Anacardic Acid Mixture Isolated from a Natural Product Cashew Nut Shell Liquid (CNSL)

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Abstract

Synthesis and antibacterial activity of some novel urea and thiourea derivatives (**7a-7k**, **8a-8f**) of anacardic acid prepared from commercially available anacardic acid which is obtained from natural product Cashew Nut Shell Liquid (CNSL). Compounds (**7a-7k**, **8a-8f**) were tested for Gram positive and Gram negative bacterial cultures. Most of the compounds were showed active compared with standard drug ampicilline.

Keywords: Synthesis, Urea and Thiourea Derivatives, Anacardic Acid, Anti-Bacterial Activity

1. Introduction

Among the different families of plants, Anacardiaceae-shrub family is very important since this plant consist of Non-isoprenoid phenolic lipids. The cashew tree, *Anacardium occidentale L.*, is a botanical species native of eastern Brazil and was introduced into other tropical countries such as India, Africa, Indonesia and South East Asia in the 16th century [1-2]. Approximately 2 - 3 cm in length kidney shaped structure is true fruit of cashew is the nut, which is attached to the end of a fleshy bulb, generally called the cashew apple. The shell consist of the raw nut (50% of the weight), the kernel (25%) and the remaining 25% consists of the natural cashew nut shell liquid (CNSL), a viscous reddish brown liquid. The CNSL is traditionally obtained as a by-product during the isolation of the kernel by roasting the raw nuts. Crude CNSL represents one of the major and cheapest sources of naturally occurring non-isoprenoid phenolic lipids such as anacardic acids (1), cardols (2), cardanols (3), methylcardols (4) (**Figure 1**) and polymeric materials. CNSL has found important commercial usage as the phenolic raw material for the manufacture of certain resins and plastics having unusual electric and frictional properties [3-6]. 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 [7]. Anacardic acid (pentadecyl salicylic acid) is a phenolic constituent present in Cashew Nut Shell Liquid (CNSL); (*Anacardium occidentale L.*) and exhibits antimicrobial properties [8-14], which have led to the preparation of various analogues [15-20] and soybean lipoxygenase-1 inhibitory activity [21-22] Kubo *et al.* [23] 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. The emergence of drug resistant strains in clinical applications [24-26] especially to Gram positive bacteria[27-28] has created a problem of global proportions [29-30] G. C. Reddy *et al.* reported the synthesis of benzamide derivatives of anacardic acid [31], sildenafil analogues [32], dihydropyridine analogues [33] as calcium channel blockers, isonicotinoylhydrazones for antimycobacterial activity [34] starting from anacardic

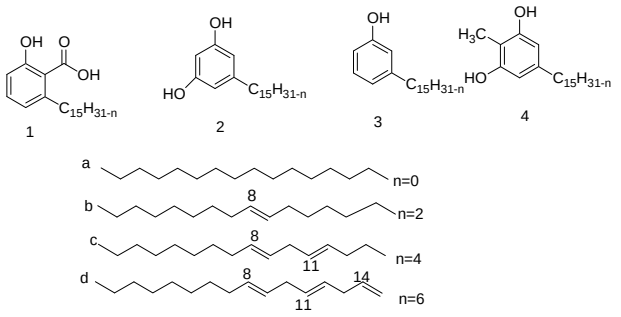


Figure 1. Naturally occurring non-isoprenoid phenolic lipids such as anacardic acids (1), cardols (2), cardanols (3) and methylcardols (4).

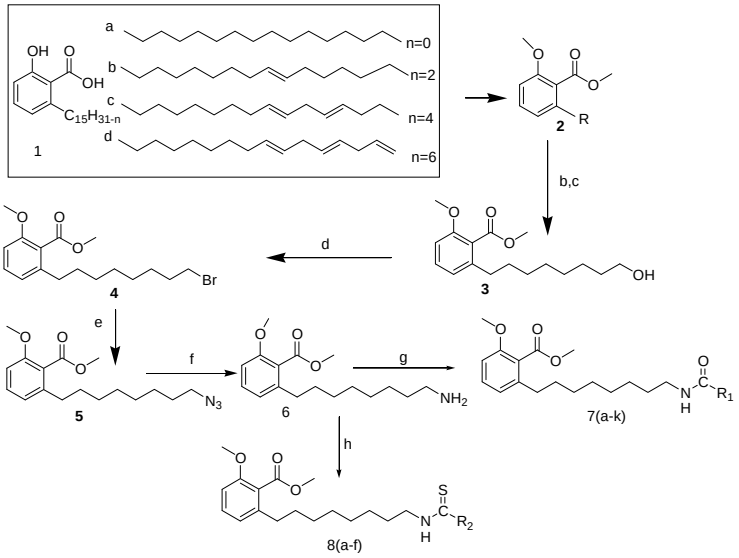
acid. Recently, a few anacardic acid derivatives exhibited various activities like affect the structure of the enzyme [35], anacardic acid is a specific activator of kinase activity of Aurora Kinase A [36], suppresses expression of nuclear factor-kB regulated gene products leading to potentiation of apoptosis [37] inhibitor of the HAT activeity of recombinant Plasmodium falciparum GCN5 [38] and as modulators of histone acetyltransferases [29]. Synthesis of lasiodiplodin from the non-isoprenoid phenolic lipids of CNSL as well as the salicylate macrolactone and other derivatives were reported by santos *et al.* [40-43].

In the present work we wish to report to synthesize novel cell permeable urea and thiourea compounds from 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 urea and thiourea derivatives at C-8 alkyl chain of anacardic acids against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes* bacterial strains.

2. Results and Discussion

Here we described the synthesis of various biologically active novel urea and thiourea 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 [44, 45]. 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. Anacardic acid ene mixture was methylated using dimethyl sulphate in presence of potassium carbonate in acetonitrile to afford **2**. Ozonolysis of Compound **2** resulted in the formation of **3**, C8-OH. The compound **3** was converted to **4** using carbon tetra bromide in Dichloromethane. The compound **4** was reacted with sodium azide followed by reduction with Pd/C under H_2 pressure to obtaine amine **6** coupled with various isocynate or isothiocynate in chloroform to obtain compounds (**7a-7k**, **8a-8f**, **Scheme 1**) of



Scheme 1. Synthesis of various biologically active urea and thiourea (at C8 alkyl chain) derivatives from anacardic acid mixture. Reagents: (a) Di methyl sulfate, K_2CO_3, Acetonitrile, 90˚C, 24 h; (b) Ozonalasis, MeOH, CH_2Cl_2, –78˚C, 6 h; (c) MeOH, $NaBH_4$, 18 h, 0˚C, R.T; (d) CBr_4, Pyridine, TPP, CH_2Cl_2, 0˚C, R.T, 8 h; (e) NaN_3, DMF, 100˚C, 4 h; (f) 10% Pd/C, 50 psi, 2 h; (g) different isocyanate, $CHCl_3$; (h) different isothiocyanate, $CHCl_3$.

urea and thiourea derivatives were purified by column chromatography to yield title compounds. The structure of urea and thiourea derivatives (**7a-7k**, **8a-8f)** was determined by using different spectroscopic techniques ^{1}H NMR, IR, Mass. The resulting compounds are screened for their antibacterial activity.

Biological Activity

The urea and thiourea derivatives (**7a-7k**, **8a-8f**) were screened for their antibacterial activity [27] 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 [46]. The anti-bacterial activity of the analogues was compared with standard drug ampicilline and the results of investigation have been presented in **Table 1** and observed that some of the compounds are showed high biological activity.

Table 1. Antibacterial activity of urea and thiourea derivatives at C-8 alkyl chain of anacardic acid mixture.

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
S* ampicilline	SD* amplicilline	20	20	18	19
7a		17	16	17	16
7b		19	19	15	19
7c		21	18	17	17
7d		19	16	18	15
7e		17	16	18	19
7f		19	18	17	15
7g		20	17	17	17
7h		17	17	17	19
7i		17	16	16	17
7j		18	17	17	15
7k		16	16	16	16
8a		16	21	17	17
8b		19	17	17	18
8c		17	16	16	18
8d		16	20	15	17
8e		22	20	16	17
8f		15	16	17	19

Based on the test results it is evident that several of synthesized anacardic acid analogues possess moderate to good activity against the Gram +ve and Gram –ve bacteria. Of all the compounds prepared entities **7a**, **7b**, **7c**, **7d**, **7f**, **7g**, **8b** and **8e** activity against *E. coli*, MTCC443, **7a**, **7b**, **8a**, **8d** and **8e** activity against *P. aeruginosa*, MTCC424; display good to excellent activity while the remaining compounds showed moderate activity. The most active antibacterial agent against *Escherichia coli* found to be compound **7c**, **7f**, **7g**, and **8e** having -*CN*,*F* groups and other compounds in the series exhibited moderate to good activity. The compounds **7d**, **7e**, **8b** and **8f** showed good activity against *S. aureus* MTCC96 and **7a**, **7b**, **7e**, **7h**, **8b**, **8c** and **8f** showed good activity against *S. pyogenes* MTCC442. This indicates chloro, dichloro, flouro, cyano and methoxy substituted compounds showed better activity when compared to other substituted groups. Here seems to be, thiourea substituted novel compounds are exhibiting better activity than urea substituted compounds. The activity depends to some extent on the R substituent, however all the compounds showed antibacterial activity. 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.

3. Conclusions

In summary, the present study describes a convenient and efficient protocol for the synthesis of sulfonamide derivatives by using anacardic acid mixture using various reagents and different conditions. We believe that this procedure is convenient, economic and a user-friendly process for the synthesis of these various novel urea and thiourea compounds from anacardic acid mixture. All compounds structures are supported by physico chemical and IR, NMR, Mass spectral data. Urea and thiourea derivatives were screened for their antibacterial activity against few bacterial strains and observed that some of the compounds are showed more biological activity than standards used.

4. Experimental Section

4.1. General Reagents and Equipment

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 and eluting with a gradient of hexane: ethyl acetate. Analytical thin layer chromatography was performed on precoated Merck silica gel (60F254/0.2 mm) plates using UV light, 5% ethanolic phosphomolybdic acid or iodine vapours to visualize the spots. 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 100 μA. The oxidative cleavages were performed with a Welsbach T-408 ozonizator and the catalytic hydrogenations in a Parr apparatus.

4.2. General Procedure: Isolation of Anacardic Acids (1)

The shells (500 g) of cashew nuts from *Anacardiumoccidentale* were extracted in a Soxhletextractor with commercial 95% ethanol (2.0 L) during 6 h, yielding a crude extract (CNSL, 157 g, 31% by weight). Anacardic acids (**1**) were removed in 61% from CNSL (15.25 g) either by precipitation with lead nitrate or calcium hydroxide according to protocols described in the literature [44,45]. The spectral properties were identical to those reported in the literature [44,45].

Preparation of Methyl anacardate methyl ethers ene mixture (2): To a solution of Compound **1** (65 g, 186.78 mmol) in acetone was added K_2CO_3 (103.1 g, 747.12 mmol), Di methyl sulfate (44.3 mL, 466.95 mmol). The contents were heated at 65˚C for 5 h. Reaction mixture was cooled to room temperature, filtered and washed with ethyl acetate. Filtrate was distilled off, crude compound was re dissolved in ethyl acetate (300 mL). Organic layer was washed with water, brine solution and dried over anhydrous sodium sulphate and distilled off ethyl acetate. Crude compound was purified by 60 - 120 silica pet ether pack column compound was eluted with 5% ethyl acetate: pet ether to get compound **2**, Yield: 58 g, light yellow liquid.

Synthesis of 2-(8-Hydroxy-octyl)-6-methoxybenzoic acid methyl ester (3): A solution of compound **2** (15 g, 40.540 mmol) in dichloro methane: methanol (1:1, 500 mL) was added a pinch of Sudan red catalyst and cooled to –78˚C. Ozone gas purged through reaction mixture until starting material was completed (8 h). Nitrogen gas was purged through reaction mixture for 30 min (to remove excess O_3 gas), dimethyl sulfide was added few drops and stirred for 20 min at –15˚C. Sodium borohydride (9.970 g, 263.51 mmol) was added portion wise over a period of 45 min. Reaction mixture was slowly bring it to room temperature and stirred at this tempera-

ture for 18 h. Reaction mixture was quenched with cold water (400 mL), dichloro methane and methanol distilled off and crude compound was diluted with water and extracted with ethyl acetate (2 × 200 mL). The combined organic layer was washed with brine solution (150 mL) dried over anhydrous sodium sulphate, filtered and evaporated under vacuum, to obtaine crude compound was purified by neutral alumina pet ether packed column, compound was eluted with 20% ethyl acetate: pet ether to obtain compound (**3**) as yellow liquid (7.1 g, 59.5%); IR (DCM film): 3401, 2930, 1728, 1586, 1467, 1268, 1110, 1071, 954, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.31 (bs, 8H), 1.53 - 1.59 (m, 4H), 2.53 (t, 2H, J = 8.0 Hz), 3.63 (t, 2H, J = 6.8 Hz), 3.81 (s, 3H), 3.90 (s, 3H), 6.75 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 7.6 Hz), 7.26 - 7.28 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ: 25.58, 29.16, 29.23, 29.63, 31.00, 32.62, 33.35, 52.10, 55.73, 62.81, 108.23, 121.37, 123.26, 130.18, 141.17, 156.10, 168.93 ppm; ESIMS (m/z): 295 $(M + H)^+$.

Synthesis of 2-(8-bromo-octyl)-6-methoxy-benzoic acid methyl ester (4): A solution of compound **2** (15 g, 51.02 mmol) in Dichloro methane (150 mL) was added dry pyridine (42 mL, 510.2 mmol) tri phenyl phosphene (22.73 g, 86.734 mmol) at 0˚C. Carbon tetra bromide (25.4 g, 76.53 mmol) was added portion wise over a period of 15 min. The contain were slowly bring it to rt and stirred at rt for 6 h. Reaction mixture was diluted with DCM (100 mL) washed with 2N HCl (2 × 150 mL), water (200 mL), brine solution (175 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum, Crude compound was purified by 100 - 200 silica pet ether column compound was eluted with 10% ethyl acetate: pet ether and distilled off solvent to obtain compound **4** (16.5 g, 90.8%) as yellow liquid; IR (DCM film): 3071, 3002, 2931, 2854, 1732, 1588, 1464, 1437, 1268, 1109, 1072, 960, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 - 1.42 (m, 8H), 1.52 - 1.59 (m, 4H), 1.80 - 1.87 (m, 2H), 2.53 (t, 2H, J = 8.0 Hz), 3.40 (t, 2H, J = 7.2 Hz), 3.82 (s, 3H), 3.90 (s, 3H), 6.76 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 7.6 Hz), 7.24 - 7.28 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ: 28.05, 28.56, 29.12, 29.26, 31.02, 32.72, 33.36, 34.02, 52.13, 55.78, 108.27, 121.39, 123.32, 130.20, 141.14, 156.14, 168.90 ppm; ESIMS(m/z): 357 $(M + H)^+$, 359 (bromo).

Synthesis of 2-(8-aza-octyl)-6-methoxy-benzoic acid methyl ester (5): A solution of compound **3** (2.0 g, 5.617 mmol) in DMF (10 mL) was added Sodium azide (548 mg, 8.426). The contain were heated at 100˚C for 3 h, reaction mixture was poured into cool water (70 mL) and extracted with diethyl ether (2 × 40 mL), the organic layer was washed with water (50 mL), brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to obtain compound **5** as yellow liquid (1.5 g, 83.7%); IR (DCM film): 3087, 3002, 2932, 2856, 2095, 1731, 1588, 1464, 1266, 1109, 1071, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (bs, 8H), 1.59 (bs, 4H), 2.53 (t, 2H, J = 7.6 Hz), 3.25 (t, 2H, J= 7.2 Hz), 3.82 (s, 3H), 3.91 (s, 3H), 6.76 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 8.0 Hz), 7.25 - 7.29 (m, 1H) ppm; ESIMS (m/z): 320 $(M + H)^+$.

Synthesis of 2-(8-Amino-octyl)-6-methoxy-benzoic acid methyl ester (6): A solution of compound **4** (2.0 g, mmol) in ethanol (30 mL) was taken into a 500 mL Parr-hydrogenation vessel and added a suspension of 10% Pd/C (220 mg, 10%) in 20 mL of ethanol under argon atmosphere and applied H_2-pressure (60 psi) for 2 h. Reaction mixture was filtered through celite bed and concentrated the filtrate under reduced pressure to obtain 2-(8-Amino-octyl)-6-methoxy-benzoic acid methyl ester (6) (1.7 g, 92.5%) as a yellow liquid. IR (neat): 3436, 2931, 2857, 1729, 1587, 1467, 1438, 1268, 1111, 1073, 829, 753 cm^{-1}; ^1H NMR (CDCl3, 400 MHz): δ 1.273 (bs, 8H), 1.54 (bs, 2H), 1.65 - 1.79 (m,2H), 2.51 (t, 2H, J = 7.6 Hz), 2.94 (t, 2H, J = 8.0 Hz), 3.79 (s, 3H), 3.89 (s, 3H), 6.74 (d, 1H, J = 8.0 Hz), 6.80 (d, 1H, J = 8.0 Hz), 7.23 - 7.27 (m, 1H) ppm ; ESIMS (m/z): 294 $(M + H)^+$.

Synthesis of urea and thio urea compounds: A solution of amine (300 mg, 1.023 mmol) in dry $CHCl_3$ was taken in seal tube was added isocynate or iso thiocynate (1.22 mmol) at rt and stirred at rt for 3 h to 8 h and distilled off solvent and crude compound was purified by column.

Synthesis of methyl 2-(8-(3-ethylureido)octyl)-6-methoxybenzoate (7a): Using **6** and ethyl isocyanate as starting materials, the title compound **7a** was obtained as a off white solid (Yield = 44.4%); m.p. 71˚C - 72˚C; IR (KBr): 3338, 2929, 2854, 1729, 1625, 1579, 1466, 1269, 1108, 1072, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.11 - 1.15 (m, 3H), 1.28 (bs, 8H), 1.45 - 1.59 (m, 4H), 2.53 (t, 2H, J = 8.0 Hz), 3.12 - 3.24 (m, 4H), 3.82 (s, 3H), 3.91 (s, 3H), 4.23 (s, 2H), 6.76 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J =7.2 Hz), 7.25 - 7.29 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ: 15.46, 26.73, 29.07, 29.18, 29.21, 30.14, 30.94, 33.35, 35.01, 40.25, 52.10, 55.78, 108.33, 121.43, 123.30, 130.24, 141.17, 156.15, 158.65, 169.05 ppm; ESIMS (m/z): 365 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-cyclopentylureido)octyl) -6-methoxybenzoate (7b): Using **6** and cyclopentyl isocyanate as starting materials, the title compound **7b** was obtained as a white solid (Yield = 60.4%); m.p. 80˚C - 81˚C; IR (DCM film): 3339, 2932, 2858, 1731, 1630, 1574, 1466, 1267, 1110, 1073, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 - 1.65 (m, 18H), 1.92 - 2.00 (m, 2H), 2.53 (t, 2H, J = 7.6 Hz), 3.12 - 3.16 (q, 2H), 3.81 (s, 3H), 3.90 (s, 3H), 3.91 - 3.95 (m, 1H), 4.31 (s, 1H), 6.75 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.0 Hz), 7.25 - 7.29

(m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ: 23.51, 26.78, 29.09, 29.19, 29.23, 30.21, 30.96, 33.35, 33.51, 40.24, 51.86, 52.09, 55.77, 108.31, 121.42, 123.30, 130.23, 141.16, 156.15, 158.34, 169.01 ppm; ESIMS (m/z): 405 $(M + H)^+$.

Synthesis of methyl 2-methoxy-6-(8-(3-phenylureido)octyl) benzoate (7c): Using **6** and phenyl isocyanate as starting materials, the title compound **7c** was obtained as a cream color semi solid (Yield = 66.2%); IR (DCM film): 3345, 3298, 3085, 3008, 2929, 2853, 1729, 1637, 1589, 1552, 1467, 1270, 1111, 1071, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (bs, 8H), 1.43 - 1.55 (m, 4H), 2.53 (t, 2H, J = 8.0 Hz), 3.17 - 3.22 (q, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 5.07 (bs, 1H), 6.76 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.0 Hz), 7.01 - 7.05 (m, 1H), 7.24 - 7.31 (m, 5H) ppm; ESIMS (m/z): 413 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(3-chlorophenyl)ureido) octyl)-6-methoxybenzoate (7d): Using **6** and 3-chlorophenyl isocyanate as starting materials, the title compound **7d** was obtained as a white color solid (Yield = 35%); m.p. 102˚C - 103˚C; IR (DCM film): 3347, 3080, 3004, 2930, 2855, 1729, 1659, 1590, 1549, 1473, 1429, 1268, 1110, 1073, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (bs, 8H), 1.40 - 1.60 (m, 4H), 2.54 (t, 2H, J = 7.6 Hz), 3.19 - 3.24 (q, 2H), 3.80 (s, 3H), 3.92 (s, 3H), 5.04 (s, 1H), 6.76 - 6.85 (m, 3H), 6.97 (d, 1H, 7.2 Hz), 7.14 - 7.37 (m, 4H) ppm ; ESIMS (m/z): 447 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(3,4-dichlorophenyl)ureido)octyl)-6-methoxybenzoate (7e): Using 6 and 3, 4 dichlorophenyl isocyanate as starting materials, the title compound **7e** was obtained as a light brown solid (Yield = 65%); m.p. 80˚C - 82˚C; IR (DCM film): 3351, 3099, 2930, 2855, 1729, 1661, 1587, 1542, 1470, 1381, 1270, 1115, 1072, 1028, 820, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (bs, 8H), 1.41 - 1.58 (m, 4H), 2.55 (t, 2H, J = 8.0 Hz), 3.17 - 3.22 (q, 2H), 3.80 (s, 3H), 3.93 (s, 3H), 5.15 (s, 1H), 6.77 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 7.6 Hz), 7.08 - 7.19 (m, 2H), 7.20 - 7.31 (m, 2H), 7.48 (s, 1H) ppm; ESIMS (m/z): 481 $(M + H)^+$. 483 (chloro).

Synthesis of methyl 2-(8-(3-(2-fluorophenyl)ureido) octyl)-6-methoxybenzoate (7f): Using **6** and 2-fluorophenyl isocyanate as starting materials, the title compound **7f** was obtained as a light brown solid (Yield = 68.2%); m.p. 92˚C - 93˚C; IR (DCM film): 3348, 3073, 3006, 2930, 2855, 1730, 1658, 1551, 1457, 1265, 1188, 1109, 1073, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (bs, 8H), 1.42 - 1.60 (m, 4H), 2.54 (t, 2H, J = 7.6 Hz), 3.21 - 3.25 (q, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 5.04 (s, 1H), 6.67 (s, 1H), 6.75 (d, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 8.0 Hz), 6.92 - 6.98 (m, 1H), 7.01 - 7.10 (m, 2H), 7.24 - 7.29 (m, 1H), 8.01 - 8.10 (m, 1H) ppm; ESIMS (m/z): 431 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(2-cyanophenyl)ureido) octyl)-6-methoxybenzoate (7g): Using **6** and 2-cyanophenyl isocyanate as starting materials, the title compound **7g** was obtained as a light green semi solid (Yield = 26.7%); IR (DCM film): 3346, 3078, 3000, 2930, 2855, 2221, 1728, 1662, 1581, 1546, 1452, 1268, 1110, 1072, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (bs, 8H), 1.51 - 1.57 (m, 4H), 2.54 (t, 2H, J = 7.6 Hz), 3.23 - 3.28 (q, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 5.33 (s, 1H), 6.75 (d, 1H, J = 8 Hz), 6.81 (d, 1H, J = 7.6 Hz), 7.02 (t, 1H, J = 7.6 Hz), 7.11 (s, 1H), 7.24 - 7.28 (m, 1H), 7.49 - 7.54 (m, 2H), 8.31 (d, 1H, J = 8.0 Hz) ppm; ESIMS (m/z): 436 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(3-cyanophenyl)ureido) octyl)-6-methoxybenzoate (7h): Using **6** and 3-cyano phenyl isocyanate as starting materials, the title compound **7h** was obtained as a pale yellow solid (Yield = 33.5%); m.p. 75˚C - 76˚C; IR (DCM film): 3355, 3083, 3006, 2930, 2855, 2230, 1728, 1664, 1587, 1552, 1470, 1431, 1271, 1111, 1072, 791, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (bs, 8H), 1.41 - 1.58 (m, 4H), 2.55 (t, 2H, J = 8.0 Hz), 3.19 - 3.24 (q, 2H), 3.80 (s, 3H), 3.93 (s, 3H), 5.2 (s, 1H), 6.78 - 6.84 (m, 2H), 7.22 - 7.33 (m, 3H), 7.57(s, 1H), 7.63 - 7.65 (m, 1H) ppm; ESIMS (m/z): 438 $(M + H)^+$.

Synthesis of methyl 2-methoxy-6-(8-(3-(3-(trifluoromethyl)phenyl)ureido)octyl)benzoate (7i): Using **6** and 3-trifluromethyl phenyl isocyanate as starting materials, the title compound **7i** was obtained as a white solid (Yield = 42.6%); m.p. 99˚C - 101˚C; IR (DCM film): 3349, 3096, 3005, 2932, 2856, 1730, 1660, 1564, 1442, 1335, 1266, 1120, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (bs, 8H), 1.41 - 1.58 (m, 4H), 2.55 (t, 2H, J = 7.6 Hz), 3.19 - 3.24 (q, 2H), 3.79 (s, 3H), 3.93 (s, 3H), 5.12 (s, 1H), 6.77 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 8.0 Hz), 7.075 (s, 1H), 7.22 - 7.36 (m, 3H), 7.55 - 7.59 (m, 2H) ppm; ESIMS (m/z): 481 $(M + H)^+$.

Synthesis of methyl 2-methoxy-6-(8-(3-(3-methoxy phenyl)ureido)octyl)benzoate (7j): Using **6** and 3-methoxy phenyl isocyanate as starting materials, the title compound **7j** was obtained as a off white solid (Yield = 88.4%); m.p. 82˚C - 83˚C; IR (DCM film): 3343, 2935, 2861, 1726, 1567, 1466, 1266, 1109, 1072, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (bs, 8H), 1.40 - 1.58 (m, 4H), 2.53 (t, 2H, J = 8.0 Hz), 3.19 - 3.22 (q, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 5.08 (s, 1H), 6.59 - 6.60 (m, 1H), 6.75 - 6.82 (m, 3H), 7.05 (s, 1H), 7.12 - 7.18 (m, 1H), 7.25 - 7.30 (m, 1H) ppm; ESIMS (m/z): 443 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(2,2-dimethyl-2,3-dihydro benzofuran-7-yl)ureido)octyl)-6-methoxybenzoate (7k): Using **6** and 7-isocyanato-2, 2-dimethyl-2, 3-dihydro benzofuran as starting materials, the title com- pound **7k** was obtained as a light brown color solid (Yield:

44.4%); m.p. 96˚C - 97˚C; IR (DCM film): 3347, 3050, 2929, 2855, 1730, 1658, 1565, 1441, 1374, 1300, 1267, 1111, 1070, 877, 765, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (bs, 8H), 1.46 (s,6H), 1.46 - 1.60 (m, 4H), 2.53 (t, 2H, J = 7.6 Hz), 3.03 (s, 2H), 3.21 - 3.26 (q, 2H), 3.81 (s, 3H), 3.90 (s, 3H), 4.85 (s, 1H), 6.21 (s, 1H), 6.74 - 6.85 (m, 4H), 7.24 - 7.28 (m, 1H), 7.54 (d, 1H, J = 8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.78, 28.20, 29.09, 29.20, 29.26, 30.01, 30.98, 33.39, 40.30, 43.32, 52.13, 55.80, 87.56, 108.33, 119.50, 119.69, 120.59, 121.46, 122.97, 123.36, 126.89, 130.22, 141.24, 148.55, 155.82, 156.20, 168.97 ppm; ESIMS (m/z): 483 $(M + H)^+$.

Synthesis of methyl 2-methoxy-6-(8-(3-phenyl thioure ido)octyl) benzoate (8a): Using **6** and phenyl thioisocyanate as starting materials, the title compound **8a** was obtained as a light brown liquid (Yield = 50.2%); IR (DCM film): 3280, 3054, 3005, 2930, 2854, 1728, 1590, 1536, 1502, 1465, 1304, 1267, 1110, 1072, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 (bs, 8H), 1.57 (bs, 4H), 2.54 (t, 2H, J = 8.0 Hz), 3.60 - 3.64 (m, 2H), 3.82 (s, 3H), 3.91 (s, 3H), 6.02 (s, 1H), 6.77 (d, 1H, J = 8 Hz), 6.82 (d, 1H, J = 8.0 Hz), 7.22 - 7.34 (m, 4H), 7.43 - 7.47 (m, 2H), 7.59 (s, 1H) ppm; ESIMS (m/z): 429 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(3-chlorophenyl) thioure ido)octyl)-6-methoxybenzoate (8b): Using **6** and 3-chloro phenyl thioisocyanate as starting materials, the title compound **8b** was obtained as a off white solid (Yield = 80.3%); m.p. 103˚C - 104˚C; IR (DCM film): 3349, 3083, 3004, 2930, 2855, 1730, 1660, 1592, 1544, 1473, 1429, 1269, 1110, 1073, 773, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.25 (bs, 8H), 1.44 - 1.60 (m, 4H), 2.54 (t, 2H, J = 7.6 Hz), 3.18 - 3.20 (m, 2H), 3.8 (s, 3H), 3.92 (s, 3H), 5.2 (s, 1H), 6.77 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 7.6 Hz), 6.95 (d, 1H, J = 8.0 Hz), 7.12 - 7.21 (m, 2H), 7.28 - 7.35 (m, 2H) ppm; ESIMS (m/z): 463 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(3,4-dichlorphenyl)thioureido)octyl)-6-methoxybenzoate (8c): Using **6** and phenyl thioisocyanate as starting materials, the title compound **8c** was obtained as a pale brown color liquid (Yield = 98.4%); IR (DCM film): 3298, 3055, 3008, 2930, 2855, 1725, 1588, 1533, 1470, 1269, 1115, 1072, 1030, 822, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37 (bs, 8H), 1.58 (s, 4H), 2.55 (t, 2H, J = 7.2 Hz), 3.60 (bs, 2H), 3.81 (s, 3H), 3.91 (s, 3H), 6.06 (s, 1H), 6.77 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 7.2 Hz), 7.13 (d, 1H, J = 8.4 Hz), 7.26 - 7.30 (m, 1H), 7.38 (s, 1H), 7.48 (d, 1H, J = 8.8 Hz), 7.67 (s, 1H) ppm; ESIMS (m/z): 497 $(M + H)^+$. 499 (chloro).

Synthesis of methyl 2-(8-(3-(2-fluorophenyl)thioureido)octyl)-6-methoxybenzoate (8d): Using **6** and 2-fluorophenyl thioisocyanate as starting materials, the title compound **8d** was obtained as a pale brown liquid (Yield = 74.3%); IR (DCM film): 3259, 3050, 3006, 2931, 2855, 1728, 1587, 1541, 1505, 1465, 1268, 1110, 1072, 956, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (bs, 8H), 1.58 (bs, 4H), 2.54 (t, 2H, J = 8.0 Hz), 3.63 (bs, 2H), 3.82 (s, 3H), 3.92 (s, 3H), 6.04 (s, 1H), 6.77 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 7.19 - 7.41 (m, 5H) ppm; ESIMS (m/z): 447 $(M + H)^+$.

Synthesis of methyl 2-(8-(3-(3-cyanophenyl)thioureido)octyl)-6-methoxybenzoate (8e): Using **6** and 3-cyanophenyl thioisocyanate as starting materials, the title compound **8e** was obtained as a yellow solid (Yield = 36.6%); m.p. 114˚C - 115˚C; IR (DCM film): 3334, 2939, 2862, 2223, 1725, 1639, 1549, 1466, 1265, 1109, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.33 (bs, 8H), 1.58 (bs, 4H), 1.80 - 1.82 (m, 2H), 2.53 (t, 2H, J = 8.0 Hz), 3.81 (s, 3H), 3.91 (s, 3H), 4.6 (s, 1H), 6.75 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 8.0 Hz), 6.95 (d, 1H, J = 8.0 Hz), 7.23 - 7.28 (m, 3H), 7.47 - 7.51 (m, 1H) ppm; ESIMS (m/z): 454 $(M + H)^+$.

Synnthesis of methyl 2-methoxy-6-(8-(3-(3-(trifluoro methyl)phenyl)thioureido)octyl) benzoate (8f): Using **6** and 3-trifluromethylphenyl thioisocyanate as star- ting materials, the title compound **8f** was obtained as a light yellow liquid (Yield = 46.7%); IR (DCM film): 3325, 3070, 3013, 2931, 2856, 1725, 1666, 1582, 1459, 1331, 1269, 1119, 1073, 894 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.288 (bs, 8H), 1.58 (bs, 4H), 2.53 (t, 2H, J = 8.0 Hz), 3.61 (bs, 2H), 3.79 (s, 3H), 3.90 (s, 3H), 6.06 (s, 1H), 6.75 (d, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 8.0 Hz), 7.25 - 7.29 (m, 1H), 7.46 - 7.55 (m, 4H), 7.74 (s, 1H) ppm; ESIMS (m/z): 495$(M - H)^+$.

Antibacterial Bioassay [27]: Urea and thiourea derivatives of Anacardic acid (**7a-7k**, **8a-8f**) were dissolved in dimethyl sulphoxide at 250 μg/mL concentration. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4. After 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 1×10^6 cell/ml. The plates were set at room temperature and later dried at 37˚C for 20 h. Paper discs (6 mm, 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.

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