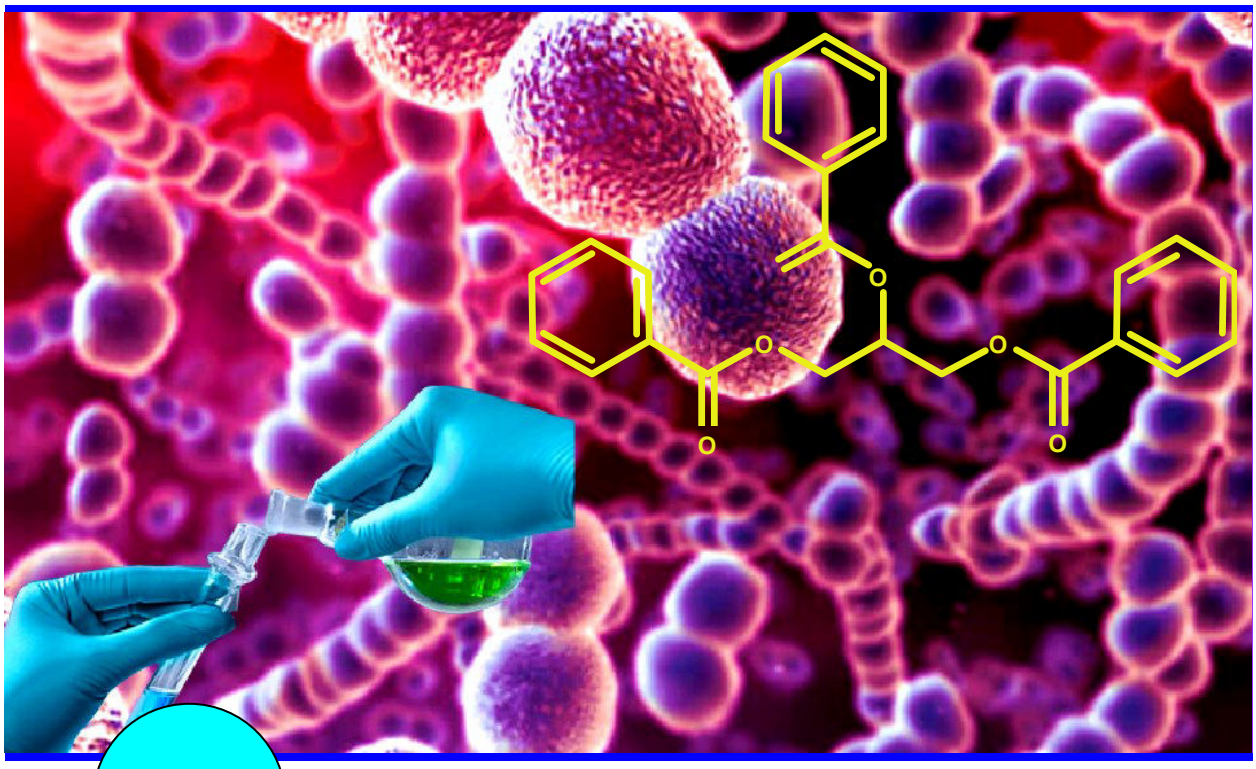

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New bioactive triaryl triglyceride esters: Synthesis, characterization and biological activities

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New bioactive triaryl triglyceride esters: Synthesis, characterization and biological activities

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Abstract

Four new bioactive aryl triester derivatives of glycerol and benzoic acids were synthesized. The synthetic compounds were studied for their antimicrobial and urease inhibition activities. Esterification was carried out by using carbonyldiimidazole to enhance the acyl elimination addition reaction with benzoic acid derivatives. The structure of triglycerides were studied by EI-MS, ^{1}H, ^{13}C-NMR, FT-IR and elemental analysis. All synthetic compounds showed urease inhibition activity with highest value of IC_{50} value 22.4 ± 0.45 µM which is nearest to standard thiourea IC_{50} value (21.6 ± 0.12 µM). Except compound (**3d**), all other compounds exhibited antimicrobial activity against *Streptococcus pneumoniae, Staphylococcus epidermidis, Bacillus pumilus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albican*.

Introduction

Triglycerides are esterified products of glycerol with fatty acids. They are the main constituents in human, animals and plants as the form of oil, fats and lipids (Nelson and Cox, 2000). In body, liver cell synthesizes certain triglycerides and store the fatty acid as the source of energy (White and Venkatesh, 2011). They are also used as lubricants, emulsifiers and plasticizers in cosmetic, food, chemical and pharmaceutical industry (Macierzanka and Szelag, 2004). In literature, many synthetic methods for synthesis of triglycerides have been reported in which, the first step is the conversion of fatty acid into fatty chloride by using thionyl chloride, oxalyl chloride, phosphate pentachloride (Quinn et al., 1967) (Mattson and Volpenhe, 1962). These inorganic acids are not environment friendly method. Another approach toward the synthesis of triglyceride involves the use of certain enzymes as free CALB (Ravelo et al., 2015; Ferreira and Tonetto, 2017), and catalysts as zinc carboxylates (Macierzanka and Szelag, 2004), triphenylphosphine dibromide (Saroja and Kaimal, 1986) which are very expensive. In this research work, synthesis of new triglyceride with benzoic acid derivatives rather than fatty acid has been reported through, an environmental friendly and inexpensive, acyl addition elimination reaction by using CDI reported by Sheikh et al. (2018).

Urease (urea amidohydrolase, E.C.3.5.1.5) enzyme catalyzes the hydrolysis of urea and converts it into CO_2 and NH_3. Urease catalyzed urea enzymatic hydrolysis is 10^{14} times faster than non-enzymatic hydrolysis (Backert and Clyne, 2011). High urease activity increases NH_3 concentration and resultant toxicity (Bremner and Krogmeier, 1989). High concentration of NH_3 can cause many human diseases like ulcer, urolithiasis, pyelonephritis, NH_3 and hepatic encephalopathy, heaptic coma, and urinary catheter encrustation (Amtul et al., 2002). In addition, almost 90% of the world population is suffering from Gram negative bacterium *Helicobacter pylori* which cause urinary tract stones and

peptic ulcer by using urease mechanism (Blaser, 1998). Because of these reasons, in recent year's urease inhibition studies have fascinated researchers and increasing concentration towards this problem caused by urease enzyme. Several urease inhibitors have been reported including hydroxamate derivatives, phosphoramidites, benzimidazole derivatives, urea derivatives, polyphenol, thiols, heavy metal ions, boric acid and phosphate (Arshad et al., 2017; Kafarski and Talma, 2018).

Many glycerol derivatives such as fatty acid glycerides have been reported as bioactive against Gram positive, Gram negative, yeast and protozoa. Examples include monolaurin and monocaprin against *Helicobacter pylori* (Bergsson et al., 2002), *E. coli* (Kabara, 1978), *Staphylococcus aureus, S. epidermidis, Streptococcus* beta-hemolytic and alpha hemolytic, *Corynebacterium*, *Giardia lamblia* (Moanta and Radu, 2008) and *Candida* (Jarrahpour et al., 2004). Benzoic acid and benzoate ester derivatives are reported for their antibacterial (Friedman et al., 2003), antifungal (Terreaux et al., 2010), anti-inflammatory (Chen et al., 2007) and anti-protozoal (Kashif et al., 2017) activities. In recent years, benzoic acid derivatives have been reported for their inhibitory activities against different enzymes like urease (Rauf et al., 2014), acetylcholinesterase (Yildiz et al., 2016), tyrosinase (Khan et al., 2010) and *Trypanosoma cruzi* trans-sialidase (*TcTS*) (Kashif et al., 2017).

In the current study, we synthesized four new triaryl triglycerides (**3a-3d**) with benzoic acid and evaluated their urease inhibitory and antimicrobial activities which were found to be comparable to previously reported monoglyceride analogs (Sheikh et al., 2018).

Materials and Methods

Solvents and reagents that were used in the synthesis were of analytical grade and purchased from the Sigma -Aldrich Chemical Company, USA and Merck Millipore. Jasco-320-A spectrophotometer was used for the IR spectroscopy by using KBr discs in the range of 400-4000 cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in the solvent $CDCl_3$ and DMSO with $Si(Me)_4$ as the internal standard at 300 on Bruker Avance AM spectrometers. ^{1}H-NMR, 13C-NMR, IR, elemental analysis and EI-MS were done in International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan. For all compounds, mass spectroscopic analysis data were collected through EI-MS using JEOL USA JMS600S instrument.

The mass spectra were taken under electron impact (EI) on MAT 312 and MAT 113D mass spectrometers. Thin layer chromatography technique was used to monitor the reactions and purity, carried out on Merck precoated silica gel 60 F_{254} 20 x 20 cm aluminum sheets and spots were seen under UV light at 254 and 366 nm.

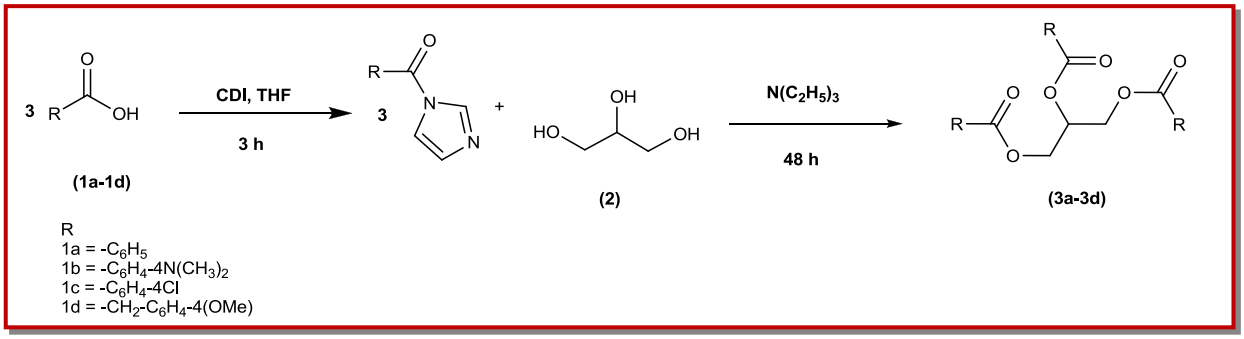
Synthesis of triaryl triglycerides (3a-3d)

Organic acid (**1a-1d**) (5 mmol) and carbonyldiimidazole (5 mmol) were dissolved in THF (30 mL). After 2 hours of stirring, the glycerol (**5**) (1.25 mmol) was added into the vessel along with triethylamine base (0.52 mL). The reaction mixture was left stirring for 48 hours after which the solvent was dried off. The solid reaction mixture was poured into 0.05 M solution of Na_2CO_3. Obtained precipitate of the product was filtered, washed again with water, extracted with dichloromethane and was dried over sodium sulfate. Evaporation of solvent gave the triaryl triglyceride ester (**3a-3d**) which was further purified through column chromatography (Scheme 1).

Propane-1,2,3-triyl tribenzoate (3a)(Figure 1)

Yield: 68%; off white solid; m.p.: 56-58°C; R_f: 0.42 (ethyl acetate: n-hexane 2:1); IR (KBr) ν_{max} (cm^{-1}): 3066 (aromatic) 2934 (C-H aliphatic), 1692 (C=O ester), 1614 (C=C aromatic), 1277 (C-O ester), 1105 (C-O ether) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, 25 °C, TMS) δ (ppm): 4.53 (4H, d, J = 6.19 Hz, C_1H_2-O-, C_3H_2-O), 4.95 (1H, m, C_2H-O-), 7.22(6H, m, C_7H, C_9H, $C_{7'}H$, $C_{9'}H$, $C_{7''}H$, $C_{9''}H$), 7.46 (3H, m, C_8H,$C_{8'}H$, $C_{8''}H$), 8.02 (6H, m, C_6H, $C_{10}H$, $C_{6'}H$, $C_{10'}H$, $C_{6''}H$, $C_{10''}H$),; ^{13}C NMR: (75 MHz, DMSO-d_6): 165.9, 133.2, 130.1,128.6, 68.9, 62.9,; EIMS: *m/z* (rel. abund. %), 404.41 (M^+,27), 403.1(70), 165.05 (100), 148 (28), 122 (4); Anal. Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.98; O, 23.74; Found: C, 71.30; H, 4.95; O, 23.72.

Propane-1,2,3-triyltris(4-(dimethylamino)benzoate) (3b)



Scheme 1: Synthesis of triaryl triglycerides (**3a-3d**)

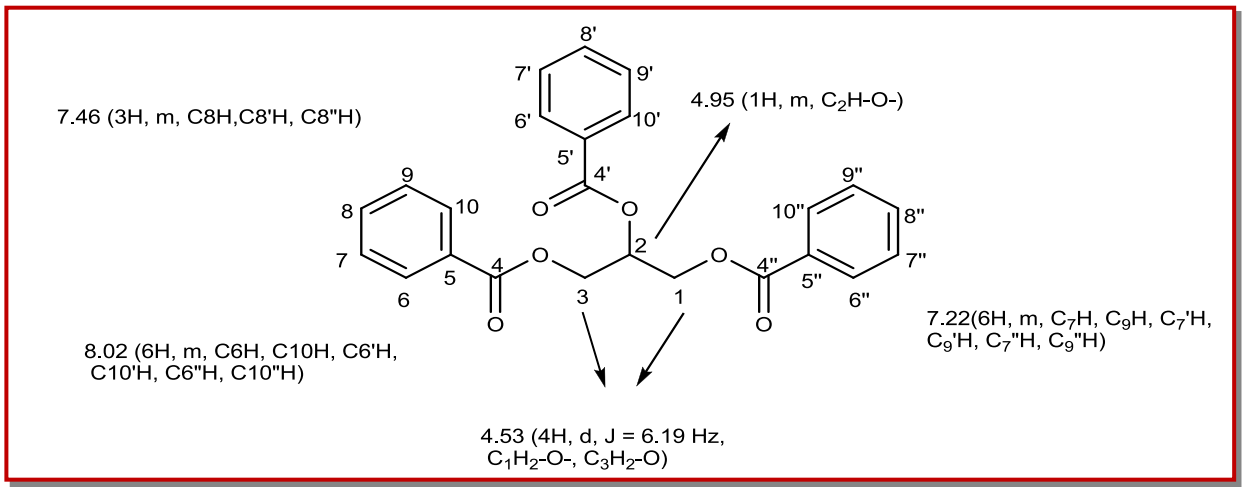


Figure 1: ^{1}H-NMR chemical shifts of compound **3a**

Yield: 56%; white solid; m.p.: 69-71°C; R_f: 0.32 (ethyl acetate : n-hexane 2:1); **IR** (KBr) ν_{max} (cm^{-1}): 3140 (C-H aromatic), 2931 (C-H aliphatic), 1690 (C=O ester), 1604 (C=C aromatic), 1274 (C-O ester), 1185 (C-N amine), 1099 (C-O ether) cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz, 25 °C, TMS) δ (ppm): 3.02 (18H, s, -$C_{11}H_3$, -$C_{12}H_3$, -$C_{11'}H_3$, -$C_{12'}H_3$, -$C_{11''}H_3$, -$C_{12''}H_3$), 3.77(1H, m, C_1H_2-O-), 4.12 (1H, m, C_1H_2-O-), 4.36 (2H, d, J = 5.1 Hz, C_3H_2-O-), 4.42 (1H, m, C_2H-O-), 6.67 (6H, m, C_7H, C_9H, $C_{7'}H$, $C_{9'}H$, $C_{7''}H$, $C_{9''}H$), 7.91 (6H, m, C_6H, $C_{10}H$, $C_{6'}H$, $C_{10'}H$, $C_{6''}H$, $C_{10''}H$),; **^{13}C NMR**: (75 MHz, DMSO-d_6): 165.7, 154.7, 130.9, 119.8.9, 112.0, 67.8, 62.9,40.8.; EIMS: *m/z* (rel. abund. %), 533.25 (M^+,27),; Anal. Calcd for $C_{30}H_{35}N_3O_6$: C, 67.52; H, 6.61; N, 7.87; O, 17.99; Found: C, 67.55; H, 6.59; N, 7.88; O, 18.00.

Propane-1,2,3-triyltris(4-chlorobenzoate) (3c)

Yield: 75%; white solid; m.p.: 83-85°C; R_f: 0.37 (ethyl acetate : n-hexane 2:1); **IR** (KBr) ν_{max} (cm^{-1}): 3156 (C-H aromatic), 2981 (C-H aliphatic), 1691 (C=O ester), 1599 (C=C aromatic), 1275 (C-O ester), 1079 (C-O ether) cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz, 25 °C, TMS) δ (ppm): 3.92 (4H, d, J = 8.6 Hz, C_1H_2-O-, C_3H_2-O-), 4.44 (1H, m, C_2H-O-), 7.65 (6H, m, C_7H, C_9H, $C_{7'}H$, $C_{9'}H$, $C_{7''}H$, $C_{9''}H$), 7.99 (6H, d, J = 8.2 Hz, C_6H, $C_{10}H$, $C_{6'}H$, $C_{10'}H$, $C_{6''}H$, $C_{10''}H$),; **^{13}C NMR**: (75 MHz, DMSO-d_6): 166.2, 139.7, 133.6, 130.4, 128.5, 127.9, 67.6, 63.5.; EIMS: *m/z* (rel. abund. %), **506**.00 (M^+,100), 508.1(M+2, 95), 510.03 (M+4, 30),; Anal. Calcd for $C_{24}H_{17}Cl_3O_6$: C, 56.77; H, 3.37; Cl, 20.95; O, 18.91; Found: C, 56.76; H, 3.39; Cl, 20.94; O, 18.93.

Propane-1,2,3-triyltris(2-(4-methoxyphenyl)acetate) (3d)

Yield: 68%; white solid; m.p.: 5-77°C; R_f: 0.49 (ethyl acetate : n-hexane 2:1); **IR** (KBr) ν_{max} (cm^{-1}): 2931 (C-H aliphatic), 1691 (C=O ester), 1607 (C=C aromatic), 1275 (C-O ester), 1102 (C-O ether) cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 300 MHz, 25 °C, TMS) δ (ppm): 3.56 (6H, s, -C_5H_2-, -$C_{5'}H_2$-, -$C_{5''}H_2$-), 3.77 (9H, s, -O-$C_{12}H_3$, -O-$C_{12'}H_3$, -O-$C_{12''}H_3$), 3.92 (4H, d, J = 8.6 Hz, C_1H_2-O-, C_3H_2-O-), 4.44 (1H, m, C_2H-O-), 6.63 (6H, d, J = 9 Hz, C_8H, $C_{10}H$, $C_{8'}H$, $C_{10'}H$, $C_{8''}H$, $C_{10''}H$), 7.91 (6H, d, J = 9 Hz, C_7H, $C_{11}H$, $C_{7'}H$, $C_{11'}H$, $C_{7''}H$, $C_{11''}H$),; **^{13}C NMR**: (75 MHz, DMSO-d_6): 172.4, 154.3, 131.5, 127.9, 115.3, 68.6, 63.2, 39.8, 41.8; EIMS: *m/z* (rel. abund. %), 536.59 (M^+,27),; Anal. Calcd for $C_{30}H_{32}O_9$: C, 67.15; H, 6.01; O, 26.84; Found: C, 67.16; H, 6.00; O, 26.86.

In vitro urease assay and antimicrobial activity

A mixture of 25 µL of enzyme (jack bean urease) and 100 mm urea containing 55 µL of buffer was incubated with 5 µL of compound (**3a-3d**) which concentration was 1 mM. Incubation process was carried out at 30°C for 15 min in 96-well plates. Indophenol method is described in the literature (Weatherburn, 1967), in which the activity was measured through the NH_3 production. In brief, 45 µL each of 1% w/v phenol and 0.005% w/v sodium nitroprusside (phenol reagent) and 70 µL of 0.5% w/v NaOH and 0.1 % active chloride NaOCl (alkali reagent) were added to each well. The increasing absorbance at 630 nm was measured after 50 min, using a microplate reader (molecular device, USA). All the assays were performed at pH 8.2 (0.01 m $K_2HPO_4.3H_2O$, 1 mm EDTA and 0.01 m $LiCl_2$). Percentage inhibition was calculated from the formula given as follows:

$100-(OD_{testwell}/OD_{control}) \times 100$

Thiourea was used as the standard inhibitor of urease.

Antimicrobial activity

The agar well diffusion method was used to determine the antibacterial activity by plant extract and its fractions (Ahmed et al., 1998). In this procedure, 100 µL of inoculums (diluted to 106 CFU/mL) of test culture was mixed with 20 mL of molten sterile tryptic soya agar. This mixture was poured into pre-sterilized petri dishes under sterile condition. Plates were allowed to

set at 4°C for 30-40 min. Holes (6 mm diameter) were made in the center of each seeded plate. 0.1 mL of the test solution i.e. compound **(3a-3d)** was then filled in holes with two concentrations (0.1 and 0.05%). Standard disc of antibiotic gentamicin (10 µg) served as positive antibacterial control. DMSO was used as negative control. All plates were then incubated at 37 ± 1°C for 24 hours. The zone of inhibition around the wall was observed for the evaluation of the antibacterial activity. Vernier caliper was used to measure the diameter (in mm) of inhibition zone. Readings were made repeatedly to minimize test error.

Results

Urease inhibition activity

All compounds (**3a-3d**) were evaluated for inhibition activity. Standard (thiourea) was used with IC_{50} value 21.6 ± 0.12 µM. All compounds were showed inhibition activity with the IC_{50} values between 22.4 ± 0.45 to 41.2 ± 0.16 µM. Compound (**3c**) was the most active compound with the IC_{50} value near to the standard that is 22.4 ± 0.45 µM, while the least active compound was (**3d**) with the IC_{50} value two times less than (**3c**). All the values were listed in Table I.

Antimicrobial activity

All synthetic compounds (**3a-3d**) were evaluated for their antimicrobial activity against Gram positive (*S. pneumoniae, S. epidermidis* and *Bacillus pumilus*), Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and yeast (*Candida albican*). In the current study, gentamycin (10 µg) was used as standard while synthetic compounds (**3a-3d**) were used in two concentrations 0.1 and 0.05%. The antimicrobial activity results are listed in Table II.

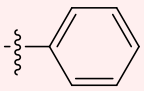
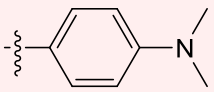
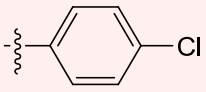
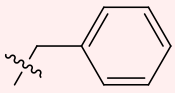
Discussion

In the synthesis of triaryl triglyceride (**3a-3d**), glycerol was esterified with only once with one benzoic acid. The esterification was carried out by CDI which incorporated the imidazole as leaving group in place of basic group –OH. Being an aromatic ring, the imidazole anion is highly stable (closed bonding shell and resonance) (Verma et al., 2012), hence elimination step of acyl addition elimination reaction becomes energetically facile. Acyl addition elimination is facilitated by the same scheme of the replacement of the leaving group usually by reaction of the acid with an inorganic acid such as $SOCl_2$, oxalyl chloride, PCl_3 and PCl_5 (Roy et al. 2016). Glycerol being a triol polyhydric alcohol (Bieleski, 1982) wields three Lewis basic OH sites for bonding with bioactive moieties, in this research work these OH sites bonds with C=O of three benzoic acids. Other than glycerol, higher polyol sugar alcohols can also be used on the same pattern with even higher number of Lewis basic sites in them to be bonded with aryl rings.

Some bonded benzoic acid rings had activating and deactivating (resonating and inductive) groups on the aryl ring inducing an overall electron rich or deficient character on the bonded aryl ring respectively. Hence, substitution on the aryl ring had an impact on the

Table I

Urease inhibition results of compounds (3a-3d)

SL. No.	Compound	R	Urease inhibition
		Substituents	(IC_{50} ± SEM µM)[a]
1	3a		26.4 ± 0.5
2	3b		36.5 ± 0.3
3	3c		22.4 ± 0.5
4	3d		41.2 ± 0.2
Standard	Thiourea		21.6 ± 0.1

a = (Mean ± Standard error of mean)

Table II

Antimicrobial activity of compounds (3a-3d)

	Zone inhibition (mm)																	
	Yeast			Gram positive									Gram negative					
	Candida albican			*Streptococcus pneumoniae*			*Staphylococcus epidermidis*			*Bacillus pumilus*			*Escherichia coli*			*Pseudomonas aeruginosa*		
Conc. %	0.1	0.05	Std.	0.1	0.05	Std.	0.1	0.05	Std.	0.1	0.05	Std.	0.1	0.05	Std.	0.1	0.05	Std.
3a	18.2	15.4	20	17.5	16	20	18	16	20	17.5	19.6	20	12	15.6	22	18.3	17	20
3b	19	17.3	20	18.3	16.6	21	15	-	20	18.3	13.6	22	20	22.3	23.5	18	12.6	19.3
3c	20	19.6	21	19	18.5	20	18.9	14.6	21	18.7	17.6	20	23	22.3	24	17.6	16.7	20
3d	16	-	20	14	-	20	-	-	21	14.	-	20	16.3	-	22	14	-	20

bioactivity and also on the interaction with substrates.

The ^{1}H-NMR of all compounds were studied at 300 MHz. In ^{1}H-NMR of (**3a**), alkyl protons of C1, C2 and C3 appeared between 4 to 5 ppm, due to the deshielding effects of sp^2 O atom which is in conjugation with the C=O bond of the ester. Aryl protons are deshielded by sp^2 carbonyl carbon of ester, appearing between 7 to 8 ppm.

Because of the presence of the symmetry element in (**3a-3d**) half of the resonance spectra were achieved. All aryl ring proton showed 2nd order coupling with AA'BB'C system. This system referred to as Pople notation spin spitting designation protocol (Pople et al., 1957), otherwise in 1st order spectra of aryl ring spin splitting system would at least doublet of doublet (dd) with ^3J and ^4J. Similarly, the *beta* carbon (C2) proton should have been doublet of doublet (dd) but there was also 2nd order interaction between the mutually spin splitting protons in the alkyl aliphatic range. The higher vicinal coupling constant means (sp^3-1s) σ orbital is parallel to the 1s σ orbital, this implies that the orbital-orbital overlap is strong according to Dirac modal and electronic spin interaction is facile (Minch, 1994). This orbital overlap is possible when angle is either 0^o or 180^o. In case of 180^o the interaction is in between σ and σ* orbital. The alkyl aliphatic system is deshielded by the sp^2 O which is in conjugation with the C=O bond of ester. Aryl section is deshielded by sp^2 carbonyl carbon of ester group. Whether the symmetry was axial or planer can be verified by the stereochemical analysis such as NOE, NOESY.

Limited structural activity relationship showed that compound (**3c**) was the most active compound with the IC_{50} value 22.4 ± 0.45 µM and it had Cl at para position of the aryl ring in all three substituents R. The next active most compound was (**3a**) with IC_{50} value 26.4 ± 0.47 µM, it had unsubsituted aryl ring. Compound (**3b**) also showed good activity with the IC_{50} value 36.5 ± 0.33 µM, it had *N,N*-dimethyl substituents on para position in all three aryl rings. The least active compound was (**3d**) with the IC_{50} value 41.2 ± 0.16 µM. From the results, it was found that urease inhibition activity depends on the number of aryl rings and substituents on it. As the number of aryl ring increases, the probability of π-π stacking of aryl rings with the active sites of enzyme or its side chain which contains cysteine or methionine groups also increase (Rego et al., 2018). As a result, good urease inhibition activity was shown by the synthesized triaryl triglycerides (**3a-3d**), compared to the monoglycerides reported by Sheikh et al., (2018). Taha et al. (2016) reported that the incorporation of electron-withdrawing groups on aryl ring increase the polarizbility and inhibition activity towards urease enzyme. As results showed that the most active compound (**3c**) also contains three Cl at para position of all aryl rings and was found most active among rest.

All compounds showed activity against all microorganisms the most active molecule was (**3c**), it exhibited good activity against all bacteria and yeast at both concentrations and its zone inhibition values was very close to standard values. The least active compound was (**3d**) which showed moderate level activity at 1% concentration and inactive at 0.05%. It was also inactive against *S. epidermidis* at both concentrations. As compared to the previously reported fatty glycerides and monoglycerides (Sheikh et al., 2018), the synthesized triaryl triglycerides exhibited good to excellent level bioactivity against the given microbes.

Conclusion

Potent bioactive triaryl triglyceride esters (**3a-3d**) were synthesized with benzoic acid derivatives through facile one-step and environmental friendly synthesis. All synthetic triglycerides (**3a-3d**) inhibit the enzyme urease and show the good antimicrobial activity even better than previously reported monoglycerides.

Conflict of Interest

Authors declare no conflict of interest.

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