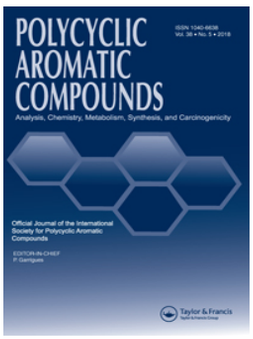

Polycyclic Aromatic Compounds

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First Report of the Synthesis, Characterization, DFT Calculations of the New Oxoethyl Methacrylate and *o*-Acetamide and Evaluation of Antimicrobial, Antibiofilm and Antioxidant Effect

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ABSTRACT

In this study, 2-chloro-N-(2-methoxyphenyl)acetamide (*o*-acetamide) and 2-(2-methoxyphenylamino)-2-oxoethyl methacrylate (2MPAEMA), which is unreported in the literature were synthesized and characterized. Characterization of the 2MPAEMA and *o*-acetamide were performed by elemental analyses, FT-IR, ^{1}H and ^{13}C NMR spectroscopic techniques. Global reactivity descriptors such as HOMO-LUMO gaps and chemical hardness, electronegativity, chemical potential, electrophilicity index, as well as NBO, MEB analyzes were performed at the DFT/B3LYP/6-311++G(d,p) level and interpreted in detail. From the theoretical results, in parallel with the experimental results, it was concluded that the *o*-acetamide compound had greater stability and lower toxicity than the 2MPAEMA compound. In biological studies, in vitro antioxidant activity was explained by DPPH. Agar-well diffusion effect and disk diffusion method were applied to determine the antimicrobial effect, and the effect on biofilm formation was investigated. The both compounds were found to have the high antifungal (isolated from herbal sources; *Trichoderma longibrachiatum, Fusarium solani, Penicillium janthinellum* and *Mucor plumbeus*). But only o-acetamide was found to have the antibacterial activity. The both compounds have a very high scavenging effect on free radicals. There is a need for the development of new nontoxic antimicrobial agents that can be used in agriculture around the world that do not endanger public health. We think that these substances can be used as fungicidal in agriculture.

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1. Introduction

There are many commercially available acrylate species and acrylate derivatives. The use of acrylates in biomedical applications such as tissue engineering, biologically active agent in delivery control systems, contact lenses and bone cements is extensively researched. In addition, acrylate is used in different applications such as slides, cosmetics, orthopedics, paints and coatings, adhesives and textiles.[1] Studies on synthesizing new acrylate monomers and polymers and evaluating their biological activities are increasing in importance because of the wide range of use areas.

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The biological activity of the acrylate species and acrylate derivatives are related to the functional group and the nature of the substance. The advantage of acrylate derivatives depends on amide or ester linkage. These properties provide longer delivery times with lower dosages.[2] It is expected to increase the therapeutic efficiency of chemicals while lowering their toxicity phenyl acrylate polymers are recently improved commercial materials.[3]

Acrylate polymers used in cutaneous wound healing have been reported.[4] Specifically, a copolymer of ethylene glycol dicyclopentenyl ether acrylate (EGDPEA) and di(ethylene glycol) methyl ether methacrylate (DEGMA) were formed among a wide panel of monomers using polymer microarrays for antibacterial and antibiofilm properties.[5] Same acrylate species and acrylate derivatives have also shown antioxidant action.[6] In free-radical polymerization, acrylic monomers like acrylic, methacrylic acid and acrylamide show strong reactivity. Hydrophilic polymers can be chosen as the main monomeric base of hydrogels. Acrylic hydrogels (Aquasorb®, Aquaterra®) were successfully utilized in agriculture.[7]

Today, fungal and bacterial diseases are a major threat to public health as well as to plants and animals. Especially the increase in the world population has led to an increase in the demand for agricultural products. Therefore, there is worldwide pressure to increase the quality and yield of agricultural products. Antimicrobial agents are widely used in the agricultural industry to prevent fungal diseases. However, the irregular use of antifungal endangers other living things in the ecosystem. There is a need for the development of new nontoxic antimicrobial agents that can be used in agriculture around the world that do not endanger public health.[8]

Density Functional Theory (DFT) based on a theoretical calculation of molecular structural properties, HOMO and LUMO are strongly interpreted with the design of various molecules. There is a demand for synthesis of innovative compounds with antimicrobial, antifungal, antioxidanti and other activity. Biological activity and physicochemical parameters of compounds are also discussed with the theoretical calculation.[9,10]

In the literature, there are many acrylate derivatives originally synthesized and characterized.[5–7,11,12] Our team is also conducting monomer and polymer studies on acrylate and acrylate derivatives. In our previous studies, our team synthesized and characterized the 2-(4-methoxyphenylamino)-2-oxoethyl methacrylate (MPAEMA) monomer.[3,12] In addition, we studied the cytotoxicity of MPAEMA by XTT cell proliferation analysis,[13] physical, electronic and vibration properties, and characterization of LB thin films.[3] In this study, we first synthesized and characterized *o*-acetamide and 2-(2-methoxyphenylamino)-2-oxoethyl methacrylate (2MPAEMA), which were not available in the literature. The quantum chemical properties of the *o*-acetamide and 2MPAEMA compounds were examined and also we investigated the effects of antimicrobial, antifungal, antioxidant, antibiofilm properties.

2. Experimental

2.1. Materials and instrumental measurements

Triethylamine (NR_3), dimethyl sulfoxide (DMSO), 4-methoxyaniline, sodium acrylate, chloroacetyl chloride, triethylbenzylammoniumchloride (Tebac) as a phase transfer catalyst, and acetone and acetonitrile as solvent [Aldrich®] were used as received.

The FT-IR spectrum of all samples were performed with a Perkin Elmer Spectrum Two (UATR) IR spectrometer in the range of 4000–450 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Topspin Ultra Shilt 400 MHz spectrometer at room temperature in $CDCl_3$ and DMSO-d_6, respectively. Elemental analyses (carbon, hydrogen, and nitrogen) were carried out on a Leco CHNS-O model 932 elemental analyzer.

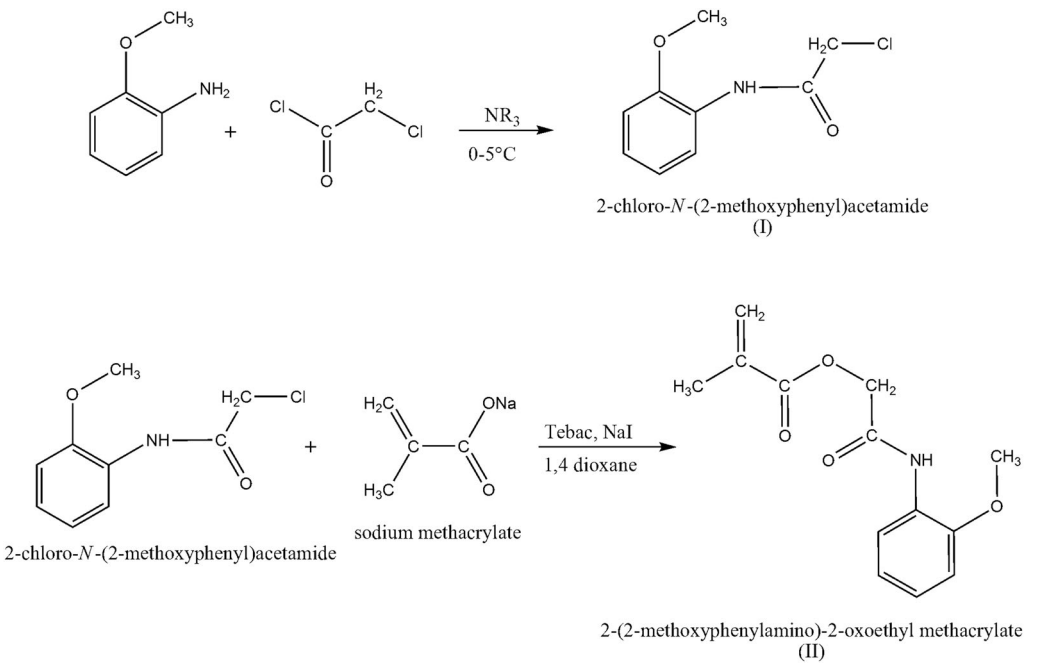

Figure 1. (I). Synthesis of the 2-chloro-N-(2-methoxyphenyl)acetamide (*o*-acetamide) (II). Synthesis of the 2-(2-methoxyphenylamino)-2-oxoethyl methacrylate (2MPAEMA).

2.2. Synthesis of 2-chloro-N-(2-methoxyphenyl)acetamide (o-acetamide)

2-methoxy aniline (1 mmol) and NR_3 (1.1 mmol) were dissolved in pure acetone, and then chloroacetyl chloride (1.1 mmol) was added drop wise to the solution at 0–5 °C. After the reaction was stirred for 24 hours, it was filtered to remove the salt formed in the resulting brown solution, and the excess solvent was removed. Subsequently, the substance dissolved in the solvent was precipitated in ice water, resulting in bright purple-brown crystals (yield 84%) Anal. calc. for $C_9H_{10}NO_2Cl$: C, 54.15; H, 5.05; N, 7.02; O, 16.03. Found: C, 54.19; H, 5.04; N, 7.05; O, 16.06.[3,10] The reaction scheme of the synthesized *o*-acetamide is shown in Figure 1(I).

2.3. Synthesis of 2-(2-methoxyphenylamino)-2-oxoethyl methacrylate (2MPAEMA)

For the synthesis of 2MPAEMA monomer, *o*-acetamide (1 mmol) compound, sodium methacrylate (1.1 mmol), Tebax-NaI as phase transfer agent and hydroquinone was used to prevent polymerization. The reaction was complete with reflux at 48 hours using 1,4-dioxane as solvent. At the end of the reaction time, it was filtered to remove impurities. It was washed with diluted base solution in order to remove the hydroquinone dissolved in the substance (yield 85%) Anal. calc. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; O, 25.67. Found: C, 62.65; H, 6.08; N, 5.62; O, 25.70.[3,10] The synthesis of 2MPAEMA monomer is shown in Figure 1(II).

2.4. Antibacterial activity test

The sample concentrations were 50 mg/mL with DMSO as the solvent (Many concentrations have been tried by our researchers, and no results were obtained at low concentrations, and the most appropriate result was obtained in 50 mg/mL DMSO solution). All microorganism strains were obtained from the Culture Collection of Microbiology Laboratory of Uşak University (Turkey). In this study, *Staphylococcus aureus ATCC 29213, Candida glabrata, Bacillus subtilis, Enterococcus*

faecalis, Escherichia coli ATCC 25922, Klebsiella pneumoniae, Pseudomonas aeruginosa ATCC 27853, Listeria monocytogenes were used as bacteria. Antibacterial susceptibility tests were performed by the disk diffusion standard method by Bauer et al.[14] 0.5 McFarland bacterial culture (1.5×10^8 CFU/mL) was used to lawn Muller Hinton agar plates using a sterile swab. The disks had been impregnated with 50 µL of each sample were placed on the MuellerHinton agar surface. DMSO were used as negative controls. Vancomycin (VA30), penicillin (P10), tetramycin (TE30), erythromycin (E15) and chloramphenicol (C30) were used as reference antimicrobial agents. Subsequently, petri dishes were incubated at 37 °C for 24 hours. Antimicrobial activity was determined by measuring the zones around the disks.

2.5. Antifungal activity test

Samples of the untreated textile waste water and activated sludge *Trichoderma longibrachiatum, Penicillium janthinellum*, *Fusarium solani* and *Mucor plumbeus*, which were isolated from plant material in Uşak province, Turkey, were used to determine the antifungal activity. Agar well diffusion method was used to determine the antifungal activity. 6 mm wells were opened on the Potato Dextrose Agar (PDA) (Merck 1.10130) and inoculated with 50 µL test substances into the opened wells. Placed mycelial surface down on the center of the dishat equal distances and incubated for 5 days at room temperature in the dark. Antifungal activity was determined by measuring the distance of the fungi to the wells.[15]

2.6. Detection of antibiofilm formation

P. aeruginosa ATCC 11778 isolate, which is known to generate biofilm, was used as positive control and microorganism free medium was used as negative control. 1 mL of 0.5 McFarland *P. aerouginosa* ATCC 27853 culture strain and 1 mL test material (5, 10, 20%) was mixed in the test tube. These tubes incubated at 37 °C for 24 hours. After incubation, the liquid medium was poured and washed 3 times with distilled water 2 mL of crystal violet solution (0.5% (v/v)) was added and incubated 45 minutes. The tubes were washed again with distilled water 3 times. Then 2 mL of ethanol:acetic acid (95:5) was added and left to stand for 10 minutes to dissolve the dye. After this step the absorbance values of each well at 570 nm were determined using spectrophotometer.[16]

The ability of biofilm was determined using the following formula.

$$\text{Inhibition } \% = [(A_{\text{Blank}} - A_{\text{Sample}})/A_{\text{Control}}] \times 100$$

2.7. Determination of antioxidant activity by radical scavenging assay α,α-diphenyl-β-picrylhydrazyl (DPPH) test

The antioxidant activity of the test substance was determined by the DPPH assay, as previously described in some modifications.[17] 300 mL of the test substance was mixed with 5700 mL of DPPH solution and incubated in the dark for 1 h at 27 °C. Absorbance was measured by Shimadzu UV-1800 spectrophotometer at 515 nm. Then the absorbance was measured at 515 nm (Shimadzu UV-1800 spectrophotometer) against a blank (water instead of test sample and DPPH solution). Gallic acid was used as positive control. The ability of the sample to remove the DPPH radical was determined using the following formula.

$$\text{Inhibition } \% = [(A_{\text{Blank}} - A_{\text{Sample}})/A_{\text{Blank}}] \times 100$$

Blank: Absorbance of control
Sample: Absorbency of the test compound

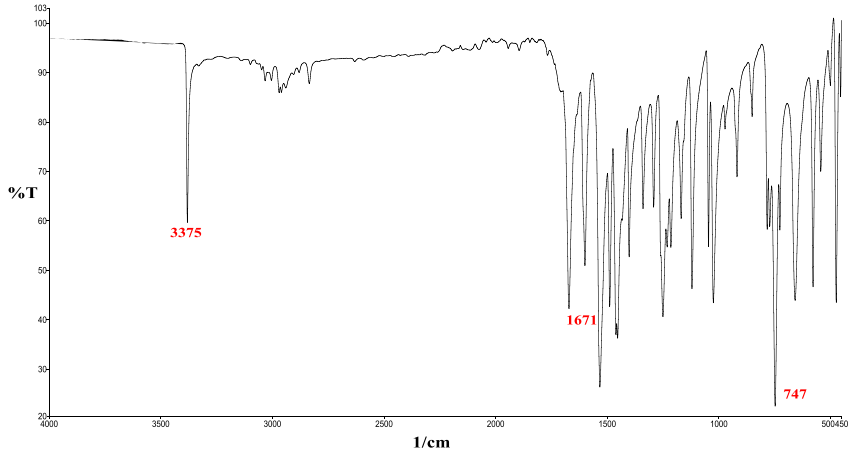

Figure 2. The FT-IR spectrum of the *o*-acetamide.

3. Results and discussion

3.1. Characterization of o-acetamide

The elemental analyses data of the new compounds were within ±0.4% of the theoretical data calculated for the proposed formulas. FT-IR, ^{1}H and ^{13}C NMR spectra of *o*-acetamide are indicated in Figures 2 and 3. In Figure 2, FT-IR (cm^{-1}, the most characteristic bands): 1671 (C = O amide stretching vibration), 1600 (C = C stretching vibration on aromatic ring), 2850 (C-H aliphatic stretching vibration), 3375 (N-H stretching vibration), 747 (C-Cl stretching vibration).

^{1}H-NMR spectrum of *o*-acetamide following peaks appear; at 8.9 ppm for N-H, 8.3, 7.1 and 6.9 ppm for aromatic ring protons, 4.2 ppm for CH_2-Cl, 3.9 ppm for O-CH_3, 7.3 ppm for $CDCl_3$ proton. ^{13}C-NMR spectrum of *o*-acetamide following peaks appear; at 164 ppm for amide C = O, 149, 127, 125, 121, 120 and 110 ppm for ring carbons, 77 ppm for $CDCl_3$, 56 ppm for O-CH_3, 43 ppm for CH_2-Cl carbons.[3,11,12,18,19]

3.2. Characterization of 2MPAEMA monomer

FT-IR spectra of monomer are given in Figure 4. FT-IR (cm^{-1}, the most characteristic bands): 1253 and 1538 cm^{-1} (C-O-C symmetrical and asymmetrical stretching vibrations), 1599 cm^{-1} (C = C stretching vibration on aromatic ring), 1635 cm^{-1} (C = C olefinic stretching vibration), 1683 cm^{-1} (amide C = O stretching vibration), 1723 cm^{-1} (ester C = O stretching vibration), 2942 cm^{-1} (aliphatic C-H stretching vibration), 3405 cm^{-1} (N-H stretching vibration).

^{1}H-NMR spectrum of monomer following peaks appear; at 9.3 ppm for N-H, 8.0, 7.1, 6.9 ppm for aromatic ring protons, 6.1 and 5.8 ppm = CH_2 olefinic protons, 4.8 ppm O-CH_2, 3.8 ppm O-CH_3, 1.9 ppm C-CH_3; and 3.6 and 2.5 ppm for DMSO-d_6-H_2O and DMSO-d_6 protons, respectively. ^{13}C-NMR spectrum of monomer following peaks appear; at 166 ppm for amide C = O, 165 ppm for ester C = O, 136 ppm for CH_3-C=, 150 (C-OCH_3), 127.2, 126.9, 125, and 121 ppm for ring carbons, 122 ppm for =CH_2 olefinic, 63 ppm for O = C-CH_2-O, 56 ppm O-CH_3, 18 ppm for C-CH_3, 40 ppm for DMSO-d_6 carbons.[3,11,13,19] ^{1}H and ^{13}C NMR spectra are shown in Figure 5.

3.3. Antioxidant activity, antimicrobial effects and detection of antibiofilm formation

Phenolic compounds are prepared by the addition of benzyl groups, alkyl, phenyl and halogen as a substituent on the aromatic ring from chemical modifications of phenol. *o*-benzyl-*p*-

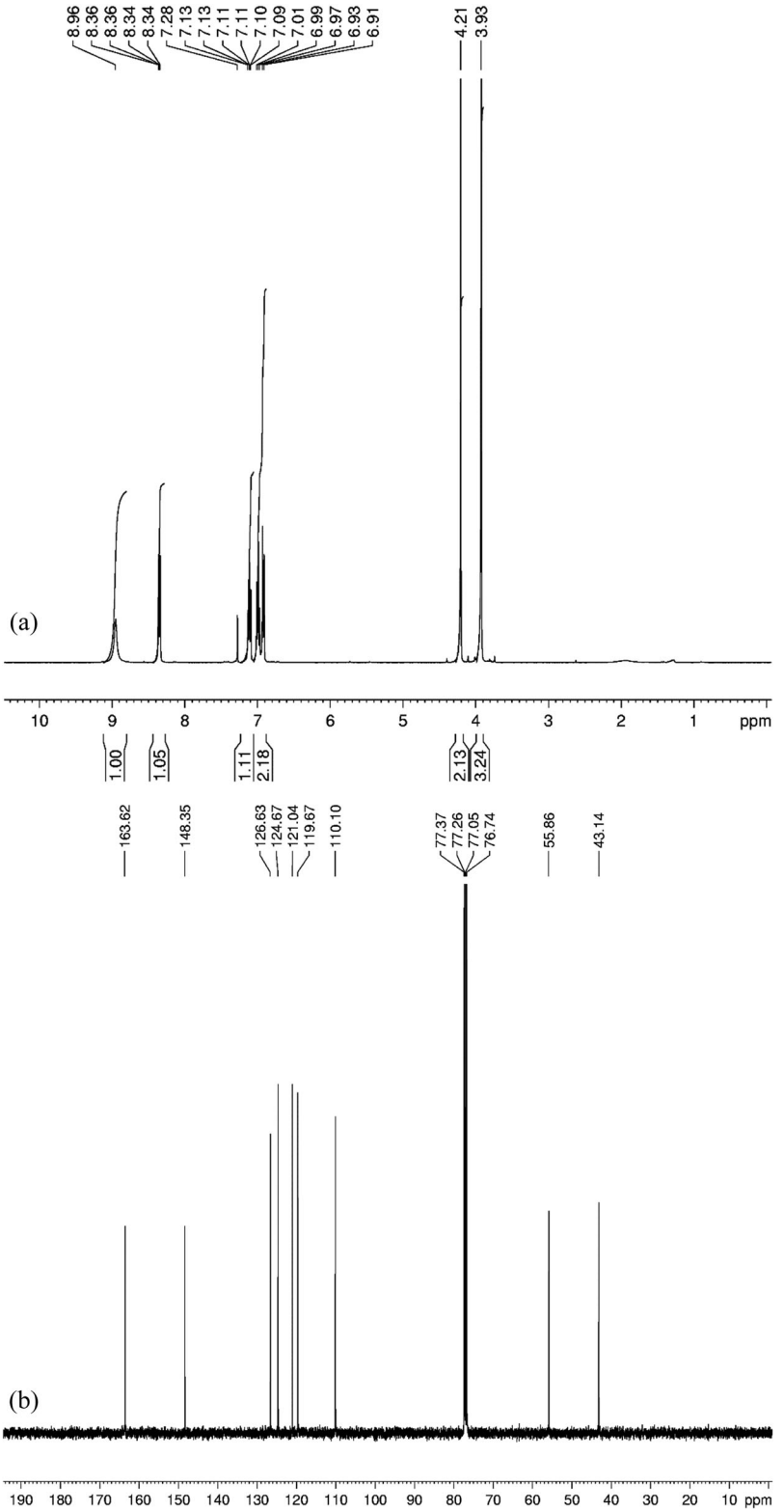

Figure 3. a) The ^{1}H NMR and b) ^{13}C NMR spectra of the *o*-acetamide.

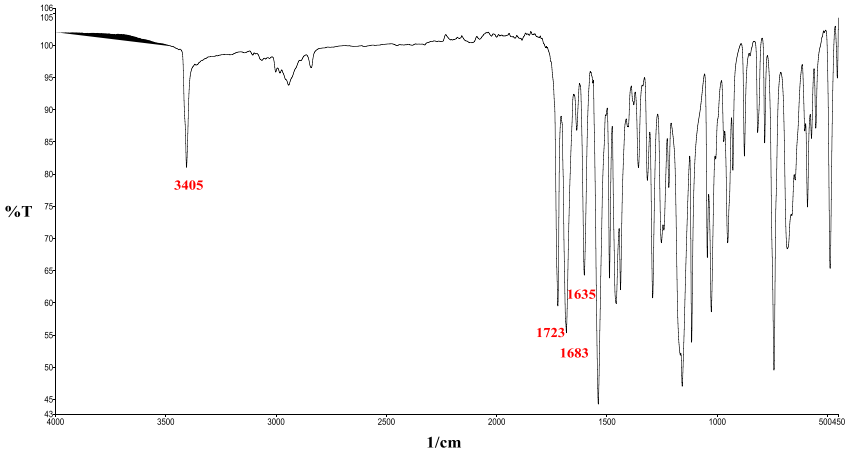

Figure 4. The FTIR spectrum of the 2MPAEMA.

chlorophenol and *o*-phenylphenol commonly are used as phenol derivatives in disinfectants Phenolic compounds tend to have a greater potential for antimicrobials than phenol.[20]

Phenol serves as a penetrating and harmful agent on the cell walls of organisms, as well as growing aggregation of important proteins in cells resulting in high concentrations of cell death. Phenol and phenolic compounds decompose bacterial cells by inactivating the enzyme and weakening the cell wall at lower concentrations.[21] The two materials we used in our study contain a phenyl ring. Also *o*-acetamide contains chlorine (Figure 1). Chlorine tends to induce degradation of sulfhydryl enzymes and amino acids, resulting in loss of intra-cellular material with decreased cell absorption of nutrients. Chlorine also appears to reduce the production of adenosine triphosphate and to prevent DNA synthesis and increase the destruction of DNA.[22,23] The antimicrobial activity of chemicals is related to the hydrophilic, hydrophobic, or polyelectrolytic functional group.[2,24] In this study, FT-IR analysis showed that *o*-acetamide and 2MPAEMA contain functional groups of antimicrobial such as C = O, C-H and N-H (Figure 2 and 4).

Evaluation of antibacterial and antifungal activity of both 2MPAEMA and *o*-acetamide were demonstrated in Tables 1 and 2. The results revealed that *o*-acetamide was potentially effective in suppressing Gram-positive and Gram-negative bacterial growth. Results of antibacterial activity of the *o*-acetamide can suggested that *P. aerouginosa* (15 mm) was the most resistant strain to *o*-acetamide while *E. fecealis* (32 mm) was the most susceptible strains (Table 1). On the other hand, 2MPAEMA was not found to have the antibacterial activity. Chlorine destroys bacterial cell wall by color initiating the lipid protein substance.[25] It can be said that the chlorine content in *o*-acetamide plays an important role in conferring antibacterial activity.

The antifungal activities achieved by 2MPAEMA and *o*-acetamide on 4 different species of fungi (*T. longibrachiatum, F. solani, P. janthinellum and M. plumbeus*) (Figure 6). 2MPAEMA was found to have the antifungal activity on *T. longibrachiatum, F. solani and P. janthinellum* while *o*-acetamide was found to have the antifungal activity on all fungal species tested (Table 2). It can therefore be suggested that, *o*-acetamide are promising both antibacterial and antifungal agent.

The cell walls of microorganism have different composition. For example, fungi cell wall is composed of chitin. Gram-positive bacteria contain 90% peptidoglycan but Gram-negative bacteria presents a thin layer of peptidoglycan surrounded by a secondary lipid membrane.[26]

The cell walls of microorganism have different composition. Fungi and yeast cell walls are chiefly composed of chitin and polysaccharides. Gram-positive bacteria contain 90% peptidoglycan and teichoic acid. In Gram-negative bacteria, peptidoglucan is about 10% and also contains

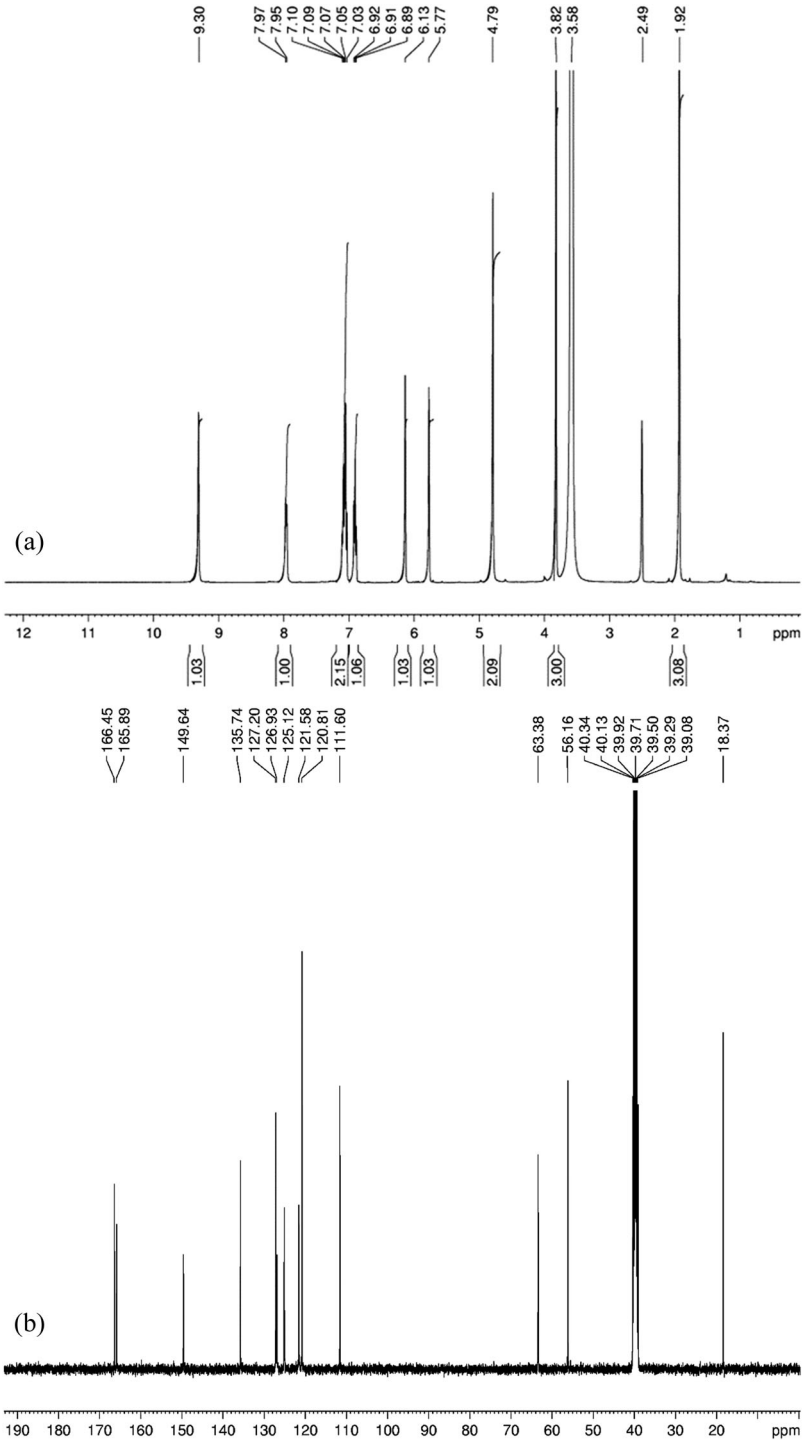

Figure 5. (a) The ^{1}H NMR and (b) ^{13}C NMR spectra of the 2MPAEMA.

Lipopoli saccharide (LPS) layer cell wall structure is a barrier in the entry of chemicals into the cell and determines the antimicrobial effect of the drug.[27] In addition, the effect of antimicrobial active substance may differ even among the same type of microbial strains.

Table 1. Antibacterial activity test of 2MPAEMA and *o*-acetamide.

	Inhibition zones (mm)							
	Positive control					Negative control	Test material	Test material
Test bacteria	VA (30)	TE (30)	C (30)	E (15)	P (10)	DMSO	*o*-acetamide	2MPAEMA
S. aureus	21	30	27	30	40	–	30	–
C. glabrata	8	19	28	–	7	–	22	–
B. subtilis	22	16	36	29	31	–	30	–
E. fecealis	22	27	30	12	23	–	32	–
E. coli	25	12	30	26	33	–	23	–
K. pneumoniae	20	12	25	21	32	–	19	–
P. aerouginosa	6	9	12	6	6	–	15	–
L. monoyctogenes	25	30	32	11	25	–	30	–

Vancomycin (VA30), Penicillin (P10), Tetramycin (TE30), Erythromycin (E15) and Chloramphenicol (C30)

Table 2. Antifungal activity test of 2MPAEMA and *o*-acetamide (50 mg/mL).

	Colonyinhibition of tested fungi (%)			
Test material	*Tl*	*Fs*	*Pj*	*Mp*
***o*-acetamide**	86.95%	24.00%	8.33%	94.54%
2MPAEMA	76.92%	20.83%	ND	98.85%

Tl: *T. longibrachiatum*; Fs: *F. solani*; Pj: *P. janthinellum*.; Mp: *M. plumbeus;* ND: Not determinated

Chlorine-based disinfectants 80%-diluted alcohols are effective against a wide range of bacteria and they are used as disinfectant. In the antibacterial studies on, compounds bearing a fluoro group in addition to a chloro group exhibited greater activity than those bearing only the chloro group.[28] In another study, the antimicrobial activity of nicotinamide containing oxoethyl group was showed good activity.[29] In this study, substitution of chloro groups in the chemical resulted in increased antimicrobial activity, but the oxoethyl group did not show good antibacterial activity. In this study, substitution of chloro groups in the chemical resulted in increased antimicrobial activity, but the oxoethyl group did not show good antibacterial activity. This may be due to the fact that water diluted alcohols have antibacterial effects. As a result, acrylide derivatives containing phenyl ring are used in agriculture, especially fungicidal such as the pyrimidinyloxy-phenyl acrylates (USA patent number 5,633,256).

It has been shown in *P. aeruginosa* that the gene (algC) which controls the phosphomannomutase involved in the synthesis of exopolysaccharide is up-regulated within minutes of adhesion to a solid surface.[30] Multi-system including weak antibiotic penetration, nutrient limitation and slow development, adaptive stress responses and persistent cell formation are hypothesized to constitute the resistance of organisms to antibiotics in biofilms.[31] The biofilm acts as a microbial reservoir for recurrence of infection after the treatment course of the infection. Biofilm infections can persist for months, years or even for life unless the colonized surface is removed from the body.[31]

Preventing the production of biofilms or counteracting the mechanisms of resistance due to biofilms will simplify the treatment of infections caused by organisms generating biofilms and bring back the utility of antibiotics, which are out of use due to biofilm resistance.[31] Many substances, both natural and synthetic, have been found to inhibit biofilm formation. For example, salicylic acid-releasing polyurethane acrylate polymers significantly reduced biofilm formation by *E. coli* for up to 5 days under conditions that simulated physiological urine flow.[32]

These substances effectively prevent biofilm formation and kill bacteria in established biofilms produced by clinical strains such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus mutans*.

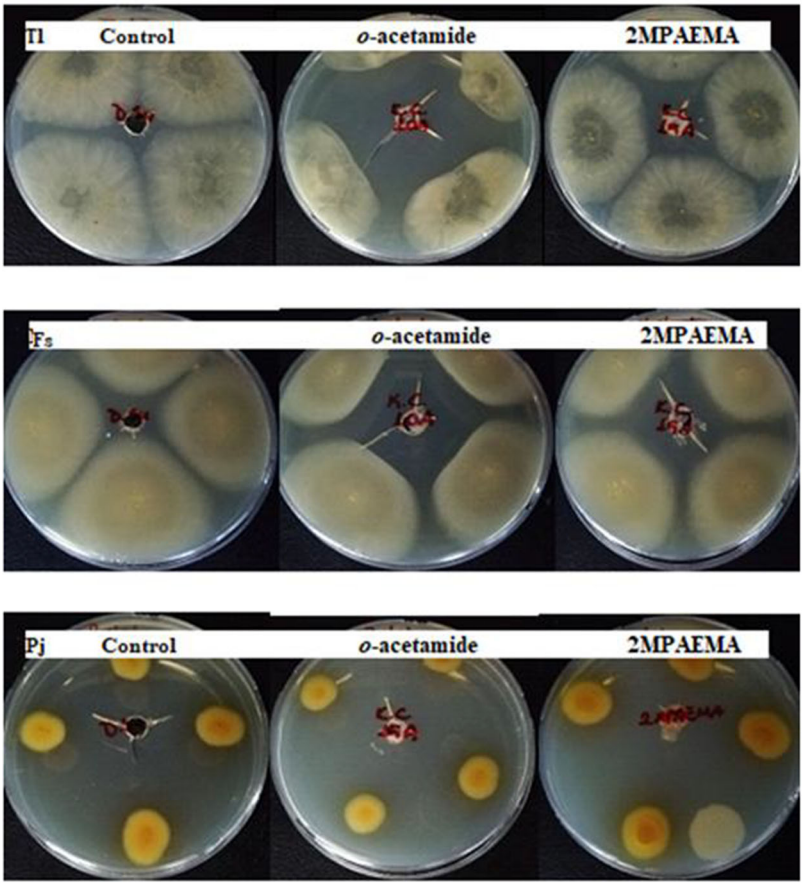

Figure 6. Determinetion of antifungal activity by agar well diffusion method.
Tl: *T. longibrachiatum;* Pj: *P. janthinellum;* Mp: *M. plumbeus.*

Those substances effectively prevent the formation of biofilms and kill bacteria in established biofilms produced by clinical strains including *Acinetobacter baumannii and Pseudomonas aeruginosa,* methicillin-resistant MRSA and *Streptococcus mutans.* Anti-biofilm formation activity of AgNPs was more pronounced on Gram-negative than Gram-positive bacteria although both groups exhibit equal antibacterial activity to the substance.[33] It has been known that bacterial biofilms are important for infections and approximately from 60% to 80% of persistent bacterial infections were found to be associated with biofilms. Quorum-sensing (QS) system is a cell density-dependent method of cell-to-cell communication and maturation of biofilms. Therefore, QS is indirect modes of action by which bacteria are resistant to antibiotics.[34] According to the antibiofilm activity analysis results, the inhibition percentage values of 2MPAEMA and *o*-acetamide on *P. aeruginosa* ATCC 11778 are shown in Table 3. It was determined that 2MPAEMA and *o*-acetamide the tested isolate inhibited biofilm formation at rates ranging 17.50 and 83.75. Decrease *P. aeruginosa* ATCC 11778 of biofilm formation was found with an increase in the concentration % of the 2MPAEMA and *o*-acetamide.

Carboxyle group ionizes to release hydrogen ions from the -COO group resulting in the negatively charged -COO group; this leads to the hydrophilic character of any molecule contained on it. Some functional groups, like the carbonyl group, have a slightly negatively charged oxygen atom which can form hydrogen bonds with water molecules, making the molecule more

Table 3. Inhibition percentage of antibiofilm formation.

Test material (Consantration)	*P. aerouginosa ATCC 27853* (biofilm inhibition%)
5% *o*-acetamide	33.33
10% *o*-acetamide	75.83
20% *o*-acetamide	83.75
5% 2MPAEMA	17.50
10% 2MPAEMA	48.13
20% 2MPAEMA	79.79

Table 4. Antioxidant activity by DPPH.

Test material	Inhibition %
***o*-acetamide**	99.96
2MPAEMA	99.92
Control (Gallicacid)	99.98

hydrophilic *o*-acetamide and 2MPAEMA has stable hydrophilic oxygenated groups, such as -COO, carbonyl (-C = O), which promotes its dispersion into water (Figure 2).[3,12,13,19]

Reactive oxygen species (ROS) are important for the vital activities of an organism, but excessive ROS production causes oxidative stress and chronic diseases like cardiovascular disease, diabetes and cancer. Phenolic compounds are well known for reducing and detoxifying ROS. We have previously determined that MPAEMA has low-toxic antitumor activity according to the results obtained in HeLa cells.[12]

The DPPH may be decreased by accepting an electron or hydrogen in the existence of an antioxidant, widely used to estimate the antioxidant's free-radical scavenging activities. Some polysaccharides can give hydrogen have been shown to decrease the stable radical DPPH to yellow diphenylpicrylhydrazine.[35] In the presented study, we showed that *o*-acetamide and 2MPAEMA had a noticeable effect on scavenging free radicals (Table 4). -COOH, -OH and -NH groups have been reported to be functional groups responsible for antioxidant properties in in-vitro studies.[36] Similarly, in both acrylate derivatives synthesized in this study, it may arise from the -COOH and -NH groups in the antioxidant property structure. These radical scavenging activities have also been shown to be associated with phenolic -OH bond dissociation enthalpy, ionization potential, proton dissociation enthalpy, proton affinity, and electron transfer enthalpy.[37,38] This antioxidant activity may be due either to its ability to scavenge peroxyl radicals or to hydroperoxide reduction. We think that antioxidant activity of *o*-acetamide and 2MPAEMA may originate from phenyl ring and other functional groups (Figure 1).

3.4. Theoretical study

3.4.1. Molecular structure and chemical reactivity analysis

DFT theory is an advanced quantum chemical method that gives very reliable results for synthesis and commercial molecules.[39–42] Geometry optimizations of the *o*-acetamide and 2MPAEMA compounds were carried out by the Density Functional Theory (DFT)[43] and are shown in Figure 7. The total energy of 2MPAEMA was calculated as −860.3085 a.u, and that of *o*-acetamide as −1014.5589 a.u. Thus, it is understood that *o*-acetamide molecule is more stable than 2MPAEMA. Parameters such as the energy of the high occupied molecular orbital (E_{HOMO}), the energy of low the unoccupied molecular orbital (E_{LUMO}), the energy difference between them (E_{gap}), Electron affinity (A), Ionization energy (I), Chemical hardness (η) and softness (S), Electronegativity (A), Chemical potential (μ) and the Electrophilicity index (ω) values were obtained using the TD-DFT/B3LYP/6-311++G (d,p) level of theory and were tabulated in Table 5. Koopman[44] defines closed shell components η, μ, and χ as $\eta = I\text{-}A$, $\mu = (I\text{-}A)/2$, $\chi = (I + A)/2$.

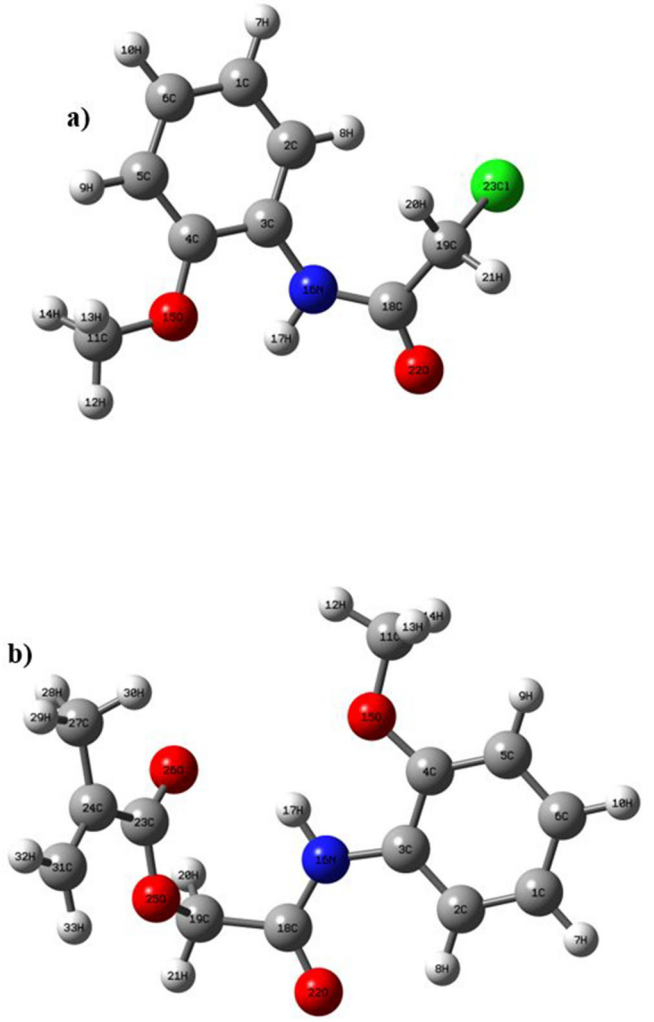

Figure 7. The optimized molecular structures of a) *o*-acetamide b) 2MPAEMA.

Table 5. The calculated energies values of the *o*-acetamide and 2MPAEMA.

C_1symmetry	*o*-acetamide	2MPAEMA
E_{total} (Hartree)	−1014.5589 (a.u)	−860.3085 (a.u)
Dipole moment (Debye)	5.7922	4.2431
E_{HOMO} (eV)	−6.37	−5.95
E_{LUMO} (eV)	−1.32	−1.86
E_{HOMO-1} (eV)	−7.12	−6.72
E_{LUMO+1} (eV)	−0.71	−0.86
$E_{HOMO-1-LUMO+1\ gap}$ (eV)	**−6.41**	**−5.86**
$E_{HOMO-LUMO\ gap}$ (eV)	**5.06**	**4.09**
Chemical hardness (h)	2.53	2.04
Electronegativity (χ)	3.85	3.91
Chemical potential (μ)	−3.85	−3.91
Electrophilicity index (ω)	−2.92	−3.73

Electron affinity and ionization potential can be estimated through HOMO and LUMO orbital energies as A=-E_{LUMO} and I= -E_{HOMO}. The electronegativity and chemical hardness are often used to make chemical reactivity prediction. Also, a molecule with small frontier orbital gap is

named as a soft molecule. Soft molecules are more polarizable and have a high chemical reactivity as well as low kinetic stability.[45,46] The *o*-acetamide molecule is $E_{HOMO} = -6.37$ eV, the $E_{LUMO} = -1.32$ eV, the 2MPAEMA molecule is $E_{HOMO} = -5.95$ eV, $E_{LUMO} = -1.86$ eV. The energy gap value of *o*-acetamide is $E_{gap} = 5.06$ eV, the energy gap of 2MPAEMA is $E_{gap} = 4.09$ eV. Therefore, it can be said that the toxicity and reactivity of the 2MPAEMA is better than the *o*-acetamide. The chemical potential values of *o*-acetamide and 2MPAEMA −3.85 eV and −3.91 eV respectively. It is more stable than *o*-acetamide 2MPAEMA in terms of both energy gap value and chemical potential. Furthermore, since the 2MPAEMA molecule's energy range is smaller than that of *o*-acetamide, 2MPAEMA is softer and better polarized. The contour graphics, 3 D structures and energy values of the HOMOs and LUMOs of the studied molecules are presented in Figure 8(a–b). As can be seen from Figure 8a, while HOMO orbitals of *o*-acetamide molecule spread to all molecules except CH_2 group, LUMO orbitals spread to all molecules except methoxy group. In Figure 8b, the HOMO orbitals of the 2MPAEMA molecule spread to all molecules except the oxoethyl and methacrylate group, while the LUMO orbitals showed the opposite spread. Therefore, it can be said that 2MPAEMA is a chemically more reactive molecule than *o*-acetamide.

3.4.2. NBO analysis

The Natural Bonding Orbital (NBO) method is used to analyze parameters such as chemical reactivity, stability and polarizability for a wide variety of chemical systems, from monomers to complexes.[47,48] This method is based on electron donor (i) (occupied) and electron acceptor (j) (vacant) bonds and the interaction between them with the help of a second order Fock matrix.[49] NBO analysis for the title compounds was performed on the B3LYP/6–311++G(d,p) basis set. The interaction between donor and recipient in NBO analysis is characterized by their stabilization energies $E^{(2)}$. The value of the stabilization energy is proportional to the degree of interaction between the donor and electron acceptor. The larger the $E^{(2)}$ value, the more intense the interaction between the donor and electron acceptor. For this purpose, the interactions of *o*-acetamide and 2MPAEMA compounds are given in Tables 6 and 7, respectively. As seen in the table, the stabilization energy of *o*-acetamide is greater than the stabilization energy of 2MPAEMA for the same molecular orbital interactions. Examples as σ (N16-H17)-σ^* (C18-O22) ($E^{(2)}$=4.89 kcal/mol), π (C4-C5)-π^* (C1-C6) ($E^{(2)}$= 19.26 kcal/mol), LP(1) N16-π^* C18-O22 ($E^{(2)}$ = 65.21 kcal/mol) and π^* (C4-C5)-π^* (C1-C6) ($E^{(2)}$ = 217.32 kcal/mol) can be reproduced. Therefore, with NBO analysis, *o*-acetamide has a more stable structure than 2MPAEMA.

3.4.3. Molecular electrostatic potential (MEP) analysis

The electrostatic molecular potential (MEP) surface, which is helpful in understanding the physicochemical structure of a molecule, provides a three-dimensional graphical representation of the molecule depending on its electron density.[50] In this visual presentation, red (negative) regions show electrophilic reactivity, that is, electron-rich regions, and blue (positive) regions show nucleophilic reactivity, that is, electron accepting regions, and green regions show neutral region, that is, zero potential. MEP studies were carried out using the B3LYP/6-311++G(d,p) basis set and are presented in Figure 9. The color range of the surface is between −9.07 e^{-2} and 9.071 e^{-2}, −8.519 e^{-2} and 8.519 e^{-2} for the molecules *o*-acetamide and 2MPAEMA, respectively. It is seen from Figure 5 that 2MPAEMA has more red in color. This shows that 2MPAEMA is more reactive and electrophilic than *o*-acetamide.

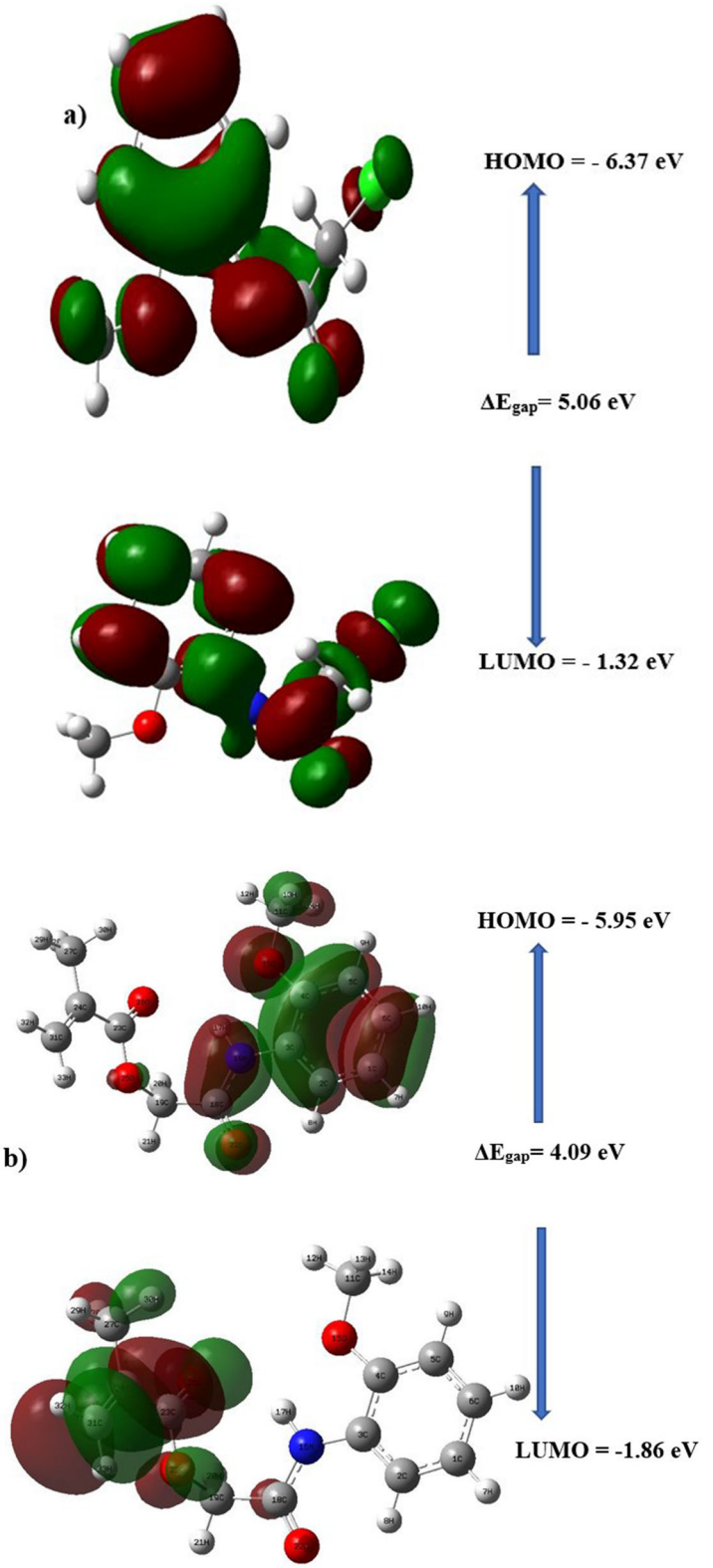

Figure 8. Frontier orbital contour plot a) *o*-acetamide b) 2MPAEMA.

Table 6. Second order perturbation theory analysis of Fock matrix in NBO basis for *o*-acetamide.

Donor (i)	Type	ED/e	Acceptor (j)	Type	ED/e	$E^{(2)a}$ (KJ mol^{-1})	E(j)-E(i)[b] (a.u)	F(i.j)[c] (a.u)
C1-C2	σ	1.96	C2-C3	σ^*	0.03	3.13	1.26	0.056
C1-C2	σ	1.96	C3-N16	σ^*	0.01	4.68	1.11	0.064
C1-C6	σ	1.59	C1-C2	σ^*	0.31	2.74	1.28	0.053
C1-C6	σ	1.59	C2-H8	σ^*	0.35	2.48	1.15	0.048
C1-C6	π	1.97	C2-C3	π^*	0.03	21.02	0.28	0.069
C1-H7	σ	1.97	C5-C6	σ^*	0.03	3.88	1.09	0.058
C2-C3	σ	1.97	C1-C2	σ^*	0.01	2.94	1.29	0.055
C2-C3	σ	1.98	N16-H17	σ^*	0.03	1.57	1.11	0.037
C3-C4	σ	1.98	C2-H8	σ^*	0.02	2.22	1.16	0.045
C3-C4	σ	1.97	N16-C18	σ^*	0.03	2.40	1.15	0.047
C3-N16	σ	1.97	C3-C4	σ^*	0.01	1.02	1.34	0.033
C4-C5	σ	1.98	C3-N16	σ^*	0.03	3.09	1.13	0.053
C4-C5	π	1.98	C1-C6	π^*	0.02	20.01	0.30	0.070
C4-C5	π	1.98	C2-C3	π^*	0.01	17.00	0.29	0.064
C11-O15	σ	1.97	C3-C4	σ^*	0.02	2.42	1.37	0.052
N16-H17	σ	1.97	C2-C3	σ^*	0.02	3.34	1.21	0.057
N16-H17	σ	1.97	C18-022	σ^*	0.02	0.79	1.25	0.028
N16-C18	σ	1.97	C3-C4	σ^*	0.02	0.98	1.37	0.033
C18-C19	σ	1.98	C18-O22	σ^*	0.03	1.00	1.27	0.032
C18-O22	σ	1.71	N16-C18	σ^*	0.31	1.05	1.50	0.036
C18-O22	π	1.71	C18-O22	π^*	0.31	0.81	0.40	0.017
C19-H20	σ	1.72	C18-O22	σ^*	0.31	3.70	1.15	0.058
O15	LP(2)	1.98	C4-C5	π^*	0.02	28.60	0.35	0.095
N16	LP(1)	1.98	C2-C3	π^*	0.02	33.19	0.29	0.074
N16	LP(1)	1.88	C18-O22	π^*	0.47	65.21	0.29	0.114
C4-C5	π^*	1.57	C1-C6	π^*	0.47	217.32	0.01	0.080

Table 7. Second order perturbation theory analysis of Fock matrix in NBO basis for 2MPAEMA.

Donor (i)	Type	ED/e	Acceptor (j)	Type	ED/e	$E^{(2)a}$ (KJ mol^{-1})	E(j)-E(i)[b] (a.u)	F(i.j)[c] (a.u)
C1-C2	σ	1.96	C2-C3	σ^*	0.03	2.96	1.26	0.055
C1-C2	σ	1.96	C3-N16	σ^*	0.01	4.76	1.10	0.065
C1-C6	σ	1.59	C1-C2	σ^*	0.31	2.66	1.28	0.052
C1-C6	σ	1.59	C2-H8	σ^*	0.35	2.22	1.17	0.046
C1-C6	π	1.97	C2 –C3	π^*	0.03	20.20	0.28	0.068
C1-H7	σ	1.97	C5-C6	σ^*	0.03	3.93	1.09	0.058
C2-C3	σ	1.97	C1-C2	σ^*	0.01	2.70	1.29	0.053
C2-C3	σ	1.98	N16-H17	σ^*	0.03	1.98	1.11	0.042
C3-C4	σ	1.98	C2-H8	σ^*	0.02	1.97	1.18	0.043
C3-C4	σ	1.97	N16-C18	σ^*	0.03	2.78	1.16	0.051
C3-N16	σ	1.97	C3-C4	σ^*	0.01	0.89	1.33	0.031
C4-C5	σ	1.98	C3-N16	σ^*	0.03	2.90	1.13	0.051
C4-C5	π	1.98	C1-C6	π^*	0.02	19.26	0.30	0.069
C4-C5	π	1.98	C2-C3	π^*	0.01	16.46	0.30	0.064
C11-O15	σ	1.97	C3-C4	σ^*	0.02	2.28	1.37	0.050
N16-H17	σ	1.97	C2-C3	σ^*	0.02	3.96	1.23	0.062
N16-H17	σ	1.97	C18-022	σ^*	0.02	4.89	1.25	0.028
N16-C18	σ	1.97	C3-C4	σ^*	0.02	1.39	1.37	0.033
C18-C19	σ	1.98	C18-O22	σ^*	0.03	0.63	0.99	0.023
C18-O22	σ	1.71	N16-C18	σ^*	0.31	1.14	1.52	0.038
C18-O22	π	1.71	C18-O22	π^*	0.31	0.58	0.39	0.014
C19-H20	σ	1.72	C18-O22	σ^*	0.31	2.23	1.14	0.045
O15	LP(2)	1.98	C4-C5	π^*	0.02	27.78	0.35	0.094
N16	LP(1)	1.98	C2-C3	π^*	0.02	33.90	0.30	0.090
N16	LP(1)	1.88	C18-O22	π^*	0.47	62.54	0.28	0.119
C4-C5	π^*	1.57	C1-C6	π^*	0.47	204.72	0.01	0.080

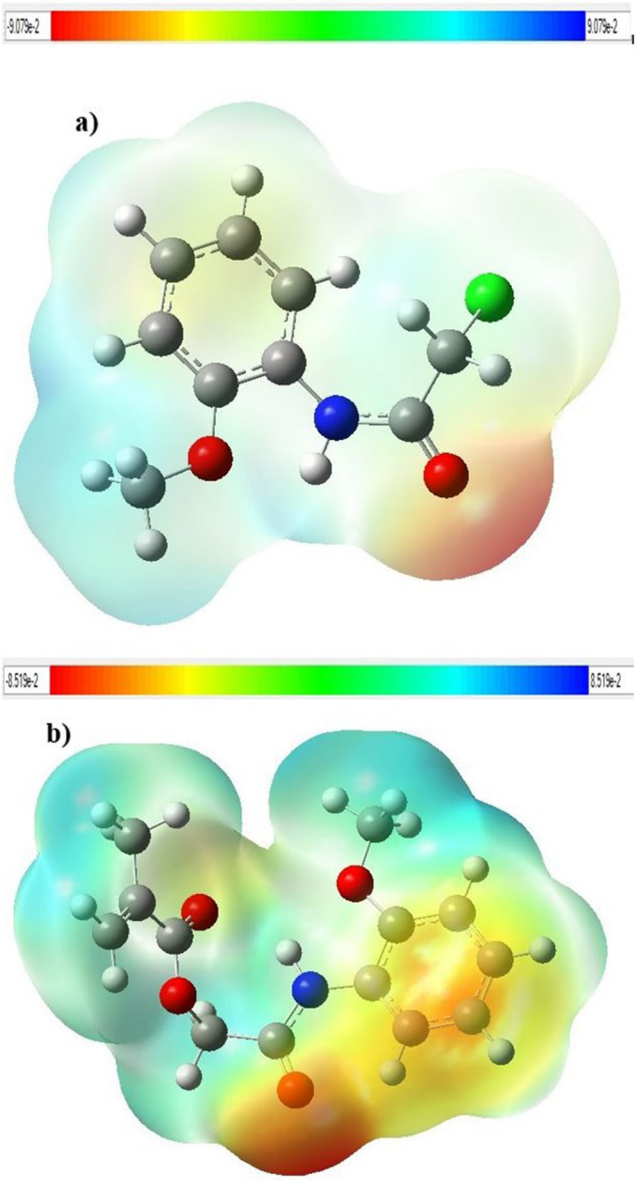

Figure 9. MEP surfaces of the a) *o*-acetamide and b) 2MPAEMA.

4. Conclusions

In this study, 2-chloro-N-(2-methoxyphenyl)acetamide (*o*-acetamide) and 2-(2-methoxyphenylamino)-2-oxoethyl methacrylate (2MPAEMA) were originally synthesized, and characterized by elemental analyses, FT-IR, ^{1}H and ^{13}C NMR spectra techniques. Spectroscopic analyzes showed that the compounds contained functional groups that would exert an antimicrobial effect. It was determined that compounds the biofilm formation of *Pseudomonas aerouginosa* ATCC 27853 inhibited at rates ranging 17.50 and 83.75. This may be due to inhibition of the QS mechanism in bacteria. This study also showed that both 2MPAEMA (99.92%) and *o*-acetamide (99.96%) have high sweeping effect of free radicals. We think that the antioxidant activity originates from functional groups such as the phenyl ring. As a result, acrylide derivatives containing phenyl ring are used in agriculture, especially fungicidal such as the pyrimidinyloxy-phenyl acrylates (USA

patent number 5,633,256). 2MPAEMA and *o*-acetamide with low toxicity and free radicals scavenging effect can be used as fungicidal in agriculture. As a theoretical study, the global reactivity descriptors such as HOMO-LUMO gaps, chemical hardness, electronegativity, chemical potential, electrophilicity index, and NBO, MEB analyzes were performed at the DFT/B3LYP/6-311++G(d,p) level. From all these calculation results, in parallel with the experimental results, it was concluded that the *o*-acetamide compound had greater stability and lower toxicity than the 2MPAEMA compound. In addition, after the other properties of these molecules are determined by *in-vivo* studies, their use in different fields such as agriculture, cosmetics, drug release can be investigated. 2MPAEMA and o-acetamide can be used as a material and may find potential applications. It is hoped that the results will provide further insight into experimental studies on the design as a material and may find potential applications.

Disclosure statement

No potential conflict of interest was reported by the authors.

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