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Synthesis, Characterization, and Antimicrobial Activities of Multifunctional Acridone Derivatives

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Abstract: The synthesis and antimicrobial application of acridone derivatives have been reported in this work. Despite the huge progress in the development of acridone and acridine-based drugs, drug resistance is on the rise hence the need to adopt new strategies for the development of more aggressive drugs. In pursuance of this principle, we have designed and developed two new bifunctional compounds **M2** and **M3** that have both the acridone and acridine moieties incorporated as one compound. This is due to the need to harness the combined synergistic effect obtainable from both the acridone and the acridine motifs. The synthesized compounds were characterized using FT-IR, NMR, and Mass Spectrometry and later screened for antimicrobial activities against three gram-negative bacteria *Escherichia coli (E-Coli), Klebsiella pneumoniae (Kleb), and Pseudomonas aeruginosa (pseudo)*, one gram-positive bacteria *Staphylococcus aureus (Staph)* and two Fungi *Mucor species* and *Aspergillus niger*. The antimicrobial test was conducted using disc diffusion methods and based on the concentrations of 100, 200, 300, and 400 µg/ mL, significant activities were recorded for both compounds for example *Klebsiella pneumonia* showed good antimicrobial activities with an inhibition zone of 15-24 mm. The result of antimicrobial activities indicates that compound **M3** has strong activity against afore mentioned microorganisms.

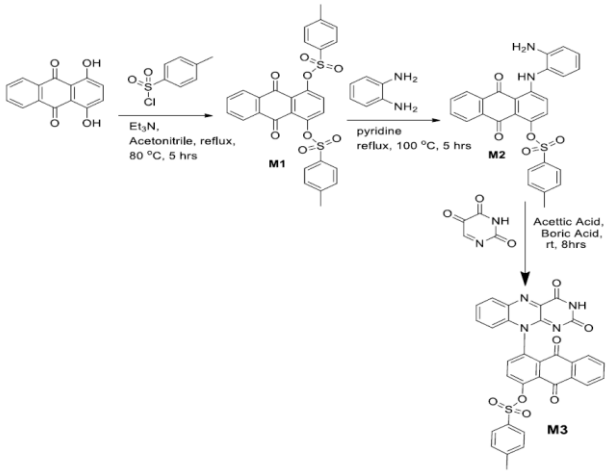
Keywords: acridone derivatives; acridines; multifunctional compounds; antimicrobial; synthesis

1. Introduction

Literature has shown that the development of new drugs based on either acridine or acridone is on the rise.[1] And this is even though the work on these two important classes of organic compounds dates back to the 1880s.where 9-acridanone was synthesized by Carl Grabe and Heinrich Caro in Germany and later named acridone in 1892.[2,3] Acridone is usually insoluble in benzene, chloroform, ether, water, and ethanol but soluble in N, N -dimethylformamide (DMF), and dimethylsulfoxide (DMSO).[3] The planar shape allows acridone to intercalate between DNA bases disrupting the intermolecular bonding networks of the DNA molecule.[4] Hence, acridone-based compounds are regarded to have chemotherapeutic properties.[5] Based on this, acridone derivatives represent a large group of biologically active compounds with activities ranging from antitumor, and anticancer to antiviral and antimalarial properties.[6] Numerous naturally occurring acridones have been isolated and studied for their biological activities, some well-recognized naturally occurring cytotoxic acridone-based compounds include acronycine[4,7] and glyfolide.[8,9] These compounds have been studied and structurally amended to increase their potency and solubility for clinical applications as anticancer drug candidates.[10]

On the other hand, acridine compounds is known ever since the 19th century when they were isolated from crude anthracene, one of them was named acridine (which means sharp and painful) due to its itching and inflammatory properties.[11] The correct structure of acridine was established by Carl Riedel, who also established quinoline, and pyridine structure relationships.[5] Acridine undergoes several reactions such as nucleophilic addition, electrophilic substitution, oxidation, reduction, reductive alkylation, and photo alkylation.[12,13] The synthesis of acridine and its derivatives has attracted large attention from organic and medicinal chemists for many years, as several natural sources have been reported to have this heterocyclic nucleus.[12] Examples of acridine-based drugs include Amsacrine,[14] Acronycine,[7,15] and Nitracrine.[3] And those in the clinical trials include asulacrine, DACA, Pyrazoloacridine and Imidazoacridones.[16-19]

However, despite the huge progress in the development of acridone and acridine-based drugs, drug resistance is on the rise hence the need to adopt new strategies for the development of more aggressive drugs. And to the best of our knowledge, there is no report on the synthesis of these novel acridone derivatives as well as their biological application.



Scheme 1. Synthetic route to target compounds

2. Results and Discussions

2.1. Synthesis

All the compounds were prepared by a modified procedure of Csuk *et al.*[20] Compound **M1** was prepared by stirring (10 and 30 mmol) equivalent of the 1,4- dihydroxyanthraquinone and 4-toluenesulphonyl chloride with triethylamine in acetonitrile for 5 hrs. Compound **M2** was prepared by stirring (5 and 15 mmol) equivalent of the 1,4- ditosyloxy-9,10-anthraquinone and O-Phenylenediamine in pyridine for 4 hrs at 100℃. And compound **M3** was prepared by stirring 1-(1,2-phenylene diamine)-4-(tosyloxy) anthraquinone and Alloxane monohydrate (1 mmol each) synthetic procedure are presented in (Scheme. 1). Compound **M1** was isolated in excellent yield 82%, compound **M2** afforded only 21% yield while Compound **M3** yields only 10.5%. Compound **M1** appeared as bright yellow crystalline solid, compound **M2** was isolated as red crystalline solid, and compound **M3** was isolated as yellow crystalline solid. All the Compounds were stable in air and soluble in dichloromethane, chloroform, ethyl acetate and DMSO.

2.2. Spectroscopic analysis

The proton NMR spectrum of **M1** confirmed the formation of the compound this is because all the expected signals and protons were accounted for. For instance, the singlet protons at δ 2.40 ppm (6H) were assigned to the two methylene (CH_3) groups in the tosyl ring, similarly, a downfield shift was seen around 7.32-8.02 ppm due to the aromatic protons. Other reasons are the observed peaks at δ 7.73 ppm (dd, 4H) which is due to CH=C-CH_3, and the 7.84 ppm (dd, 4H) aromatic C-H due to CH=C-S. The signal at δ 7.50 ppm (d, 2H) aromatic C-H was assigned to CH=C-O, δ 8.02 ppm (d, 2H) aromatic C-H due to CH=C-C, δ 7.32 ppm (d, 2H) aromatic C-H due to CH=CH. Similarly, the ^{13}C NMR data of the compound further confirmed the synthesis of **M1**. The peak at 21.67 ppm was assigned to CH_3 in the tosyl ring, while the peak at 180.1 ppm is a peak due to C=O, other peaks are aromatics peaks such as 145.96 ppm, 130.58 ppm, 128.92 ppm, 133.36 ppm, 146.12 ppm, 126.84 ppm, 128.39 ppm, 134.02 ppm, 129.85 ppm, and 132.25 ppm.

Furthermore, the FTIR spectra of **M1** showed absorption bands at 2925.08 cm^{-1} and 3099.11 cm^{-1} indicating Sp^3 and Sp^2 C-H respectively. Other absorptions bands are absorptions at 1702.59 cm^{-1} and 1112.12 cm^{-1} corresponding to C=O and C-O stretching bands respectively, a week band at 1609.85 cm^{-1} indicates the presence of the C=C absorption band. All results are in agreement with similar reports in the literature.[21-23] The HRMS m/z value calculated for $C_{28}H_{20}O_8S_2$ was 548, the experimental value found 547.3 which corresponds to the loss of a proton. These figures confirmed the formation of the product. The melting point of the compound was found to be 159-162.

Similarly, the proton NMR spectrum of **M2** is expected to reveal 20 protons and all the protons were accounted for except for the NH and NH_2 protons. And this is due to the higher rate of proton exchange on amino groups as a result of the higher electronegativity of a nitrogen atom; this means that the proton stays for a very short time so neighbouring protons cannot feel their spin orientations.[24] The upfield shift indicates the appearance of a singlet peak at δ 2.38 ppm due to the (CH_3) methylene group in the tosyl ring. The aromatic protons were seen downfield around 6.50-8.02 ppm. However, several attempts to record the ^{13}C NMR data prove abortive due to an inadequate sample. Meanwhile, the FT-IR spectrum of **M2** displays absorptions bands at 3400 cm^{-1}, 3349 cm^{-1} corresponding to N-H (secondary Amines) and N-H (Primary Amines) respectively, and the absorptions at 2925 cm^{-1} and 3099 cm^{-1} are due to Sp^3 and Sp^2 C-H respectively, other absorptions noted were C=O absorption at 1699 cm^{-1} and C=C absorption at 1614 cm^{-1} the C-O stretching bands were seen at around 1111 cm^{-1} all results are in agreement with similar reports in the literature.[21-23] The HRMS m/z value calculated for $C_{27}H_{20}N_2O_5S$ was 484, the experimental values found 485.2 which corresponds to [M+1]. The melting point of the compound was found to be 127-130℃.

The proton NMR spectrum of **M3** also confirmed the formation of the compound. Generally, 18 protons were expected and all the protons were accounted for. For instance, the singlet protons at around δ 2.33 ppm (3H) assigned to the methylene (CH_3) groups in the tosyl ring, a downfield shift was noted for the N-H around δ 11.50 ppm and the aromatic protons around δ 6.90-8.50 ppm. Similarly, the ^{13}C NMR data further confirmed the synthesis of the compound. For instance, the peak at δ 21.8 ppm was assigned to CH_3 in the tosyl ring, the downfield shifts were noted, the peak around δ 170-180 ppm is a peak due to C=O, other aromatics peaks such as 123.54 ppm, 130.21 ppm, and 145.12 ppm were all accounted for. Furthermore, The FTIR spectrum of **M3** showed absorption bands at 3374.20 cm^{-1}, 1758.88 cm^{-1}, and 1143.24 cm^{-1} corresponding to N-H, C=O, and C-O stretching bands respectively. Other absorption bands observed at 2951.91 cm^{-1} are typical of sp^3 C-H bond stretching bands. A week band at 1684.82 cm^{-1} indicates the presence of an aromatic C=C absorption band. All results are in agreement with similar reports in the literature.[21-23] The m/z value calculated for $C_{31}H_{18}N_4O_7S$ was 590, and the experimental value was found to be 591.2 which correspond to (M+1). These figures confirmed the formation of the product. The melting point of the compound was found to be 135-137.

Table 1. Antimicrobial Assay of compounds **M1-M3**

Organisms	Concentration (µg/mL)												STD
	M1				M2				M3				
	100	200	300	400	100	200	300	400	100	200	300	400	
Staphylococcus aureus	NA	NA	NA	NA	11	15	16	18	18	15	11	16	23
Pseudomonas aeruginosa	11	10	11	9	13	13	14	16	17	19	18	14	25
Klebsiella pneumonia	15	10	21	17	20	24	21	12	16	19	15	24	26
Escherichia coli	6	10	7	10	10	12	11	10	11	6	8	8	32
Mucor specie	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11
Aspergillus niger	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
Chloroform	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Ethyl acetate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	

2.3. Antimicrobial Activities

The synthesized compounds were screened for in vitro antimicrobial activities against three-gram negative *Escherichia Coli (E-coli), Klebsiella Pneumoniae (K. Pneumoniae)* and *Pseudomonas aeruginosa gram-positive* positive *Staphylococcus aureus* (*S.aureus*) bacteria strains. The test was conducted using disc diffusion methods because of its affordability ease of work, efficiency, and convenience.[25] The stock solution was prepared by dissolving 5 mg of the samples in 5 mL of chloroform and ethyl acetate solvent. A serial dilution of different concentrations of 100 µg/mL, 200 µg/mL, 300 µg/mL and 400 µg/mL was then prepared from the stock. The solvent chloroform and ethyl acetate were used as negative control and the standard antibacterial drug Ciprofloxacin (CPX) 10 µg/disc was used as a positive control for comparison of activities with the synthesized compounds. The bacteria were sub-cultured in the Muller Hilton agar medium. Whatman filter paper discs of size 6 mm diameter were sterilized in an autoclave and then soaked in the chosen concentration of the compounds and placed in the Petri dishes containing the Muller Hilton agar media seeded with the respective bacteria strain. The culture was then incubated in an oven at 37℃. The diameters of the zones of inhibition were measured after 24 hours of incubation. The antimicrobial activities were calculated as an average of three replicates (Table 1). The zones of inhibitions were measured using a ruler in millimeters (mm). The antimicrobial activities were calculated as an average of three replicates (Table 1). The zones of inhibitions were measured using a ruler in millimeters (mm), and the following criteria were adopted. Strong activity (> 14 mm), moderate activity (9–14 mm), weak activity (5–8 mm), NA; no activity (inhibition zone < 5 mm), solvent: Chloroform and Ethyl acetate.[26,27]

In Compound **M1** (Table 1), at 100 µg/mL the compound shows strong activity against *Klebsiella pneumonia*, moderate activity against *Pseudomonas aeruginosa,* and weak activity against *Escherichia coli*, while, at 200 µg/mL the compound shows moderate activity against *Klebsiella pneumonia*, *Pseudomonas aeruginosa,* and *Escherichia coli*, however, at 300 µg/mL the compound shows strong activity against *Klebsiella pneumonia*, moderate activity against *Pseudomonas aeruginosa* and weak activity against *Escherichia coli*, furthermore at 400 µg/mL compound shows strong activity against *Klebsiella pneumonia*, moderate activity against *Pseudomonas aeruginosa* and *Escherichia coli*, whereas no activity was recorded against *Staphylococcus aureus, Mucor species* and *Aspergillus niger*. All results are in agreement with similar reports in the literature.[27,28]

In Compound **M2** (Table 1,) at 100 µg/mL the compound shows strong activity against *Klebsiella and pneumonia*, and moderate activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and *Escherichia coli*, while at 200 µg/mL the compound shows strong activity against *Klebsiella pneumonia* and *Staphylococcus aureus*, moderate activity against *Pseudomonas aeruginosa* and *Escherichia coli*. However, at 300 µg/mL the compound shows strong activity against *Klebsiella pneumonia, Staphylococcus aureus* and *Pseudomonas and aeruginosa*, and moderate activity against *Escherichia coli*, furthermore, at 400 µg/mL the compound shows strong activity against *Klebsiella pneumonia* and *Staphylococcus aureus*, moderate activity against *Pseudomonas aeruginosa* and *Escherichia coli*, whereas no activity was recorded against *Mucor species* and *Aspergillus niger*. All results are in agreement with similar reports in the literature.[29,30]

In Compound **M3** (Table 1), at 100 µg/mL the compound shows strong activity against *Klebsiella pneumonia*, *Staphylococcus aureus* and *Pseudomonas aeruginosa,* moderate activity against *Escherichia coli*, while at 200 µg/mL the compound shows strong activity against *Klebsiella pneumonia*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, weak activity against *Escherichia coli*. However, at 300 µg/mL the compound shows strongactivity against *Klebsiella pneumonia* and *Pseudomonas aeruginosa* and moderate activity against *Staphylococcus aureus* and *Escherichia coli*, furthermore, at 400 µg/mL compound shows strong activity against *Klebsiella pneumonia, Staphylococcus aureus* and *Pseudomonas aeruginosa* and moderate activity against *Escherichia coli*. Whereas no activity was recorded against *Mucor species* and *Aspergillus niger*. All results are in agreement with similar reports in the literature.[27,28]

3. Experimental

3.1. General information

All reactions were performed using standard procedure; all chemicals were purchased from Sigma-Aldrich and used without further purification. Progress of the reaction was monitored by TLC using ethyl acetate. All solvents were dried and purified using standard procedures before use. Glassware was dried in an oven at 120℃. Pure cultures of all experimental bacteria and fungi were obtained from Federal Teaching Hospitals Gombe. The pure bacterial cultures were maintained on nutrient agar (NA) medium and fungal culture on potato dextrose agar (PDA) medium. Each bacterial and fungal culture was further maintained by sub-culturing regularly on the same medium and stored at 4℃ before use in experiments (Sen and Batra, 2012). Infrared spectra were recorded on a Perkin Elmer universal ATR Spectrum 100 FT-IR spectrometer, melting points (m.p)

were determined using Veego microprocessor-based programmable melting point apparatus, in open capillaries, Mass spectrometry was recorded on Waters Micromass LCT Premier TOF MS-ES$^+$, ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-II 400 MHz spectrometer at ambient temperature with tetramethylsilane (TMS at 0.00 ppm) as an internal standard. All chemical shifts are quoted in δ (ppm). Abbreviations used for the multiplicity of the NMR signals are s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of the doublet. Thin Layer Chromatography (TLC) was carried out on Machery-Nagel Polygram Sil/G/UV254 pre-coated plates.

3.2. Procedure for the synthesis of the compounds

3.2.1. Synthesis of (1,4-ditosyloxy-9,10-anthraquinone) ***M1***

Into a round-bottomed flask containing 1,4-dihydroxyanthraquinone (2.40 g, 10 mmol) and 4-toluenesulphonyl chloride (5.72 gm, 30 mmol) acetonitrile (50 ml) was added and the mixture was allowed to stir for 5 minutes. Triethylamine (4.04 gm, 40 mmol) was slowly added and the reaction was heated to reflux for 5 hours. The second amount of triethylamine (4.04 g, 40 mmol) was added and allowed to stir overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, dissolved in chloroform (50 ml,) and washed with two equivalents of acidic water (100 ml) After two further washes, the organic layer was isolated and dried with Na_2SO_4, a yellow crystalline solid was produced and isolated by filtration under reduced pressure to yield the crude 1,4-ditosyloxy-9,10-anthraquinone as a bright yellow crystalline solid of **M1**. The progress of the reaction was monitored by TLC using ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 ppm (s, 6H), δ 7.73 (dd, 4H), δ 7.84 ppm (dd, 4H), 7.50 ppm (d, 2H), 8.02 ppm (d, 2H), 7.32 ppm (d, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): 180.1, 146.12, 145.96, 134.02, 133.36, 132.25, 130.58, 129.85, 128.92, 128.32, 126.84, 21.67; FT-IR. (KBr) cm^{-1}: 3099.11 (Sp^2 C-H stretch), 1705.59 (C=O stretch), 1609.85 (C=C aromatic stretch), 1112.12 (C-O stretch); HRMS (ESI) calculated for $C_{28}H_{20}O_8S_2$ was 548; found: 547.3 (M-H).

3.2.2. Synthesis of 1-(1,2-phenylene diamine)-4-(tosyloxy) anthraquinone ***M2***

Into a round-bottomed flask containing 1,4-ditosyloxy-9,10-anthraquinone (2.74 gm, 5 mmol) and O-Phenylenediamine (1.62 gm, 15 mmol), pyridine (20 ml) was added and the reaction mixture was heated to reflux for 4 hrs at 100℃. Upon cooling, the solvent was evaporated to dryness under reduced pressure, dissolved in a minimum amount of hot ethyl acetate, and purified by column to give a red crystalline solid. The progress of the reaction was monitored by TLC using ethyl acetate.

^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (s, 3H), 7.82 (d, 2H), 8.02 (s, 4H), 7.01 (s, 2H), 7.47 (s, 1H), 6.51 (s, 1H), 7.31 (s, 1H), 6.79 (s, 1H), 8.22 (s, 2H); ^{13}CNMR ($CDCl_3$): 21.3, 138.2, 130.3, 126.7, 132.4, 146.8, 120.2, 123.9, 135.5, 116.8, 122.9, 133.6, 126.8, 132.1, 129.5, 132.4, 119.0, 115.2, 139.3,138.8 and 182.1; FT-IR (KBr) cm^{-1}: 3700.00 (N-H stretch 2^0), 3801 (N-H stretch 1^0), 3092.10 (Sp^2 C-H stretch), 1705.59 (C=O stretch), 1614.33 (C=C aromatic stretch), 1111.85 (C-O stretch); HRMS (ESI) calculated for $C_{27}H_{20}N_2O_5S$ was 484; found: 485.2 (M+H).

3.2.3. Synthesis of (1-benzo[g]pteridine-4-tosyloxy-9,10-antraquinone) ***M3***

Into a round-bottomed flask containing [1-(1,2-phenylene diamine)-4-(tosyloxy) anthraquinone] (0.5 g, 1 mmol) acetic acid (10 ml) was added followed by alloxan monohydrate (0.16 g, 1 mmol) and boric acid (0.06 g, 1 mmol), the reaction mixture was allowed to stir overnight at room temperature. Upon evaporating the solvent, an orange crystalline solid was obtained and upon carrying out the TLC of the product in 100% ethyl acetate, two different spots were revealed upon purification by column chromatography, and compound **M3** was isolated as a yellow crystalline solid (0.06 g, 10.5 %). The progress of the reaction was monitored by TLC using ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (s, 3H), 7.65 (d, 2H), 7.79 (s, 4H), 7.12 (s, 2H), 7.39 (s, 1H), 7.80 (s, 1H), 8.58 (s, 1H), 6.90(s, 1H), 7.37 (s, 2H) 7.70 (d, 1H), 7.76 (d, 1H) and 11.58 (s, 1H); ^{13}CNMR ($CDCl_3$): 21.75, 140.38, 132.13, 130,31, 133.04, 142.51, 123.54,128.87, 133.76, 119.56, 181.50, 171.23, 134.02, 130.56, 132.27, 126.81, 145.47, 151.53, 141.43, 138.58, 129.71, 128.26, 132.68, 125.72; FTIR (KBr) cm^{-1}: 3799.11 (N-H stretch 2^o), 2951.91 (Sp^3 C-H stretch), 1758.88 (C=O stretch), 1684.82 (C=C aromatic stretch), 1143.24 (C-O stretch); HRMS (ESI) calculated for $C_{31}H_{18}N_4O_7S$ was 590; found: 591.2 [M+H].

3.3. Procedure for Antibacterial Screening

The agar disc diffusion method was adopted for the antibacterial susceptibility test with slight modification.[29] Briefly, clinical isolates of *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Staphylococcus aureus, Mucor species* and *Aspergillus Niger* were incubated overnight in nutrient agar (NA) (40 gm/L) prepared according to manufacturer's standard. The cultures were standardized using 0.5 McFarland turbidity standards. About 25 mL of sterilized Mueller Hinton agar was poured into 100 mm petri dish and allowed to solidify. 100 µL inoculums size of microbes containing approximately 1 x 106 cfu/mL was smeared unto agar surfaces. Punched sterile filter paper discs impregnated with extracts at 100 µg/mL, 200 µg/mL, 300 µg/mL and 400 µg/mL were placed on the agar surface together with standard commercially manufactured discs of ciprofloxacin at 10 µg/disc. The plates were incubated overnight at 37℃ for bacteria. After 24 hrs plates were examined for inhibition zones.[30] All determinations were carried out in duplicates.

4. Conclusions

In the present research work, we have successfully designed and synthesized three substituted acridone derivatives (1,4-ditosyloxy-9,10-anthraquinone) **M1**, 1-(1,2-phenylene diamine)-4-(tosyloxy) anthraquinone **M2** and (1-benzo [g] pteridine-4-tosyloxy-9,10-antraquinone) **M3**. All the synthesized compounds were confirmed by spectral data performed by FT-IR, NMR, and Mass Spectrometry. Furthermore, all the 3 compounds were screened for antimicrobial activities against three gram-negative bacteria *Escherichia Coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and one gram-positive bacteria *Staphylococcus aureus* and two Fungi *Mucor species* and *Aspergillus niger*. The antimicrobial test was conducted using the agar disc diffusion method at concentrations of 100, 200, 300 and

400 µg/mL. Significant activities were recorded for all the compounds with **M3** being the most promising candidate after recording higher activity against all the selected microorganisms.

Supporting Information

NMR, FT-IR and Mass spectra of the compounds are provided in the supporting information.

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Conflicts of Interest

The authors declare no conflict of interest.

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