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Synthesis and Antibacterial Activity of Aromatic Diacetates

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ABSTRACT

The need to discover new generation of antibiotics with novel mechanism of action has continued to be of paramount importance due to the growing cases of resistant strains of bacterial species. In this work, some known aromatic diacetates were synthesised and characterised using NMR and FTIR spectroscopic techniques. The obtained compounds were subjected to in vitro susceptibility test using a disc diffusion method, and the minimum inhibitory concentration (MIC) of the compounds was also evaluated. Further testing for minimum bactericidal concentration (MBC) for the active compounds was also carried out. The susceptibility test recorded in comparison with a standard drug (ciprofloxacin) showed that all the compounds exhibited high activities against the organisms at 1,000 µg/ml except compound 2d which had no activity on Bacillus megaterium. The highest zone of inhibition of Staphylococcus aureus, Bacillus subtilitis, Bacillus megaterium, Pseudomonas aeruginosa, Escherichia coli, and Salmonella typhimurium were found to be 34 mm, 24 mm, 25 mm, 36 mm, 28 mm, 36 mm respectively. While, the lowest MIC and MBC values of 15 µg/ml were found for some of the compounds against some of the bacterial species.

التخليق والفاعلية ضد البكتيريا لمركبات ثنائية الاسيتات الاروماتية

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الكلمات المفتاحية:
ثنائية الاسيتات الاروماتية.
النشاط المضاد للبكتيريا.
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الحد الأدنى للتركيز المثبط.
الحد الأدنى للتركيز القاتل للبكتيريا.

الملخص

ظلت الحاجة لاكتشاف جيل جديد من المضادات الحيوية ذات آلية عمل مبتكرة ذات أهمية قصوى بسبب تزايد حالات السلالات البكتيرية المقاومة. في هذا العمل، تم تحضير وتشخيص بعض ثنائيات الأسيتات الرومانية المعروفة باستخدام تقنيات مطيافية الرنين النووي المغناطيسي (NMR) ومطيافية الأشعة تحت الحمراء بتحويل فوريه (FTIR). ثم اختبرت المركبات المحضرة باختبار الحساسية في المختبر باستخدام طريقة انتشار القرص، كما تم تحديد الحد الأدنى للتركيز المثبط (MIC) والحد الأدنى للتركيز القاتل للبكتيريا (MBC). بالإضافة إلى ذلك، تم إجراء اختبار إضافي لل MBC للمركبات النشطة. أظهر اختبار الحساسية، المُسَجَّل بالمقارنة مع دواء قياسي (سيبروفلوكساسين)، أن جميع المركبات أظهرت فعالية عالية ضد الكائنات الدقيقة عند تركيز 1000 ميكروغرام/مل، باستثناء المركب d2 الذي لم يظهر أي نشاط على الباسيلوس ميغاتيريوم. وجد أن أعلى قطر لمنطقة تثبيط المكورات العنقودية الذهبية، العصوية الرقيقة، الباسيلوس ميغاتيريوم، الزائفة الزنجارية، الإشريكية القولونية، والسالمونيلا التيفيموريوم كان 34 ملم، 24 ملم، 25

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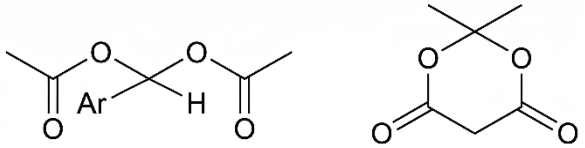
ملم، 36 ملم، 28 ملم، 36 ملم على التوالي. بينما تم الحصول على أقل قيم لل MIC ولل MBC بلغت 15
ميكروغرام/مل لبعض هذه المركبات ضد بعض الأنواع البكتيرية.

1. Introduction

The continuous rise in antibiotic resistance presents a global threat, reducing the effectiveness of the existing antibiotics against various bacterial infections. An alarming resistance rates among prevalent bacterial pathogens has recently been highlighted by the 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report. It revealed a median reported rate for third-generation cephalosporin-resistant *Escherichia coli* (42%) and methicillin-resistant *Staphylococcus aureus* (34%) in 76 countries. Also, in the case of urinary tract infections caused by *Escherichia coli*, it showed that 1 in 5 cases demonstrated reduced susceptibility to standard antibiotics such as ampicillin, co-trimoxazole, and fluoroquinolones in 2020 [1]. Thus, the need for the discovery of new antibiotics is of paramount importance. Recent progress in the discovery of new antibacterial agents involves the exploration of various chemical scaffolds such as 1,3-oxazines, 3-alkylidene-2-indolone derivatives, polyalthic acid analogs, quinoline analogues, indoline-dione derivatives, 3-(4,5-diphenyl-1H-Imidazol-2-yl)-1H-indole derivatives, heteroaryl (aryl) thiazole derivatives, aminothiazole hybrids, Michael type adducts, 2-thiomethyl-benzimidazole, derivatives, 1,2,3-triazole glycoside clickamers, flavone derivatives, 1,2,4-triazoles and 1,3,4-oxadiazoles, 1,2,4-triazolo thiadiazine derivatives, benzoxazin-3-one derivatives, quinoline-8-ol derivatives, ouble-tailored acyclo C-Nucleosides, bisimidyl sulfonamide ketone, phthalazine derivatives, and 4-aminoantipyrine derivatives [2-21]. In continuation of our search for biologically active small molecules, we decided to explore the antibacterial potential of some aromatic diacetates which possess some structural similarity with Meldrum's acid (Fig. 1a). Meldrum's acid is a cyclic diacetate in which the two carboxylate groups are connected by a methylene and quaternary carbons (Fig. 1b). Derivatives of Meldrum's acid have been reported to have a wide spectrum of biological activities. Thus, this continued to attract the attention of medicinal chemists in drug design [22]. Hence, in this work, some known aromatic diacetates were synthesised and for the first time evaluated their activity against six bacterial species *in vitro*.



a **b**

Fig. 1. Structures of (a) Diacetate motif (b) Meldrum's acid

2. Materials and Methods

All reagents and solvents used in this work were obtained from Sigma-Aldrich (Darmstadt, Germany). NMR spectroscopic analysis was recorded on Bruker AVANCE 400 MHz, while FTIR spectra were recorded on a Perkin–Elmer BX spectrophotometer. Melting points were determined on electrothermal IA 9100.

2.1 General Procedure for the Preparation of Aromatic Diacetates, 2a-h

A mixture of aldehyde (10 mmol), acetic anhydride (40 mmol), and powdered H_2SO_4-silica as catalyst (3 mg, 1 mol %) was stirred at room temperature. The reaction was monitored by TLC until completion. After completion, the catalyst was filtered by washing with ethyl acetate. The collected organic layers were further treated with saturated $NaHCO_3$ solution (3 × 10 mL), water (10 mL), and finally dried with anhydrous Na_2SO_4. The solvents were removed *in vacuo* and the products recrystallized from ethyl acetate/hexane mixture (1:1) to afford the pure compounds, **2a-h** [23].

Phenylmethylene diacetate, 2a

White crystal; 92% yield; mp 45-46 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.13 (6H, s, CH_3), 7.41 (3H, m, Ar-H), 7.52 (2H, m, Ar-H), 7.68 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.79, 89.68, 126.66, 128.59, 129.74, 135.48, 168.76; FTIR 1751.85, 1498.39, 1237.48 cm^{-1}.

(4-Chlorophenyl)methylene diacetate, 2b

White crystal; 94% yield; mp 83-84 ˚C; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm 2.12 (6H, s, CH_3), 7.37 (2H, d, *J* = 12, Ar-H), 7.45 (2H, d, *J* = 8 Ar-H), 7.63 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.90, 89.16, 128.26, 128.94, 134.09, 135.79 168.80 ; FTIR 1736.94, 1416.3, 1058.56 cm^{-1}.

(4-Hydroxyphenyl)methylene diacetate, **2c**

White crystal; 96% yield; mp 63-64 ˚C; ^{1}H NMR (400 MHz, CDCl3) δ ppm 2.12 (6H, s, CH_3), 5.30 (s, -OH), 6.98 (2H, d, *J* = 12, Ar-H), 7.63 (1H, s, CH), 7.89 (2H, d, *J* = 8 Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.90, 89.00, 116.00, 127.16, 128.59, 159.99, 168.80; FTIR 3354.60, 1736.94, 1505.84, 1058.56 cm^{-1}.

(4-(Trifluoromethyl)phenyl)methylene diacetate, **2d**

White Crystal; 93% yield; mp 52-53 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.12 (6H, s, CH_3), 7.37 (2H, d, *J* = 8, Ar-H), 7.45 (2H, d, *J* = 12 Ar-H), 7.63 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.00, 21,41 89.91, 126.73, 129.32, 132.7, 139.92, 168.95 ; FTIR 1759.30, 1520.75, 1326.93 1118.20 cm^{-1}.

(4-Methylphenyl)methylene diacetate, **2e**

White Crystal; 95% yield; mp 62-63 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.12 (6H, s, CH_3), 2.37 (3H, s, CH3), 7.22 (2H, d, *J* = 8, Ar-H), 7.41 (2H, d, *J* = 8 Ar-H), 7.64 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.00, 21.41 89.91, 126.73, 129.38, 132.71, 139.92, 168.95; FTIR 1736.93, 1565.48, 1058.56 cm^{-1}.

(3-Nitrophenyl)methylene diacetate, **2f**

Yellowish Crystal; 97% yield; mp 66-67 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.16 (6H, s, CH_3), 7.62 (1H, t, *J* = 8, Ar-H), 7.72 (1H, s, CH) 7.83 (1H, d, *J* = 8 Ar-H), 8.27 (1H, d, *J* = 8 Ar-H), 8.39 (1H, s, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.82, 88.41, 121.95, 124.64, 129.86 , 133.04, 137.59, 148.40, 168.69 ; FTIR 1751.85, 28.21, 1349.30 1192.75 cm^{-1}.

(4-Methoxyphenyl)methylene diacetate, 2g

Pale yellow oily; 95% yield; mp 63-64 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.08 (6H, s, CH_3), 3.71 (3H, s, OCH_3), 6.86 (2H, d, *J* = 8 Ar-H), 7.4 (2H, d, *J* = 8 Ar-H), 7.5 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.36, 55.12, 89.36, 113.9, 127.49, 129.55, 131.5, 168.95; FTIR 1766.70, 1513.30, 11155.42 1021.29 cm^{-1}.

(4-Hydroxy-3-methoxyphenyl)methylene diacetate, **2h**

White powder; 96% yield; mp 64-65 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.12 (6H, s, CH_3), 2.32 (3H, s, OCH_3), 3.86 (1H, OH), 7.02 (1H, d, *J* = 8 Ar-H), 7.06 (1H, d, *J* =8 Ar-H) 7.12, (1H.s, Ar-H) 7.65 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.04, 55.12, 89.36, 110.9, 119.34, 123.01, 134.29.140.83, 151.24, 164.25; FTIR 1744.39, 1513.30, 1200 cm^{-1}.

2.2 Antibacterial activity

2.2.1 Test microorganisms

The bacterial strains used for the assay were clinical isolates obtained from various patients at local hospitals. The isolates were identified and characterised at the Department of Microbiology, Umaru Musa Yar'adua University, Katsina, Nigeria using the established biochemical protocols. Thus, the Gram-positive bacteria, *Staphylococcus aureus, Bacillus subtilis, Bacillus megaterium* were cultured in the medium prepared from mannitol salt agar. While, the Gram-negative bacteria *Escherichia coli*, *Salmonella typhimurium*, and *Pseudomonas aeruginosa* were cultured in the medium prepared from nutrient agar.

2.2.2 Bacterial Susceptibility Test

The aromatic diacetates prepared at the concentration of 1,000 µg/ml were screened for their *in vitro* antibacterial activity against the bacterial species using disc diffusion method. Thus, the inoculation medium containing 24 hr grown culture was added aseptically to the nutrient medium and mixed thoroughly to get the uniform distribution. This solution (25ml in each petri dish) was poured into the petri dishes

and then allowed to attain room temperature. Ciprofloxacin as the control drug was also treated as appropriate. The plates were all incubated at 37˚C for 48 hr, and the zones of inhibition were measured in millimeters [13].

2.2.3 Determination of Minimum Inhibitory Concentration (MIC)

The MIC of the compounds was determined using the tube dilution method at 2.5 µg/ml, 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml, 40 µg/ml, 45 µg/ml, and 50 µg/ml as per the literature [13].

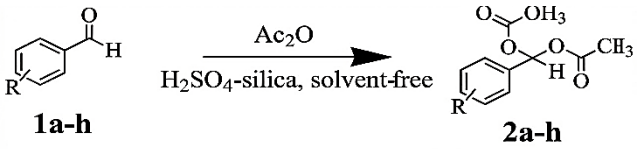
2.2.4 Determination of Minimum Bactericidal Concentration (MBC)

The MBC was determined following the MIC assay by subculturing 5 µL of the compounds from wells showing no visible growth onto fresh inoculation medium plates. The plates were incubated at 37˚C for 24 hr. The MBC was defined as the lowest concentration of the compound that resulted in a 99.9% reduction in the initial bacterial inoculum [3].

3. Results and Discussion

3.1 Chemistry

Aromatic diacetates, **2a-h** were synthesized by reacting the appropriate aldehyde with acetic anhydride using H_2SO_4-silica as a catalyst (Scheme 1).



Substrate	R
a	H
b	4-Cl
c	4-OH
d	4-CF_3
e	4-CH_3
f	3-NO_2
g	4-OCH_3
h	4-OH, 3-OCH_3

Scheme 1. Synthesis of Aromatic Diacetates

The obtained products were characterised using NMR and FTIR spectroscopic techniques. According to the ^{1}H NMR spectrum (Fig. 2) of compound **2a**, a signal found at 2.13 ppm was assigned to the six protons of the methyl groups of the diacetoxy groups, $(OCOCH_3)_2$. The two aromatic protons in proximity to the methine carbon bonded to the diacetoxy group appeared at 7.41 ppm, while the signal at 7.52 ppm was assigned to the other three aromatic protons on the benzene ring. The signal at 7.60 ppm was assigned to the methine carbon, -CH bonded to the diacetoxy group $(OCOCH_3)_2$.

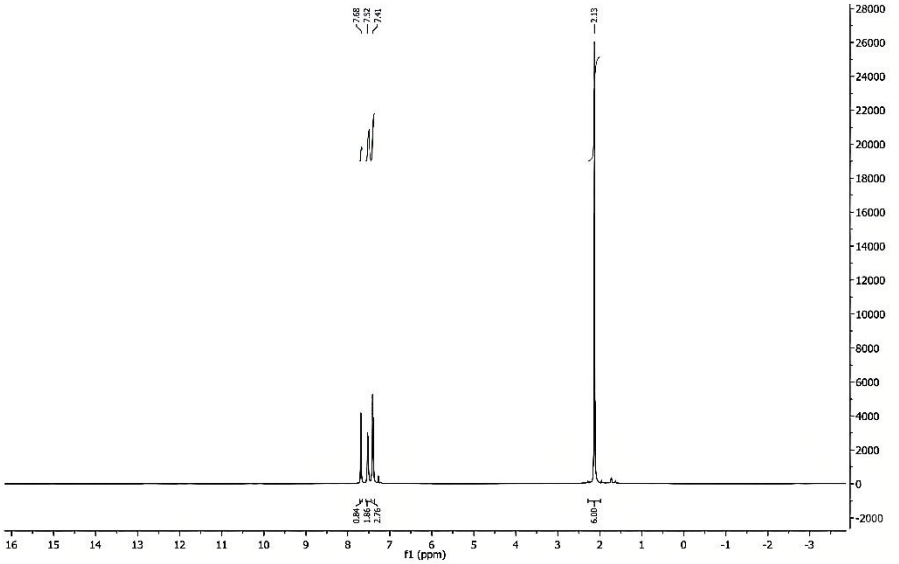


Fig. 2. ^{1}H NMR Spectrum of Compound 2a

The ^{13}C NMR spectrum (Fig. 3) showed a signal at 20.79 ppm for the two methyl carbons (-CH_3), and 89.68 ppm was assigned to the methine carbon (-CH) bonded to the diacetoxy groups, $(OCOCH_3)_2$. The signals at the range 126.66 ppm - 135.48 ppm were for the aromatic carbons. Finally, the signal at 168.76 ppm was assigned to the two carbonyl carbons of the diacetoxy group, $(OCOCH_3)_2$. The FTIR spectrum indicated the absorption band for the C-O stretch at 1498.39 cm^{-1}. While the peak at 1751.83 cm^{-1} confirmed the presence of C=O groups.

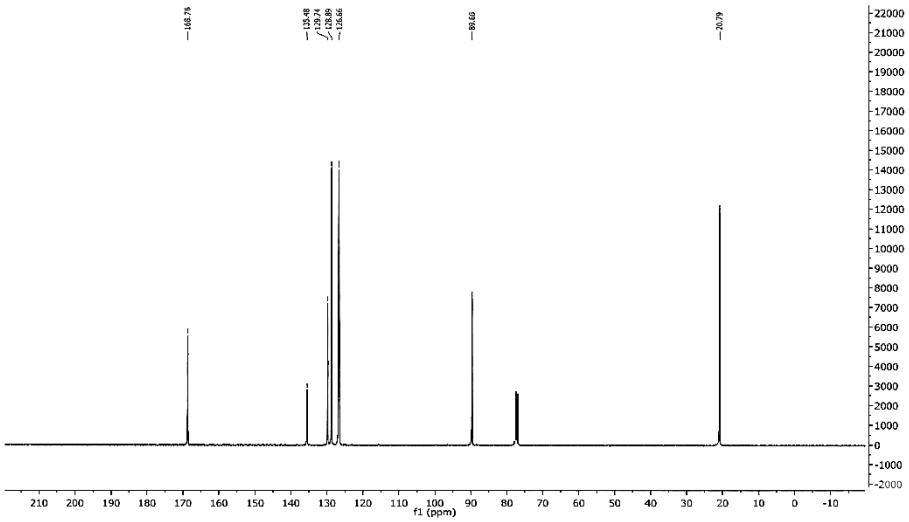


Fig. 3. ^{13}C NMR Spectrum of Compound **2a**

3.2 Antibacterial Activity

Generally, all the bacterial species were sensitive to the synthesised compounds except compound **2d** which had no activity against *Bacillus megaterium*. It was found that in the case of *Pseudomonas aeruginosa*, compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2f** showed very good activities with inhibition zones of 36 mm, 34 mm, 27 mm, 24 mm, 21 mm, 17 mm respectively, compounds **2g** and **2h** were less effective with similar zone of 11 mm. In the case of *Salmonella typhimurium*, compounds **2d**, **2e**, and **2a** exhibited greater activities than the standard drug, ciprofloxacin with an inhibition zone of 36 mm, 31 mm and 30 mm respectively. Compounds **2b**, **2c**, **2d**, **2g** and **2h** also showed a very good activity compared to the standard drug with zone of inhibition of 25 mm, 24 mm, 24 mm, 21 mm and 27 mm respectively. In the case of *Escherichia coli*, compound **2h** showed an excellent activity with an inhibition zone of 28 mm compared to control drug, Compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, and **2g** showed moderate activities compared to the standard drug. It was found that in case of *Staphylococcus aureus*, compound **2a** exhibited the highest zone of inhibition with a zone of inhibition of 34 mm followed by compounds **2d**, **2h**, **2c**, **2g**, **2e**, **2f** with a zone of inhibition of 29 mm, 26 mm, 25 mm, 25 mm, 23 mm, and 23 mm respectively. In the case of *Bacillus subtilis*, compound **2d** gave an excellent inhibition zone of 24 mm comparable to the 26 mm exerted by the standard drug. Compounds **2a**, **2b**, **2c**, **2e**, **2g**, **2h** gave 10 mm, 21 mm, 14 mm, 16 mm, 12 mm, 18 mm zones of inhibition respectively, while compound **2g** gave 09 mm zone of inhibition. Lastly, compounds **2a**, **2f**, **2h**, and **2c** gave greater zones of inhibition of 29 mm, 29 mm, 26 mm, and 22 mm than the standard drug which has 21 mm against *Bacillus megaterium* (Table 1).

Table 1. Zone of inhibition of Compounds **2a-h**

Compound 1,000 µg/ml	**Zone of Inhibition (mm)[a]**					
	Bacillus megaterium	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Salmonella typhimurium*	*Escherichia coli*
2a	29	10	36	34	31	-
2b	18	21	34	22	25	12
2c	22	14	27	25	24	11
2d	-	24	24	29	24	15
2e	20	16	17	23	30	18
2f	29	12	11	23	36	10
2g	18	09	11	25	21	11
2h	26	18	21	26	27	28
Ciprofloxacin	21	26	28	36	28	33

[a] = Mean values of triplicate tests; - = No activity

Appendix A. The compounds were further evaluated for minimum inhibitory concentration (MIC). It was found that compounds **2a** and **2c** gave the lowest concentration of 10 µg/ml against *Bacillus subtilis* and *Pseudomonas aeruginosa* followed by compounds **2d**, **2f**, **2h** with MIC values of 15 µg/ml. Compound **2b** and **2c** exhibited moderate antibacterial activity with MIC value of 15 µg/ml against *Staphylococcus aureus*. Compounds **2a** and **2f** has the lowest MIC values of 15 µg/ml against *Bacillus megaterium* followed by compounds **2b**, **2c**, and **2h** with MIC values of 20 µg/ml. Compound **2b** has MIC value of 10 µg/ml followed by compounds **2d** and **2e** with MIC value of 15 µg/ml against *Escherichia coli*. Lastly, compounds **2e** and **2f** have the lowest MIC values of 10 µg/ml against *Salmonella typhimurium* (Table 2). The minimum bactericidal concentration (MBC) of the compounds was also evaluated. It was found that compound **2a** and **2d** showed an MBC value of 15 µg/ml againt both *Staphylococcus aureus* and *Bacillus megaterium*. Compounds

Appendix B. 2f and **2g** showed no effect on *Pseudomonas aeruginosa* at all the concentrations tested. The MBC results indicated that their activities were concentration dependant (Table 3).

Table 2. Minimum Inhibition Concentration of Compounds **2a-h**

Compound	**Concentration (µg/ml)**					
	Bacillus megaterium	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Salmonella typhimurium*	*Escherichia coli*
2a	15	10	10	20	15	-
2b	20	25	20	15	20	10
2c	20	10	20	15	20	20
2d	-	15	25	10	15	15
2e	25	20	15	20	10	15
2f	15	15	-	10	10	25
2g	25	-	-	20	15	20
2h	20	15	15	20	20	15

- = No activity

Table 3. Minimum Bactericidal Concentration of Compounds **2a-h**

Compound	**Concentration (µg/ml)**					
	Bacillus megaterium	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Salmonella typhimurium*	*Escherichia coli*
2a	15	20	20	25	25	-
2b	20	25	30	25	20	35
2c	20	20	25	30	30	30
2d	ND	25	25	15	25	20
2e	30	20	20	20	10	30
2f	35	25	ND	20	20	35
2g	25	ND	ND	25	30	30
2h	20	35	20	35	20	35

- = Not activity

4. Conclusion

Synthesis of aromatic diacetates was achieved by reacting acetic anhydrides with the corresponding aromatic aldehydes in the presence of catalytic amount of a mixture of sulphuric acid-silica powder. The structural characterisation of the compounds using NMR and FTIR spectroscopic techniques agreed with the literature. Disc diffusion method was employed to test the susceptibility of the compounds against six bacterial species, and it was found that compounda **2a** and **2f** demonstrated higher zones of inhibition than the standard drug, ciprofloxacin. Although, the activity against *Escherichia coli* was

found to be less effective. This work revealed that those compounds with the lowest MIC values against some bacterial species were found to have a relatively higher MBC values against the same bacterial species.

5. Acknowledgement
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