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Microwave Assisted Synthesis of phthal and maleimide derivatives with Studying of Antimicrobial Activities.

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ABSTRACT:

A series of phthal and maleimide compounds have been synthesized by the condensation reaction of phthalic and maleic anhydride with four different amino compounds.

The structures of all the synthesized compounds were characterized using (^{1}HNMR, ^{13}CNMR, IR and UV. VIS.) spectral analysis. The synthesized compounds were screened for their anti-microbial activity. The results show that the compounds 1 and 3 exhibited good to moderate activity gainst Gram-positive and negative bacteria. while the compound 8 had no effect organism. Finally, the other compounds exhibit moderate to low activity on all gram-positive and negative bacteria under study.

تحضير مشتقات الفثالئيمايد والماليئمايد بأستخدام الموجات المايكروية و دراسة فعاليتها البايولوجية .

الخلاصة :

تضمن البحث تحضير مجموعة من مركبات الماليئمايد والفثالئيمايد عن طريق تكثيف انهيدريد الماليك و الفثاليك مع اربعة امينات مختلفة بأستخدام الموجات المايكروية.

التراكيب لجميع المركبات المحضرة تم تشخيصها بأستخدام التحاليل الطيفية (الاشعة تحت الحمراء ,الفوق البنفسجية و الرنين النووي المغناطيسي.) .

الفعالية البايولوجية تمت دراستها و اظهرت النتائج ان المركبات (1-3) أظهرت فعالية جيدة الى معتدلة ضد البكتريا الموجبة و السالبة . بينما المركب (8) لم يكن له تأثير يذكر. اما المركبات الاخرى فقد اظهرت فعالية معتدلة الى منخفضة على انواع البكتريا قيد الدراسة.

INTRODUCTION

The preparation of imides has received considerable attention during recent years. Imides are versatile intermediates in the synthesis of nitrogen-containing heterocycles [1,2]. The imide functionality is also an important component in many natural products that exhibit a broad range of activities including immunosuppressants [3]. Imide derivatives are a valuable group of bioactive

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compounds showing androgen receptor antagonists[4], anti-inflammatory[5], anxiolytic[6], antiviral[7], antibacterial [8] ,and antitumor[9] properties.

Microwave (MW) irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. The application of MW irradiation to provide enhanced reaction rate and improved product field in chemical synthesis has been extending to modern drug discovery in complex multi-step synthesis and it is proving quite successful in the formation of a variety of carbon-heteroatom bonds[10]. Structures of all synthesized compounds and their in vitro activities were also investigated.

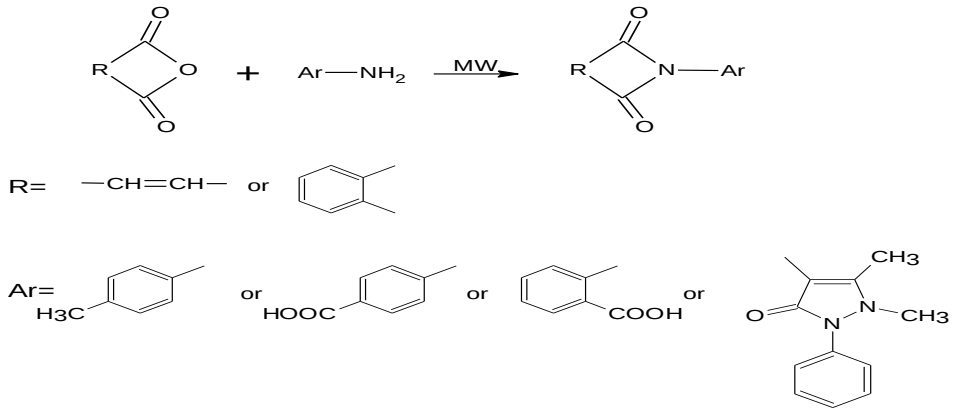
Experimental

All melting points are uncorrected and were determined by open end capillary tube method in Gallen Kamp MFB-600-Melting Point apparatus . The reactions were made by using Microwave Oven Russell hobbs 850 watt. The FTIR spectra were recorded on a Shimadzu FT-IR 8400s spectrophotometer using KBr discs. 1H-NMR spectra were recorded on Burker DMX- 500 NMR SPECTROPHOTOMETER on a 300 MHz, with TMS as internal standard and DMSO as solvent . UV-VIS. spectrophotometer using UV-VIS.1650PC spectrophotometer and absolute ethanol as solvent. The physical data of all the synthesized compounds is presented in Table 1.

Synthesis

The synthesis of imides 1–8 was achieved by microwave irradiation technique, which briefly consists of the following.[11, 12]

Maleic or phthalic anhydride was thoroughly grounded with appropriate solid arylamine in a dry mortar with the help of a pestle to make an easy flowing powder. This material was subsequently taken in a dry conical flask. The mixture was irradiated under microwave for (2-15min) at 800 W, 2450MHz with constant shaking. After completion of the reaction, the contents of the flask were cooled down until the liquid solidified. It was then inverted and the walls were scraped out to give the compounds 1-8. The residue was recrystallised from chloroform.



Antibacterial Activity Tests

The compounds were investigated against Gram-negative (Escherichia coli, Serratia marcescens , and Proteus mirabilis) and Gram-positive (Staphylococcus aureus). The antibacterial activity tests were performed according to agar diffusion method [13] using Cefotaxime (CTX) 30µg, and gentamicin (CN) 10µg as the reference compounds. The sterile cotton swabs were separately dipped into each of the adjusted organism cultures and excess inoculum was removed by pressing and rotating the swab firmly several times against the wall of the tube above the level of the liquid. The swab was streaked all over the surface of the nutrient agar in three dimensions at an angle of 60° to obtain an even distribution of the inoculum.

The plates were then left to dry at room temperature for few minutes. Disks impregnated with DMSO solutions of the compounds under study (75, 150 and 300 µg/disk) were placed on the surface of precultured agar. The plates were then incubated for 24 h at 37ºC and inhibitory zones were recorded.

Result and Discussion

The condensation of anhydride with arylamine, in a solvent free reaction afforded imide compounds (1-8). The condensation reaction is carried out under domestic microwave oven.

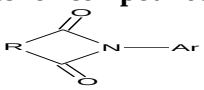
Structures of all products were confirmed by analytical and spectral methods. IR spectral data showed in general disappearing of (N–H) band and the (C=O) stretching band at (1784, 1674 cm-1). The H^1- NMR showed dublate in the range δ 6.95- 7.98 and δ 6.63 corresponding to C=CH- aromatic ring and C=CH- olifinc ring of both condensation group.

The C^{13}- NMR showed 123-134ppm for Aromatic carbon, 133-135ppm for C=CH olifen in malic ring, 162-163ppm for C=O imide and 165-168ppm for C=O carboxylic group. The UV-Visible spectrum of these derivatives showed intense maxima at (256 -276 nm) and (272 - 323 nm) which belonged to π→π* and n→π* transitions. The data that give further evidence for the formation of compounds were listed in (table 2).

Biological screening: antimicrobial activity tests

The antibacterial activities of compounds (1-8) were tested against selected types of organisms. After incubation, the diameters of inhibition zones around the wells were measured, to the nearest mm, in three different directions using a ruler and the average diameter was recorded and compared to that of the control. From the data presented in Table 3 it is clear that compounds 1 - 7 were good to moderate activity against S.aureu, while 1-3 was also moderately active against the other microorganisms. Finally, compounds 5 and 8 were found to be inactive.

Table (1): Physical properties for compounds (1-8) which have structure:



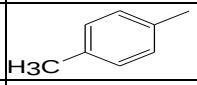
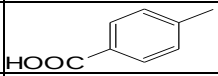
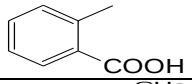
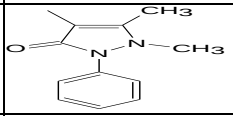
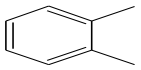
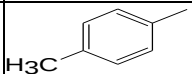
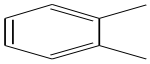
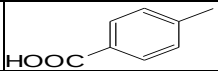
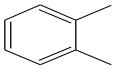
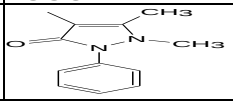
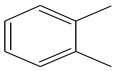
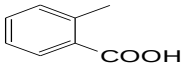
No. of Comp	R	Ar	Molec.Formula	Yield. %	MP.°C
1	—CH=CH—		$C_{11}H_9NO_2$	97	160-162
2	—CH=CH—		$C_{11}H_7NO_4$	96	298-300
3	—CH=CH—		$C_{11}H_7NO_4$	93	95-97
4	—CH=CH—		$C_{15}H_{13}N_3O_3$	90	180-182
5			$C_{15}H_{11}NO_2$	97	206-208
6			$C_{15}H_9NO_4$	96	290-292
7			$C_{19}H_{15}N_3O_3$	93	216-218
8			$C_{15}H_9NO_4$	95	210-212

Table (2): IR , UV, H^1-NMR C^{13}-NMR spectral data for compounds (1 – 8)

No. of Comp	U.V\ λmax (DMSO)	Characteristic IR bands Cm^{-1}						H^1-NMR\ ppm (DMSO\ 300 MHz)	C^{13}-NMR\ ppm (DMSO\ 300 MHz)
		C=O	C–H al.	C–H ar.	C=C	OH	Other		
1	260,293	1778,1720	2918	3043	1516	–	–	; 6.63ppm(2H,C=CH) 6.95-7.58ppm (4H, Ar–H)	_
2	259,281	1780, 1720, 1712	2901	3080	1512	3367-2540	1313 (C–O)	6.44ppm(2H,C=CH) 7.94-8.20ppm (4H, Ar–H) 12.05ppm (1H, OH)	126.0-132.1ppm (6C, Aromatic) 133.7ppm(2C,C=CH) 162.7ppm (2C, C=O) 165.5ppm (1C, HO–C=O)
3	276,323	1778, 1725, 1710	2947	3084	1518	3481-2510	1292 (C–O)	6.52ppm(2H,C=CH) 7.35-7.48ppm (4H, Ar–H) 10.98ppm (1H, OH)	126.0-134.2ppm (6C, Aromatic) 135.7ppm(2C,C=CH) 162.7ppm (2C, C=O) 165.5ppm (1C, HO–C=O)
4	256,282	1768, 1720, 1674	2933	3078	1491	–	–	–	_
5	264,272	1751, 1714	2916	3043	1514	–	–	_	_

Continuation Tble (2)

6	261,276	1782, 1747, 1726	–	3072	1512	3471-2553	1290 (C–O)	7.60-7.98ppm (8H, Ar–H) 10.48ppm (1H, CO–OH)	–
7	257,282	1784, 1720, 1674	2926	3041	1546	–	–	2.24ppm (3H, C–CH_3) 3.24ppm (3H, N–CH_3) 7.23-7.56ppm (9H, Ar–H)	–
8	258,279	1776, 1707, 1687	–	3067	1494	3410-2548	1288 (C–O)	7.19-7.89ppm (8H, Ar–H) 10.48ppm (1H, OH)	123.5-134.0ppm (12C, Aromatic) 163.7ppm (2C, C=O) 168.8ppm (1C, HO–C=O)

Table (3): Result of antimicrobial activity tests (agar diffusion method) of compounds (1-8)

Comp. No.	Susceptible microorganisms											
	Gram negative species									Gram positive species		
	E.coli			P. mirabilis			S. marcescens			S.aureu		
	Conc. in ppm			Conc. in ppm			Conc. in ppm			Conc. in ppm		
	300	150	75	300	150	75	300	150	75	300	150	75
1	+	+	-	+	+	±	++	+	+	+++	+++	+++
2	±	±	±	+	+	±	+	+	-	++	+	+
3	+	+	+	++	+	+	+	+	±	+++	++	-
4	-	-	-	+	+	+	+	+	-	++	++	++
5	-	-	-	-	-	-	-	-	-	±	-	-
6	-	-	-	+	-	-	+	±	-	++	+	-
7	+	-	-	++	-	-	+	+	+	++	++	++
8	-	-	-	-	-	-	-	-	-	-	-	-
CTX	++			±			+			+++		
CN	±			-			±			+++		

+++= zone size >21 mm; ++=zone size 21-15mm; += zone size 14-8mm; ±= zone size 7-5mm; -=not sensitive
CTX=cefotaxime; CN=gentamicin.

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