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Research Article

Synthesis and characterization of some new amide compounds derived from phthalimide derivatives and their biological activity

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Abstract

New amide compounds (8-12, and 14-18) have been produced from reaction of the phthalimide derivatives (7 and 13) with various acids hydrizdes (1-5) in absolute ethanol. The structures of the prepared amides have been examined by FT-IR and ^{1}HNMR. Furthermore, these amides have been evaluated for antibacterial activity against three pathogenic bacteria, *Staphylococcus aureu*, *Escherichia coli,* and *Bacillus* spp. The resulting amides showed inhibitory action against tested organism.

Keywords: Amide analogues, Amide compounds, Amide formation, Antibacterial activity.

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Introduction

Reactions of the amides groups are important in organic chemistry and biochemistry since amides are crucial chemicals in medicines, natural products, and physiologically active chemicals (Rachel et al. 2013; Antonella et al. 2017; Adam et al. 2020). Amides are a vital class of organic compounds with a variety of functions. Some derivatives of amides have important biological activities (Tehrani et al. 2005; Koz'minykh 2006) such as vermifuge (Kaur et al. 2015), antihistamine (Battaglia et al. 1999), fungicide, antibacterial (Greger et al. 1993; Narasimhan et al. 2004; Beck et al. 2010), antituberculosis (Hegab et al. 2007), anticonvulsant (Siddiqui et al. 2008), analgesic-anti-inflammatory (Galewicz-Walesa & Pachuta-Stec 2003; Huczyński et al. 2012), insecticidal (Graybill et al. 1996), antifungal (Moise et al. 2006), antitumor (Warnecke et al. 2007), Antimalaria (Peña et al. 2012), antiproliferative (Hranjec et al. 2013) and cyctotoxic activities (Boonya-Udtayan et al. 2012) properties.

Production of amides is traditionally performed by reacting carboxylic acids with amines at high temperatures. Because of carboxylic acid's low activity, several methods for their activation are used (Al-Zoubi et al. 2008), e.g. reaction of the activated carboxylic acid derivatives, such as chlorides, anhydrides, or esters, with amines or, the direct union of the carboxylic acids with amines using stoichiometric of coupling reagents, like carbodiimides or 1H-benzotriazole derivatives (Greenberg 2000; Rajput & Sharma 2018).

By an indirect amidation method, novel amide compounds of various acids hydrizdes were produced from phthalimide derivatives that are described in the current work i.e. we used a direct condensation procedure to produced amides and the production of acid hydrazide from acid.

Material and Methods

Melting points (m.p) were determined by a Gallenkamp melting point apparatus. FT-IR spectra were used (Shimadzu. FTIR 8400 spectrophotometer) as KBr disc. The ^{1}H NMR and

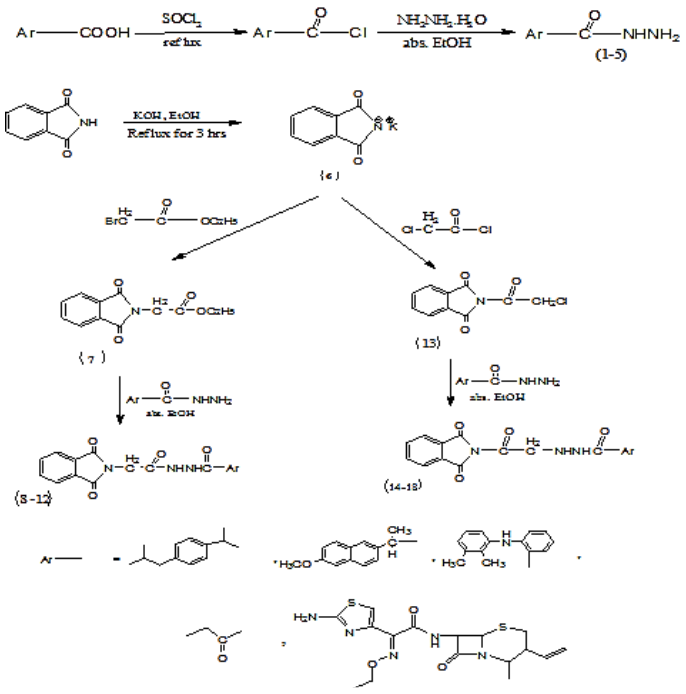


Fig.1. Preparation of the compounds 1-18.

^{13}C-NMR are recorded in DMSO-d6 using a Foruier transform varian spectrometer operating at 300 MHz and tetramethylsilan (TMS) as an internal reference. All experiments were done at Biology Department, Baghdad University.

Chemicals: All chemicals of the current study were obtained from the Fluka or Aldrich companies. The production of 6-18 derivatives are shown in Figure 1.

Synthesis of acid hydrazides 1-5: The acids hydrazides (1-5) were synthesized by reaction of their acids with thionyl chloride by taking equivalents quantities of both substances to produce its acid chlorides. Then, the acid chlorides were reacted with hydrazine hydrate to produce the compounds of 1-5 (Fig. 1), with physical attributes indicated in Table 1 (Narasimhan et al. 2004; Mohamed et al. 2007; et al. 2004; Siddiqui et al. 2008).

Preparation of the potassium phthalimide 6: The pthalimide (0.01mol) was dissolved in absolute ethanol (20ml), and then heated in a water bath. The obtained clear solution was added to an alcoholic potassium hydroxide solution with continuous stirring reflux for 3 hours and then cooled, filtered, and dried by precipitation (Fig. 1, Table 1) (Galewicz et al. 2003; Huczyński et al. 2012).

Preparation of the derivatives 7 and 13: Chloro acetyl chloride or ethyl bromoacetate (0.01mol) was dissolved into absolute ethanol (25ml), then 0.01mol compound 6 was added gradually with stirring. The resulting liquid was then cooled at room temperature after being refluxed for 6 hours with continuous stirring. The precipitate was filtered and washed with a 10% $NaHCO_3$ solution, then washed with water before recrystallization for acetone (Fig. 1). Table 1 shows the physical parameters of 7 and 13 derivatives (Galewicz et al. 2003).

Synthesis amide derivatives (8-18): In a 50ml round bottom flask 1-5 compounds (0.62mmol) were dissolved in 10ml absolute ethanol, and added 0.62mmol of compound 7 or compound 13 to it. After 12 hours of refluxing, the product was recrystallized by ethanol (Fig. 1). Table 1 shows the physical properties of these compounds (Graybill et al. 1992; Moise et al. 2004; Warnecke et al. 2007).

Antimicrobial activity: Antimicrobial activity of derivatives was examined using the agar diffusion method using bacterial species of *staphylococcus*

Table 1. Physical properties and FT-IR values of Derivatives 1-18.

Physical properties			Major FT.IR absorption cm^{-1}					
Comp. No	M.p. °C	Yield%	ν(C=O) 1.Imide 2.Ester 3.amide	ν (NH_2)	ν (NH)	ν (C-H) Arom.	ν (C-H) Aliph.	ν (C=C) Arom.
1	gammy	56	-----	3526,3462	-----	3058	2954,2870	1586, 1512
2	gammy	60	-----	3525,3443	-----	3043	2978,2939	1585, 1518
3	140-142	67	-----	3520,3462	-----	3047	2954,2922	1579, 1516
4	132-134	59	----------	3526,3455	-----	3082	2989,2922	1596, 1514
5	162-164	59	----------	3526,3462	-----	3029	2920	1585, 1520
7	110-113	73	1.1770 overlap with C=O Ester 3.---		-----	3047	2989, 2947	1578 1518
8	141-143	70	1.1774 2.--- 3.1689	---	3232	3047	2985,2923	1588 1516
9	Gammy	72	1.1774 2.--- 3.1700	---	3233	3063	2981,2943	1596 1512
10	173-175	73	1.1774 2.--- 3.1680	---	3244	3070	2985,2943	1573 1512
11	110-112	70	1.1774 2.--- 3.1696	----	3240	3047	2985,2943	1599 1515
12	116-118	73	1.1774 2.--- 3.1700	----	3268	3047	2985,2943	1596 1510
13	237-239	60	1.1774 2.1751 3.1651	----	-----	3059	2985,2923	1573 1508
14	Over than 250	62	1.1774 2.--- 3.1670	-----	3262	3062	2966,2870	1553 1512
15	162-165	64	1.1774 2.---- 3.1665	-----	3246	3047	2978,2922	1597 1510
16	185-187	60	1.1770 2.--- 3.1681	-----	3243	3093	2989,2947	1570 1504
17	169-171	63	1.1774 2.---- 3.1670	----	3244	3089	2984,2939	1535 1504
18	127-129	65	1.1774 2.---- 3.1680	----	3215	3051	2989,2918	1604 1512

Aurous, Bacillus spp. and *Escherichia coli* (Peña et al. 2012; Boonya-Udtayan et al. 2012; Hranjec et al. 2013). Mueller Hinton agar was used as culture media for antibacterial activity. The concentrations of 25, 50, 100µg/ml of the compounds were dissolved in DMSO solvent,

Results and Discussion

In the current study, we used potassium phthalimide (chemical 6) as the starting material to produce a new series of amides based on phthalimide derivatives. The synthesis of 8-18 compounds was performed according to the outline given in Figure 1. Acid hydrazides (1-5) were synthesized by reaction of different acid chlorides with hydrazine hydrate in absolute ethanol, then these hydrazides reacted with Pthalimide derivatives 7 and 13 to produce amide derivatives 8-12 and 14-18. The physical properties of these derivatives are listed in Table 1. The structures of all derivatives were confirmed by FTIR, 1HNMR, and 13CNMR spectroscopy that showed absorption bands at 3214-3280, 1770-177.4, and

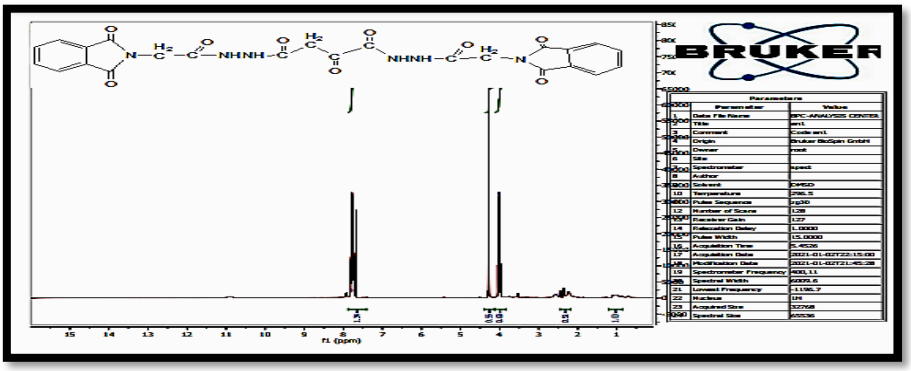
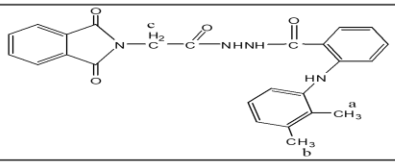
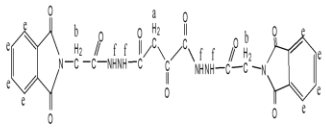
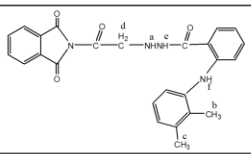
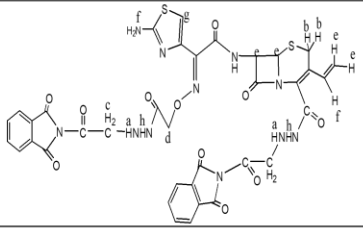


Fig.2. H NMR for derivative10.

Table 2. The 1HNMR chemical shifts for derivatives.

Derivatives	structure	Shifts (ppm)
10		a(3.14) (s,3H, CH_3);b (2.09) (s,3H, CH_3);c(4.39) (s,2H,CH_2);(6.64-8.61)(m,11H,protons of benzene rings);(10.58) (s,3H,NH).
11		a(3.97-4.04)(s,2H,CH_2);b(4.30)(s,2H,CH_2);e (7.85-7.88) (m,8H,protons of benzene erings); (10.08) (s,4H,4NH).
16		a(1.06)(s,1H,NH);b(2.08)(s,3H,methylgroup);c(2.34)(s,3H,methyl group);d(3.46)(s,2H,CH_2);(7.16-7.81) (m,11H,protons of benzene rings); e(8.15)(s,1H, NH);f (11.37)(s,1H, NH)
18		a(1.12)(s,1H,NH);b(2.90)(s,2HCH_2);c(3.36)(s,2H,CH_2);d(4.26)(s,2H,CH_2);e(5.45)(s,4H,CH_2,2CH);f(7.11)(s,3H,CH,NH_2);g(7.52)(s,1H,CH);(7.84)(m,8H,protons of benzene rings); h(11.26)(s,2H, 2NH) .

1651-1689cm^{-1}regions, confirming the presence of υ(N-H) amide, υ(C=O) imide, and υ(C=O) amide respectively. The FT-IR spectrum of compound 7 absorption bands was at 1751cm^{-1} for υ(C=O) ester which is disappearance in compounds 8-12 and the absorption bands were at 1643-1689 and 3214-3244cm^{-1} for υ(C=O) amide and υ(N-H) amide, respectively. Also the FTIR of compound 13 characteristic absorption band was at 744 cm^{-1} for υ(C-Cl) that disappeared in compounds 14-18 and but appeared its absorption bands at 1665-1681 and 3215-3262cm^{-1} for υ(C=O) amide and υ(N-H) amide, respectively (Table 1).

The chemical shifts in the 1HNMR spectra of the respective compounds verified their structures. The spectra of compounds 10, 11, 16 and 18 showed the characteristic protons of benzene and (O=C-NH) at around δ 6.64-7.88 and 10.08-11.37ppm, respectively. The 1HNMR spectra of compounds 10 and 11 exhibited characteristic 2H protons of (N-CH_2) and protons of the benzene rings at around δ 4.30-4.39 and 6.64-7.88ppm, respectively. 1HNMR spectra of compounds of the 16 and 18 exhibited characteristic 2H protons (O=C-CH_2) and 1H proton of (CH_2-NH) at around 3.36-3.46 and 1.06-1.18ppm, respectively (Table 2, Figs. 2-5).

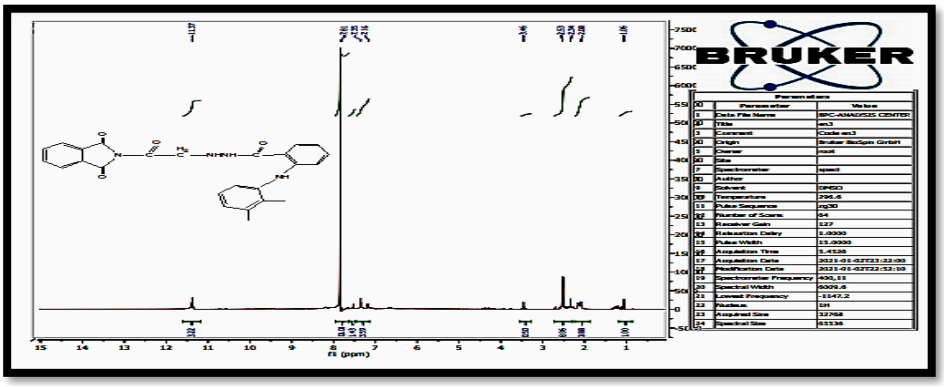


Fig.3. H NMR for derivative11.

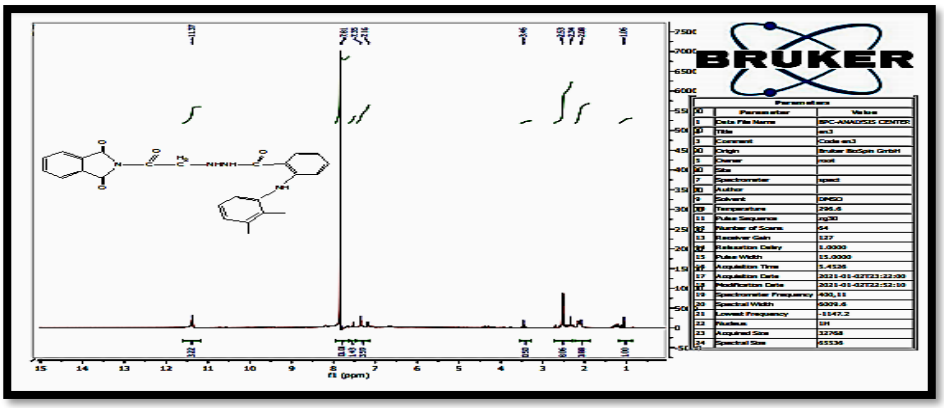


Fig.4. H NMR for derivative16.

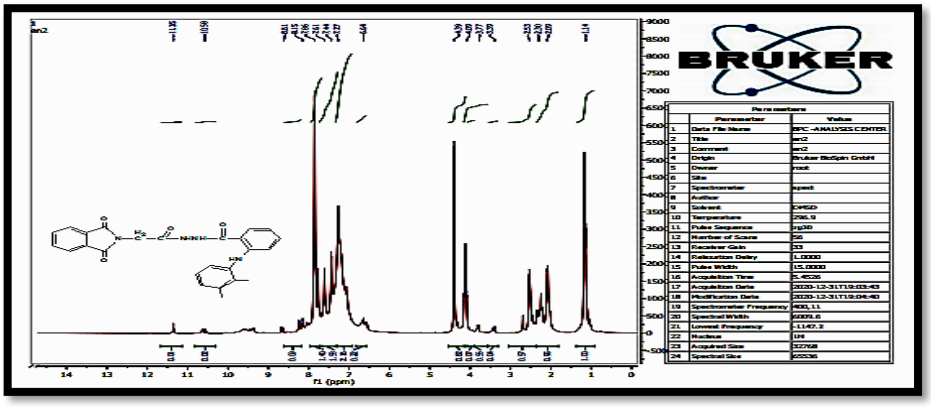


Fig.5. H NMR for derivative 18.

The ^{13}C NMR spectrum of compound 10 showed the carbon of two methyl groups at 14.53 and 17.26ppm while the carbon of the methylene group is located at 38.98ppm. The aromatic C-H carbons are assigned at their expected location (131.91-135.29ppm). The carbons of carbonyl of lactame ring were observed at 167.76ppm. The carbons of two carbonyl groups have appeared at 170.3ppm (Fig. 6). The ^{13}C NMR spectrum of compounds 11 showed the carbon that was attached by two carbonyl groups observed at 39.15ppm (Fig. 7). The ^{13}C NMR spectra of compounds 16 and 18 showed the carbons of methylene located between the carbonyl group and NHNH group were observed at 38.88 and 40.26ppm, while, the carbon atoms are located at headic of benzene ring that fused with lactame ring, were located at 123.40 and 123.26ppm. The aromatic C-H carbons of benzene ring that fused with lactame ring

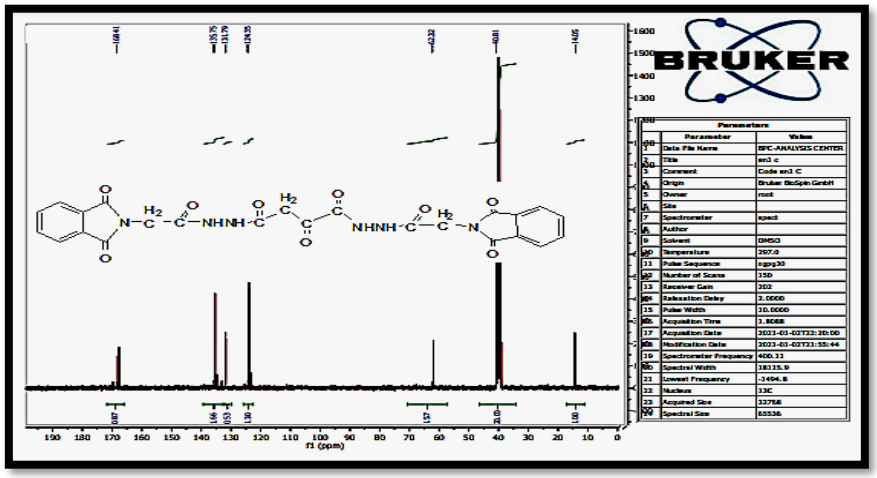


Fig.6. Spectral Analysis for derivative 10- ^{13}C NMR.

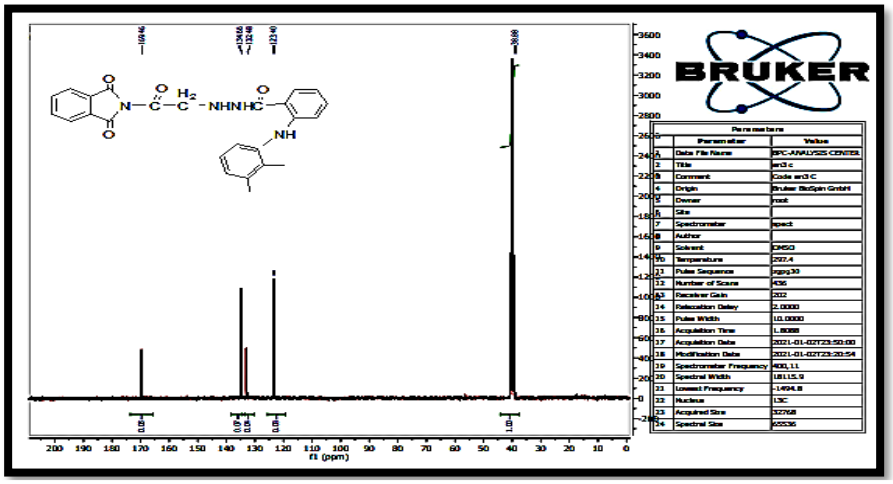


Fig.7. Spectral Analysis for derivative 11 ^{13}C NMR.

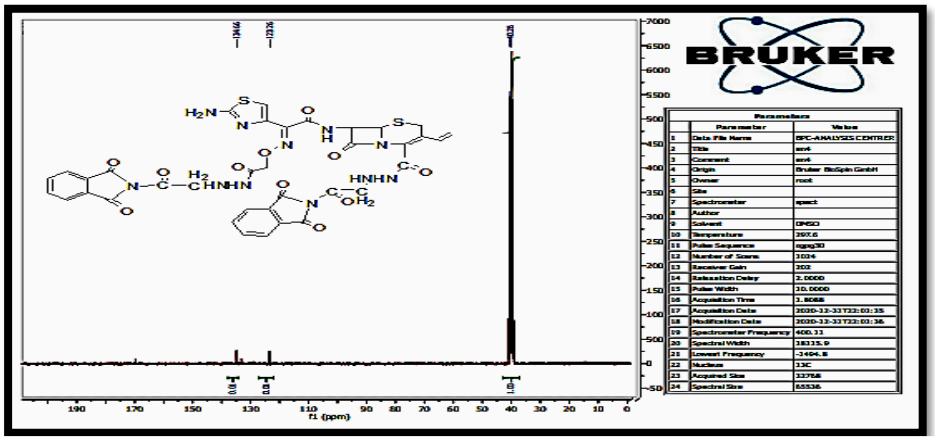


Fig.8. ^{13}C NMR for derivative 16.

are assigned at their expected location i.e. 132.48 and 132.20ppm, while the carbon atoms of two carbonyl groups for lactame rings, and were observed at 169.4 and 170ppm (Fig. 8).

Antimicrobial activity of 8-12, and 14-18 derivatives were examined using the agar diffusion method (Table 3). The antimicrobial activity of microorganisms was compared with the positive

Table 3. The antimicrobial activity of the tasted compounds after 24 hrs.

deriv. no.	*Bacillus spp* (g-)	*E.coli* (g-)	*staphylococcus*(g+)
8	24	-	23
9	12	-	-
10	42	-	10
11	40	-	24
12	-	-	40
14	26	-	25
15	24	-	12
16	9	-	25
17	26	-	23
18	10	12	22
Amoxicillin	35	13	38
DMSO	-	-	-

controls, Amoxicillin, and DMSO was the negative control. Compounds 10 and 11 showed a high growth inhibitory effect against *Bacillus* spp.. In addition, compound 12 exhibited a high growth inhibitory effect against *Staphylococcus aureus*, whereas compounds 8, 14 and 16 had moderate growth inhibitory effect against *Bacillus* spp. (g-) and *staphylococcus* (g+) and but no effect on *E. coli.*

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