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Preparation and Identification of New 1,4-bis (5,3-substituted-2,3-dihydro-1*H*-pyrazole-1-yl) Buta-1,4-Dione Derivatives with Their Antibacterial Effect Evaluation

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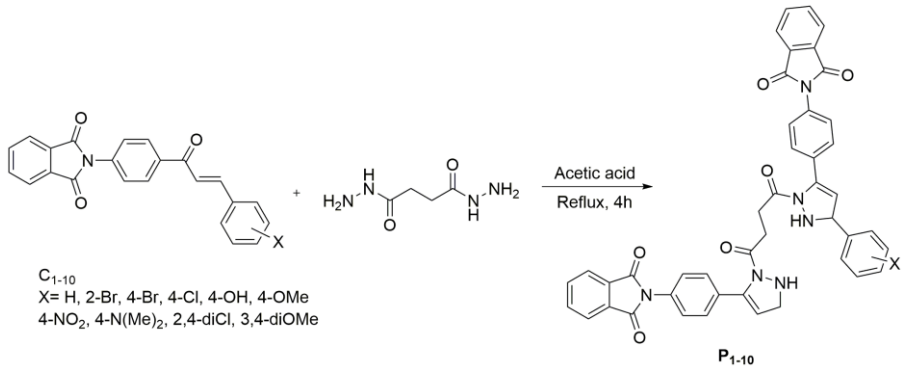
ABSTRACT

A new series of 5,3-substituted-2,3-dihydro-1*H*-pyrazole derivatives (P_{1-10}) have been synthesized via a cyclization reaction of substituted chalcones with succinichydrazide. Structures of the prepared compounds were identified by FT-IR, and some of them were characterized by Nuclear Magnetic Resonance for proton ^{1}H-NMR and Nuclear Magnetic Resonance for carbon ^{13}C-NMR. The heat of formation (HF) and steric energy (SE) have been calculated using (MOPAC) and (MM2) methods, respectively, using (CS-Chemoffice-version 6.0) program. Additionally, the biological activity for final products has been evaluated against gram-positive (*staphylococcus aureus* and *staphylococcus epidermidis*) and negative bacteria (*escherichia coli* and *pseudomonas aeruginosa*).

GRAPHICAL ABSTRACT



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Introduction

Pyrazole is considered to be a heterocyclic compound that is consisted of a five-membered ring with one double bond included. It contains three carbon atoms and two nitrogen atoms at positions 1 and 2 in a partially saturated non-aromatic ring with the formula $C_3H_3N_2H$ [1]. Pyrazoline is dihydropyrazole and can be present in three isomeric forms (1-pyrazoline, 2-pyrazoline, and 3- pyrazoline) depending on the position of the double bond [2], among the three types of these compounds, 3-pyrazoline earned a wide pharmaceutical interest. Pyrazole synthesis has been reported through a cyclization reaction of chalcones using succinicdihydrazide [3] and phenylhydrazine [4].

Pyrazoline compounds can be converted to pyrazole through an oxidation reaction using (bromine or oxygen) after the one-pot condensation reaction step of an aldehyde with ketones and hydrazine monohydrochloride [5]. Pyrazole and its derivatives showed significant activity in the biological field, such as anti-diabetic [6], antimicrobial [7], anti-breast cancer [8], antiviral [9], and antioxidant [10].

The aim of this work is comprehensive research and to achieve a further step forward for a previously published work. This includes synthesizing a new series of bisdihydropyrazolylbuta-1,4-dione derivatives and evaluating their biological activity against some gram-positive and negative bacteria. Synthesis of novel organic compounds and studying their biological activity are academically significant science values.

Materials and Methods

Melting points for the prepared compounds have been measured by a (Stuart SMP II) device in the Northern Technical University - College of Technical in Kirkuk, Department of Engineering Technologies of Fuel and Energy. A Shimadzu FT-IR 8400S with a range of (4000-400) cm^{-1} was used to identify the products. The FT-IR and KBr tablets are available in the Department of Chemistry-College of Education, the University of Tikrit. In addition, the ^{1}H-NMR and ^{13}C-NMR spectra for some of the prepared compounds have been taken as the main tool to confirm the product's structure. Dimethyl sulfoxide was used as a solvent to run the ^{1}H-NMR and ^{13}C-NMR analyses.

2-(4-cinnamoylphenyl) isoindoline-1,3-dione (C_{1-10})

A serious of chalcone compounds (C_{1-10}) was synthesized according to the previously published work.

Preparation of 1,4-bis[5-(4-(isoindolin-2-yl-1,3-dione) phenyl)-3-phenyl-2,3-dihydro-1H-pyrazol-1-yl] butane-1,4-dione (P_{1-10}).

In a circular flask (100 mL), a mixture of (0.006 mol of one of the chalcone compounds (C_{1-10}) and (0.003 mol, 0.438 g) of succinicdihydrazide was dissolved in (20 mL) of acetic acid. The mixture was refluxed for 4 hours, and the solution was cooled down at room temperature, poured on crushed ice, and left in the beaker until crystals formed. The precipitant was purified by filtered and recrystallized from ethanol [3]; some physical properties are given in Table 1.

Preparation of saturated disks of the bacterial suspension

The biological effect of final products has been evaluated against gram-positive bacteria like *(staphylococcus aureus* and *staphylococcus epidermidis)* and gram-negative bacteria like *(escherichia coli and pseudomonas aeruginosa).* The micro-organisms have been isolated and identified at Medical Laboratory Techniques Department/ Technical College in Kirkuk. The single protectorate was transferred to the test tube containing 5 mL of nutritious, and the broth brooded and kept at 37 °C for 24 hours. The bacterial suspension prepared and compared with tube number 0.5 of McFarland- standards giving a cell density of 1.5×108 cell/mL) [11].

An antiseptic cotton sweep was dunked into a bacterial suspension and wiped equally on the surface of a Muller-Hinton agar plate, and the plates were brooded at 37 °C for 30 minutes. The saturated disks have been prepared from

Whatman number 1 and maintained for 24 hours with the compounds 0.1 mg/mL, applied on Mueller-Hinton agar using Kirby–Bauer disc spread method [12]. Forceps were pressed firmly to guarantee the connection with agar, and in the next step, the plates inverted and brooded at 37 °C for 14-18 hours.

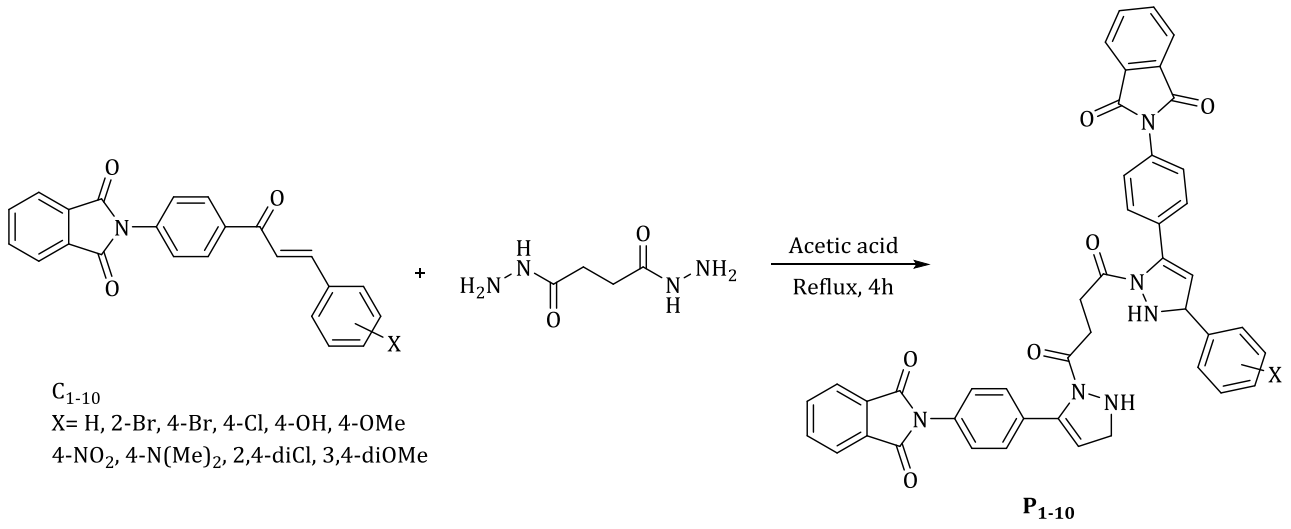
Results and Discussion

The discussion details about chalcone compounds (C_{1-10}) are available in the previously published work. 1,4-bis[5-(4-(isoindolin-2-yl-1,3-dione) phenyl)-3-phenyl-2,3-dihydro-1*H*-pyrazol-1-yl] butane-1,4-dione (P_{1-10}) have been synthesized via cyclization of substituted chalcones with succinicdihydrazide. The structures of all prepared compounds were diagnosed by FT-IR, and some of them were diagnosed by ^{1}H-NMR and ^{13}C-NMR techniques. Synthesis of 1,4-bis[5-(4-(isoindolin-2-yl-1,3-dione) phenyl)-3-substituted phenyl-2,3-dihydro-1*H*-pyrazol-1-yl] butane-1,4-dione (P_{1-10}) will be discussed as shown in Scheme 1.

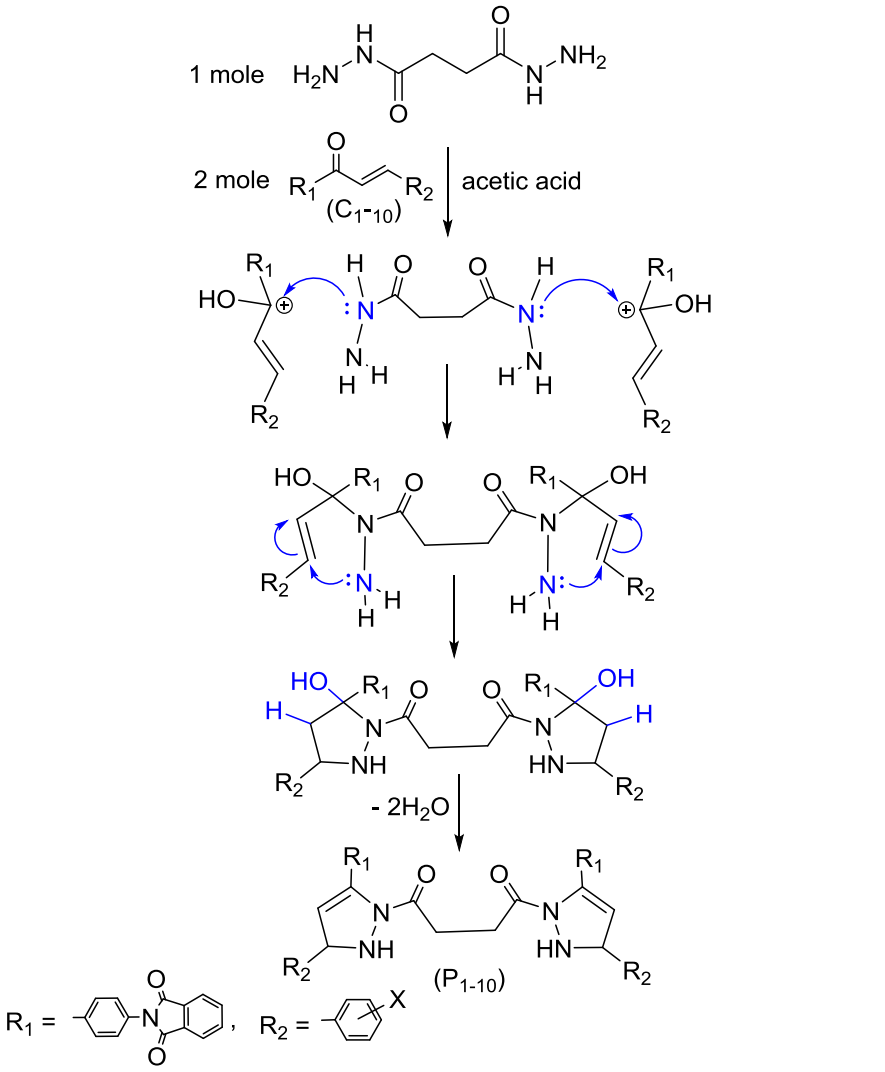
The suggested mechanism for the cyclization reaction of chalcone compounds (C_{1-10}) with succinicdihydrazide in acid media is a nucleophilic substitution, as shown in Scheme 2.

Table 1: Physical properties of pyrazole compounds (P_{1-10})

Comp. No.	X	Molecular Formula	M.wt (g/mol)	M.p (°C)	Yield (%)	Colour
P1	4-Br	$C_{50}H_{34}N_6O_6Br_2$	974.67	258-260	50	Yellow
P2	4-Cl	$C_{50}H_{34}N_6O_6Cl_2$	885.76	254-256	49	Yellow
P3	H	$C_{50}H_{36}N_6O_6$	816.87	228-225	64	Yellow
P4	4-OH	$C_{50}H_{36}N_6O_8$	848.87	236-234	44	Light Green
P5	4-OCH3	$C_{52}H_{40}N_6O_8$	876.93	118-120	32	Orang
P6	3,4-DiCl	$C_{50}H_{32}N_6O_6Cl_4$	954.64	168-170	47	Yellow
P7	4-NO2	$C_{50}H_{34}N_8O_{10}$	906.87	210-212	41	Light Brown
P8	4-N(CH3)2	$C_{54}H_{46}N_8O_6$	903.01	238-240	38	Orang
P9	2-Br	$C_{50}H_{34}N_6O_6Br_2$	974.67	150-152	56	Yellow
P10	3,4-DiOCH3	$C_{54}H_{44}N_6O_{10}$	936.98	220-222	62	Light Yellow



Scheme 1: Preparation of bis-pyrazole compounds (P_{1-10})



Scheme 2: Mechanism of bis-pyrazole compounds synthesis (P_{1-10})

The FT-IR spectra of compounds (P_{1-10}) showed bands for the secondary amine (-NH) in the pyrazoline ring at (3376-3265) cm^{-1} with the disappearance of the olefinic bond band and no shifting in the carbonyl band compared to the starting materials [13]. This could be taken as evidence for achieving a change in the olefinic bond attached to the ketone group [14]. The remaining packages appeared in their expected locations, as shown in Table 2, Figure 1 and 2.

The ^{1}H-NMR spectrum of compound (P_1) shows a singlet at δ 2.91 for the four protons in the two methylene groups, with signal δ 5.74 for the protons in the fifth position for the pyrazole ring. Moreover, aromatic protons signals are seen in the range at δ 7.40-8.30 with a signal at δ 6.20 for the two olefinic protons in the pyrazole ring, as shown in Figure 3. The interesting signal is δ 5.14 for the N-H proton, which is strong evidence for transforming chalcones to pyrazole. Compound (P_2) gives multiple signals at δ 7.40-8.29 for aromatic protons and δ 6.60 for olefinic protons in the pyrazole ring. In addition, a singlet appears at δ 2.81 and δ 4.99 for the protons in methylene and the protons of the fifth carbon in the pyrazole ring, respectively, as shown in Figure 4. The N-H group signal is clearly seen at δ 5.74, ascribed to achieving the cyclization reaction for the olefinic bond in the chalcone. The ^{1}H-NMR spectra of (P_1) and (P_2) confirmed the achieving of cyclization to the unsaturated bond attached to the ketone group.

Table 2: FT-IR data of compounds (P_{1-10})

Comound No.	X	IR (KBr) cm^{-1}					
		υ (N-H)	υ (C=C) Ar	υ (C=C) Aliphatic	υ (C=O) Imide	υ (C=N)	Other absorptions
P_1	4-Br	3376	1568-1479	1604	1655	1374	υ (C-Br) 661
P_2	4-Cl	3443	1565-1488	1602	1656	1386	υ (C-Cl) 711
P_3	H	3345	1558-1479	1607	1660	1365	-
P_4	4-OH	3285	1565-1474	1615	1634	1373	υ (C-OH) 3430
P_5	4-OCH_3	3323	1582-1435	1595	1627	1362	υ CH_3 29352873,
P_6	2,4-diCl	3345	1595-1445	1610	1677	1385	υ C-Cl 836
P_7	4-NO_2	3265	1577-1485	1594	1644	1377	υ (NO_2) 1452, 1334
P_8	4-$N(CH_3)_2$	3275	1576-1482	1604	1657	1367	υ (CH_3) asy2934, sy2852
P_9	2-Br	3288	1597-1436	1618	1655	1374	υ (C-Br) 644
P_{10}	3,4- diOCH_3	3276	1566-1450	1612	1644	1382	υ CH_3 2925,2863

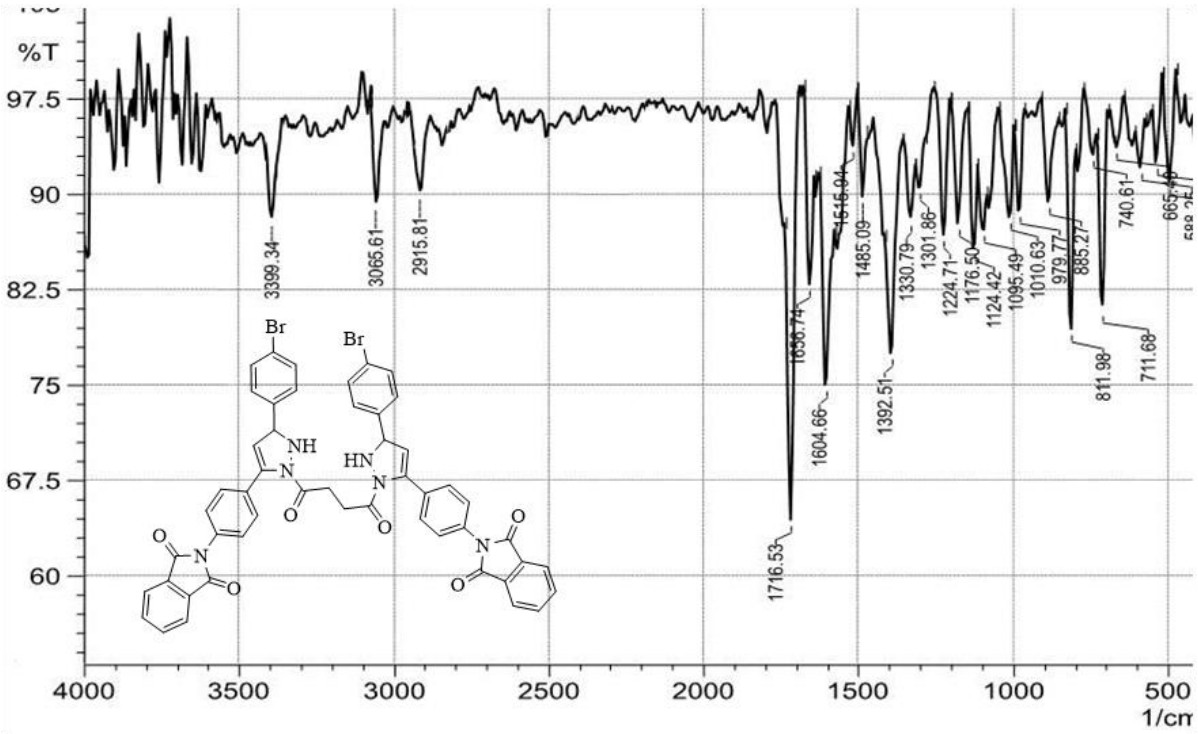


Figure 1: FT-IR spectrum of compound (P_1)

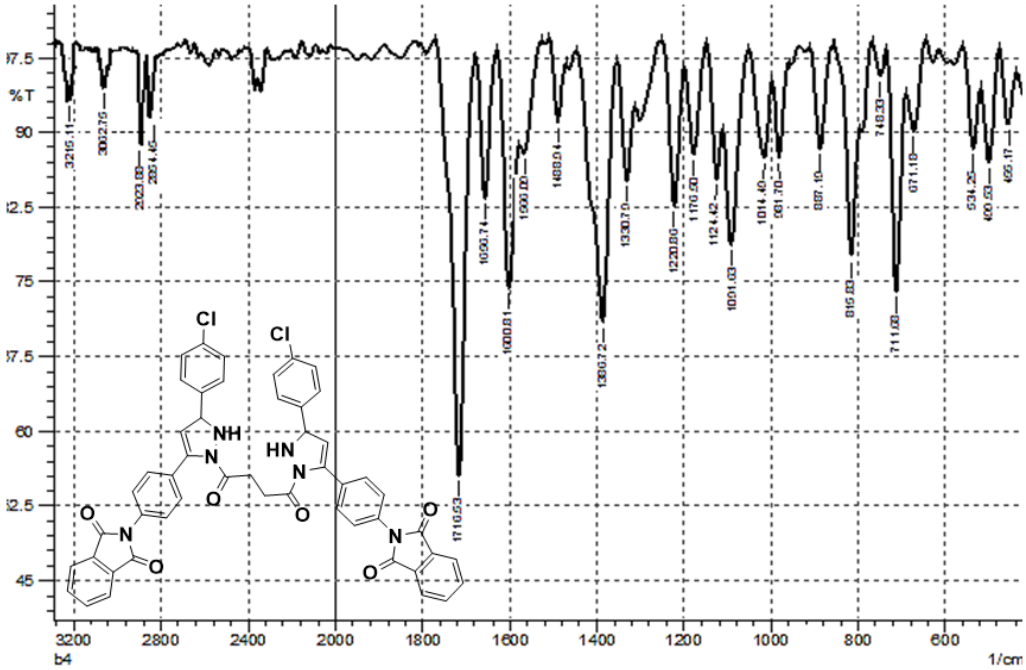


Figure 2: FT-IR spectrum of compound (P_2)

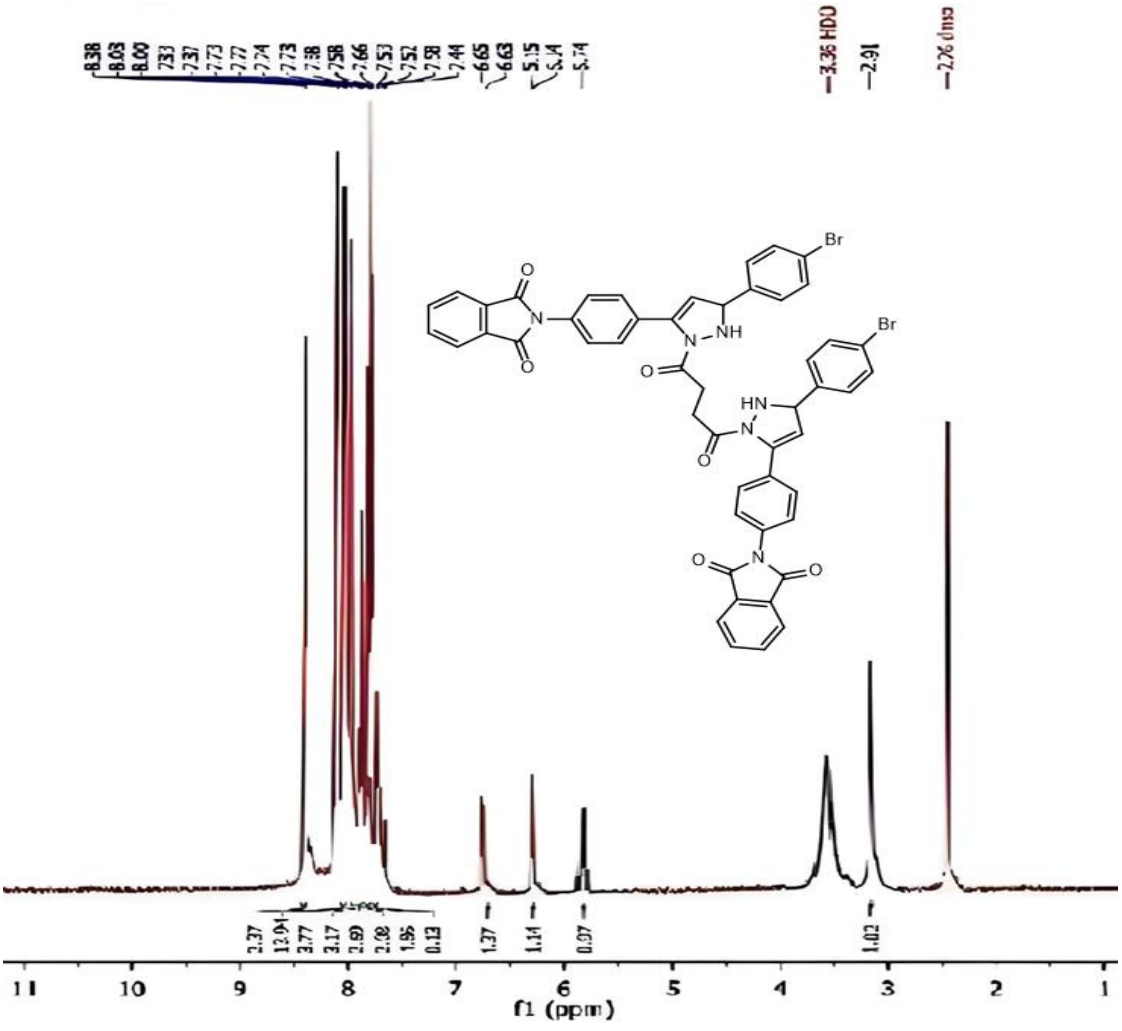


Figure 3: ^{1}H-NMR spectrum of compound (P_1)

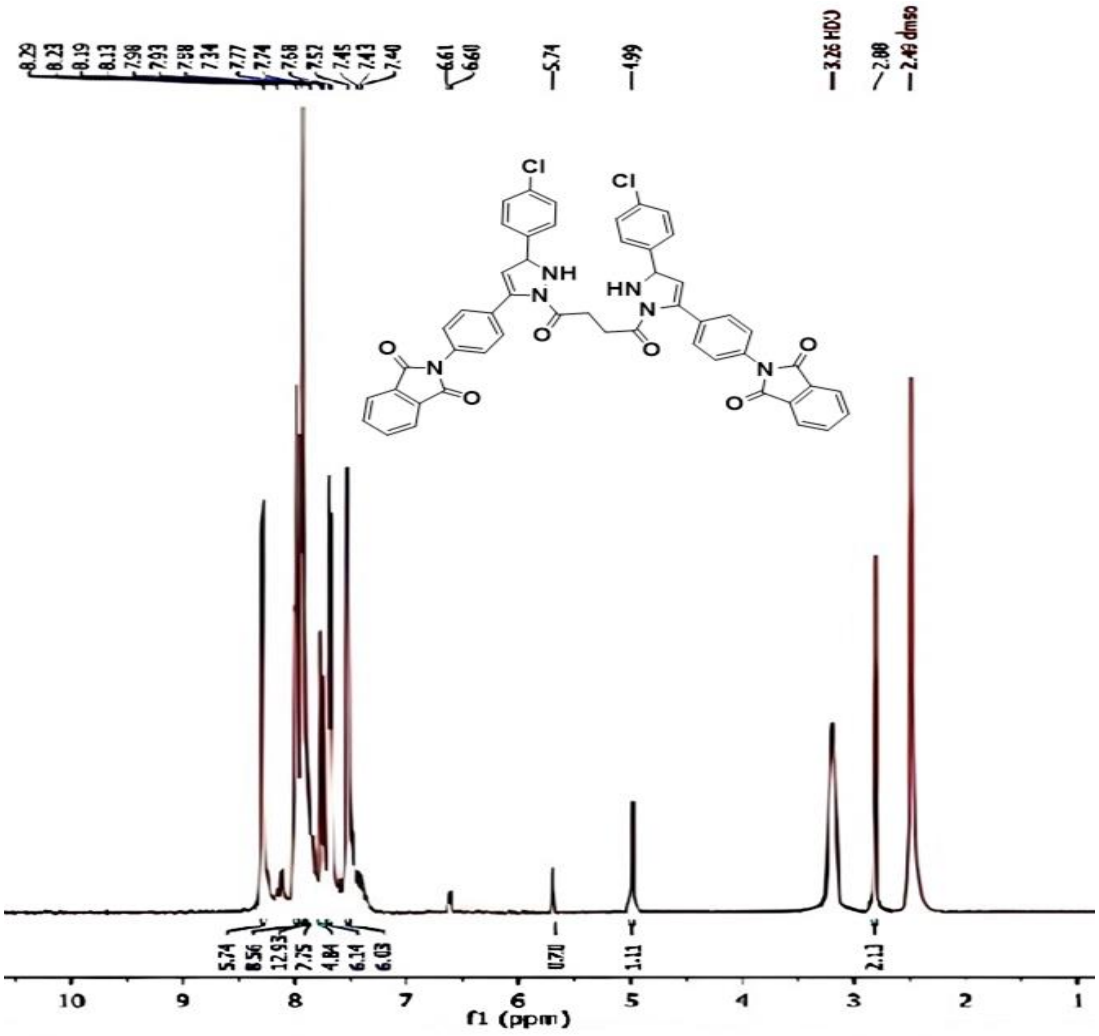


Figure 4: ^{1}H-NMR spectrum of compound (P_2)

The ^{13}C-NMR spectrum of compound (P_1) showed signals at δ 124-143 referring to the aromatic carbon group. Furthermore, signals appeared at δ 165 and δ 186 for the carbonyl in imide and ketone groups, respectively (Figure 5). The methylene carbon band clearly appeared at δ 24, which is evidence of a change in the unsaturated carbon bond bonded with the ketone group. Further confirmation of producing the interested compound is the appearance of signals at δ 65.0 and δ 93.4 for the fifth and fourth carbons in the pyrazole ring, respectively.

Compound (P_2) showed signals for the aromatic at the range δ 123-143, with signals appearing at δ 167 and δ 180 for the carbonyl in imide and ketone groups, as shown in Figure 6. In addition, signals appeared at δ 21, δ 68, and δ 113 for carbons in methylene, the fifth and the fourth carbons groups, respectively. The ^{13}C-NMR spectra of compounds (P_1) and (P_2) confirmed the cyclization reaction for chalcones. The combined spectroscopy data confirms the transformation of chalcone to pyrazole. The heat of formation and steric energy of final compounds are shown in Table 3, and the 3D structure of the most stable formula for the compounds (P_3-P_8) is shown in Figure 7.

Biological study

The antimicrobial activity of the synthesized compounds has been evaluated in vitro against several pathogenic representative microorganism's gram-positive bacteria [*staphylococcus aureus* and *staphylococcus epidermidis*] and gram-negative bacteria like [*escherichia coli, pseudomonas aeruginosa*], using agar well diffusion method [15]. Ciprofloxacin and norfloxacin were used as standard drugs for

studying the potential activities of these compounds. The compounds under the test were injected using a loop onto plates containing nutrient agar (NA) media and brooded at 37 °C for 24 hours. The agar diffusion was carried out by preparing bacterial suspensions in distilled water. The results indicated that the prepared compounds did not have any effect on the two types of gram-negative (*escherichia coli* and *pseudomonas aeruginosa*), while showed a different effect on both types of gram-positive (*Staphylococcus aureus* and *Staphylococcus epidermidis*). This relates to the difference in the cell wall structure for the gram-negative compared to the gram-positive which the former contains an outer membrane increasing bacteria resistance towards the tested chemicals as antibiotics [16].

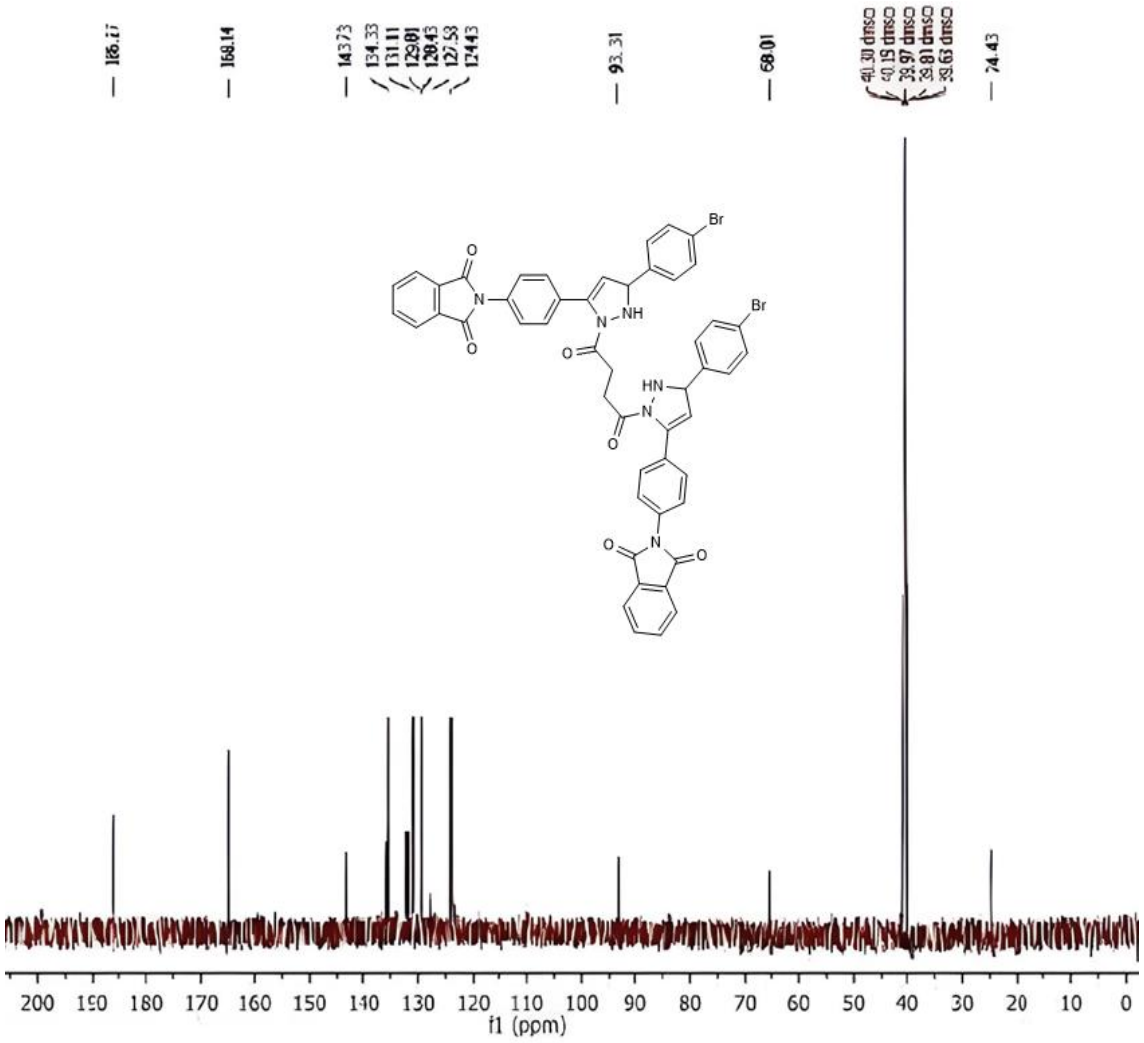


Figure 5: ^{13}C-NMR spectrum of compound (P_1)

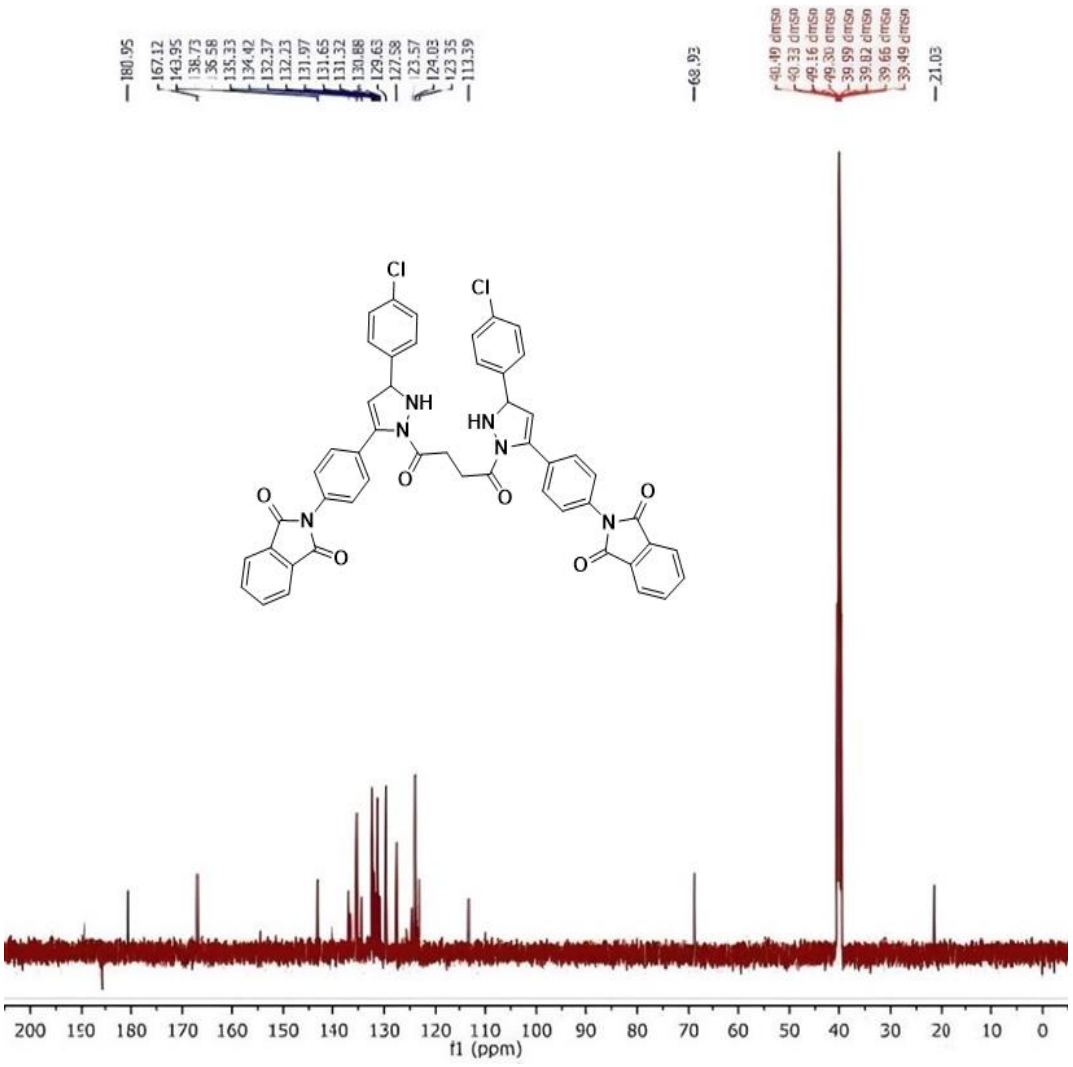


Figure 6: ^{13}C-NMR spectrum of compound (P_2)

Table 3: The Heat of formation and Steric energy of final compounds

Comp. NO.	Molecular Formula	Mol. Wt.	H.F Kcal / mol	S.E Kcal /mol
P_1	$C_{50}H_{34}Br_2N_6O_6$	975	578.05111	30.4216
P_2	$C_{50}H_{34}Cl_2N_6O_6$	886	549.76590	30.4586
P_3	$C_{50}H_{36}N_6O_6$	817	567.15967	32.8988
P_4	$C_{50}H_{36}N_6O_8$	849	483.95884	30.2574
P_5	$C_{52}H_{40}N_6O_8$	877	504.37086	34.6680
P_6	$C_{50}H_{32}Cl_4N_6O_6$	955	543.91620	33.0232
P_7	$C_{50}H_{34}N_8O_{10}$	907	610.09821	35.4576
P_8	$C_{54}H_{46}N_8O_6$	903	591.18216	33.8341
P_9	$C_{50}H_{34}Br_2N_6O_6$	975	585.09852	35.6117
P_{10}	$C_{54}H_{44}N_6O_{10}$	937	390.94790	35.9253

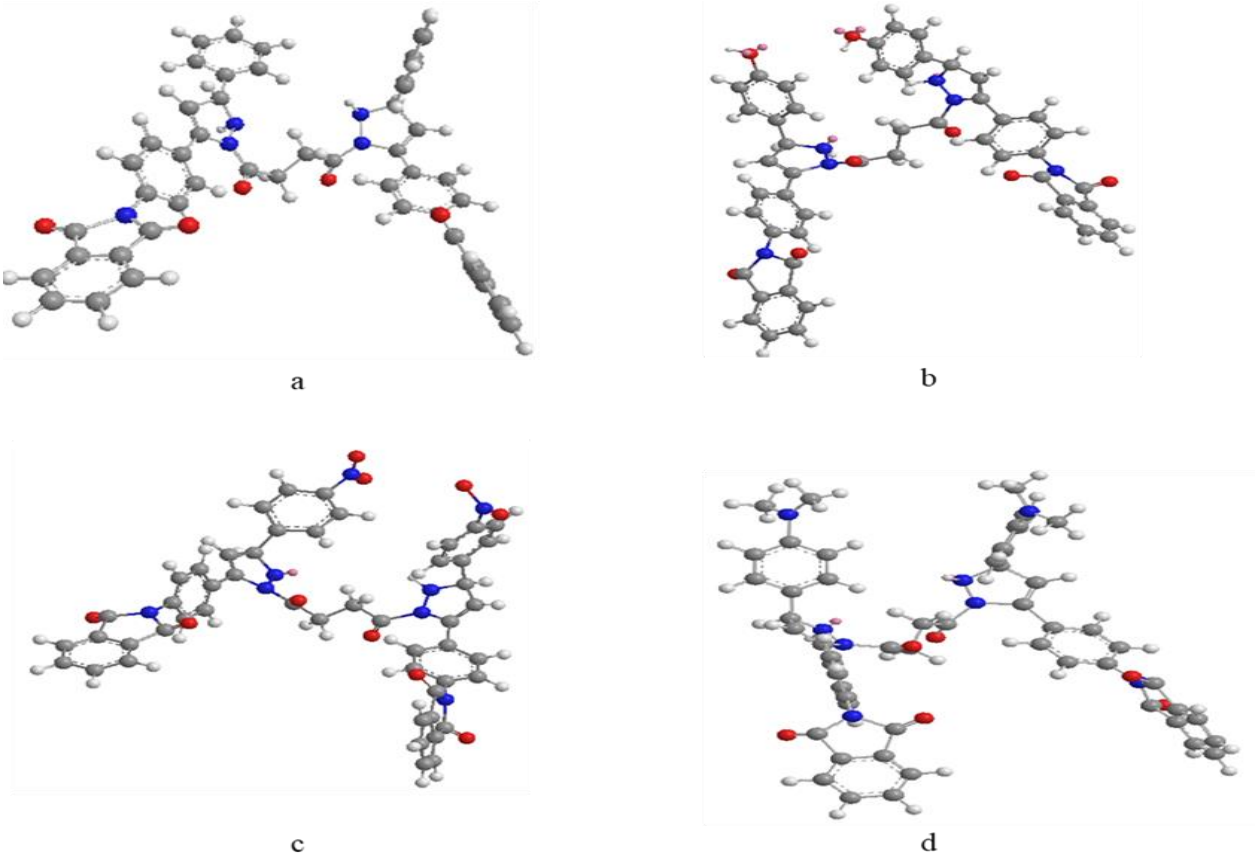


Figure 7: 3D-structure for some of synthesized compounds; (a): (P_3) and (P_4) and (b): (P_7) and (P_8)

In addition, it possesses some virulence factors such as capsule and biofilm compared to the gram negative, providing high resistivity against anti-chemical materials. This is described as the tested chemicals can be hindered for penetrating the cell wall causing to decrease in the inhibition effect [17]. Compounds (P_5-P_{10}) with the concentration of 0.01 mg/mL, showed a higher effect on bacteria (*staphylococcus aureus*) than the antibiotic norfloxacin and less than the antibiotic ciprofloxacin. However, at concentration of 0.001 mg/mL and 0.0001 mg/mL these compounds showed a similar effect less than both of the antibiotics. Similarly, to the case of (*staphylococcus epidermidis*) bacteria, compounds (P_3 and P_5-P_{10}) at a concentration of 0.01 mg/mL, and compounds (P_6 and P_7) at a concentration of 0.001 mg/mL showed a higher effect than the antibiotic norfloxacin. One of the reasons could be the presence of NO_2 and Cl withdrawal groups compared to the others, as this is reported in the literature [18]. The remaining compounds showed a similar effect less than the two antibiotics. The effect of the prepared compounds against all the tested bacteria is shown in Table 4, and the results are summarized in Figures 8 and 9. Some pictures of the biological activity disks are shown in Figures 10 and 11.

Table 4: Inhibition efficiency of compounds (P_{1-10}) on the growth of some bacteria

Comp. No.	Conc. mg/mL	Gram +ve		Gram -ve	
		Staph. Aureus	*Staph. Epidermidis*	*Escherichia col*	*Pseudomonas aeruginosa*
P_1	0.01	6	8	0	0
	0.001	5	5	0	0
	0.0001	4	3	0	0
P_2	0.01	8	6	0	0
	0.001	6	5	0	0
	0.0001	7	2	0	0
P_3	0.01	9	12	0	0
	0.001	5	5	0	0
	0.0001	4	9	0	0
P_4	0.01	10	10	0	0
	0.001	5	6	0	0
	0.0001	3	3	0	0
P_5	0.01	14	15	0	0
	0.001	6	8	0	0
	0.0001	5	5	0	0
P_6	0.01	15	16	0	0
	0.001	5	14	0	0
	0.0001	3	4	0	0
P_7	0.01	12	16	0	0
	0.001	5	12	0	0
	0.0001	3	7	0	0
P_8	0.01	13	15	0	0
	0.001	7	6	0	0
	0.0001	5	3	0	0
P_9	0.01	14	15	0	0
	0.001	8	5	0	0
	0.0001	6	4	0	0
P_{10}	0.01	15	15	0	0
	0.001	5	6	0	0
	0.0001	2	3	0	0
Ciprofloxacin	10 mg/disk	28	30	22	24
Norfloxacin	10/20 mg/disk	11	11	12	11

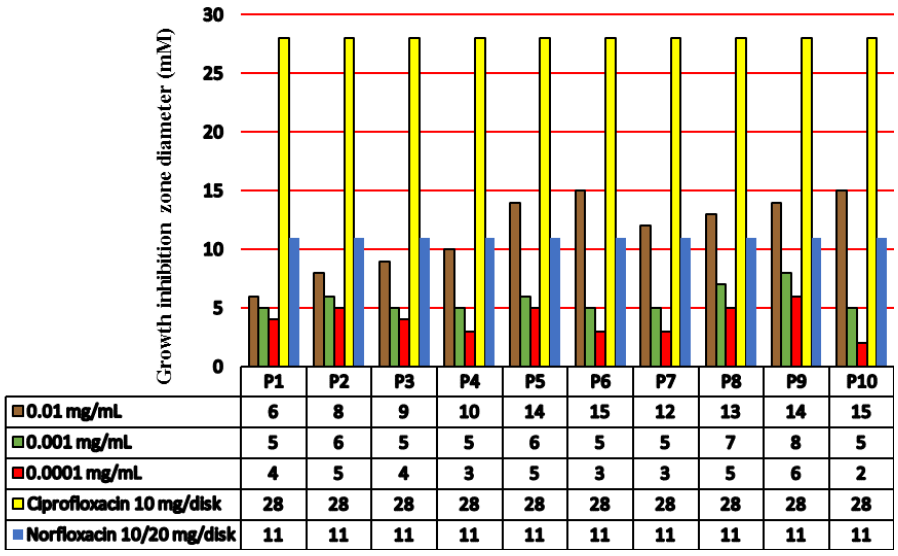


Figure 8: The inhibition efficiency of final products against *Staphylococcus aureus*

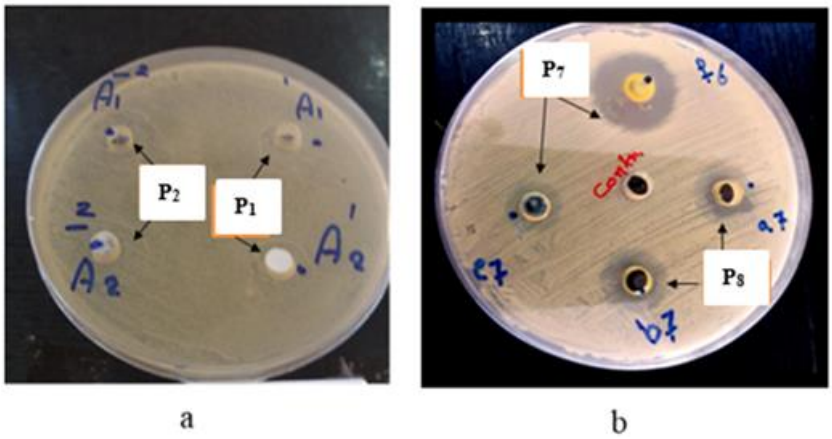
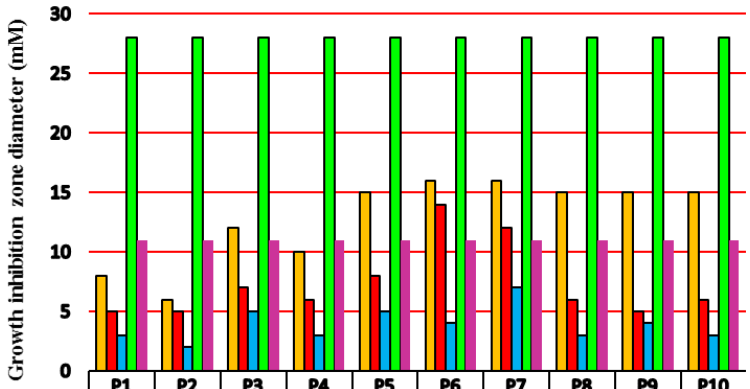


Figure 9: The inhibition efficiency of tested compounds on the growth of *Staphylococcus aureus* bacteria; (a): (P_1) and (P_2) and (b): (P_7) and (P_8)



	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
0.01 mg/mL	8	6	12	10	15	16	16	15	15	15
0.001 mg/mL	5	5	7	6	8	14	12	6	5	6
0.0001 mg/mL	3	2	5	3	5	4	7	3	4	3
Ciprofloxacin 10 mg/disk	28	28	28	28	28	28	28	28	28	28
Norfloxacin 10/20 mg/disk	11	11	11	11	11	11	11	11	11	11

Figure 10: The inhibition efficiency of final products against *Staphylococcus epidermidis*

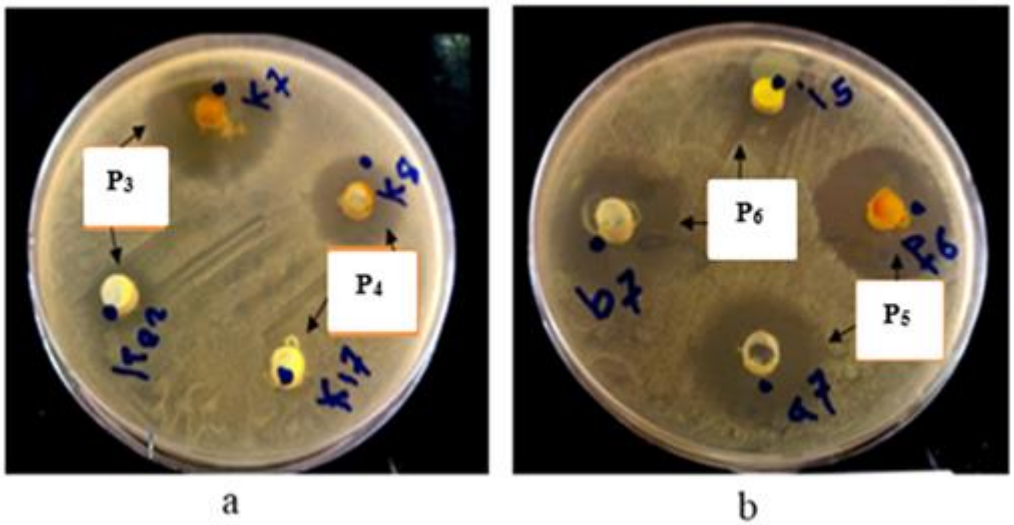


Figure 11: The inhibition efficiency of tested compounds on the growth of *Staphylococcus epidermidis* bacteria; (a): (P_3) and (P_4) and (b): (P_5) and (P_6)

Conclusion

A new series of substituted bisdihydropyrazolylbuta-1,4-dione compounds have been successfully synthesized through a cyclization reaction of new substituted chalcone compounds as starting materials with succinicdihydrazide. The results of characterization were in agreement with the structures of the prepared compounds. P_6 and P_7 compounds have a high biological effect on the gram-positive of both types (*staphylococcus aureus* and *staphylococcus epidermidis*) at a concentration of 0.01 mg/mL and 0.001 mg/mL. This may be related to the presence of withdrawal groups (NO_2 and Cl) compared to the others. The theoretical properties like the heat of formation (HF) and steric energy (SE) have been studied, the heat of formation and steric energy has a slight difference from one compound to another, and the highest value was to P_6, and P_7 compounds may have related to withdrawal group.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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