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Preparation, Characterization and In silico Study of Some Pyrimidine Derivatives That Contain a Chalcone Group and Study of Their Biological Activity †

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Abstract

An important class of heterocyclic chemicals are pyrimidine derivatives, providing a wide spectrum of biological activities in the form of antibacterial and antifungal, anti-HIV, anti-hypertensive, anti-inflammatory, anti-cancer, anti-convulsant, anti-depressant, and anti-tuberculosis acts. The chalcone group also has a significant impact on the pharmacological activity of compounds used for therapeutic purposes, acting as antibiotics, antioxidants, and anticancer agents. In this research, the derivative 1-(4-(4-(dimethylamino)-2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethan-1-one was prepared. From the reaction of thiourea with acetyl acetone and 4-dimethylamino-2-hydroxybenzaldehyde, then the product was reacted with some aldehydes in the presence of ethanol and a little hydrochloric acid as a catalyst, after that the product was reacted with some aldehydes to prepare chalcone. The prepared derivatives were characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectrum and melting point was measured as well as studying the biological activity of the prepared compounds as antibacterial. The molecular docking of these derivatives was also determined as anti-breast cancer by docking of prepared derivatives with (PDB:3eqm) protein by use (MOE 2015.10 program). The prepared compounds showed good efficacy as antibacterial agents against gram-negative bacteria at diluted concentrations. Additionally, molecular docking studies demonstrated good efficacy of some derivatives as breast cancer inhibitors, along with a study of the toxic effects of the prepared compounds using the ProTox-3.0 program-prediction of toxicity of chemicals.

Keywords: pyrimidine derivatives; biological activity; chalcone; in silico; molecular docking

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1. Introduction

Pyrimidine is a polymeric organic base that is one of the basic units for the construction of DNA and RNA (deoxyribonucleic acid and ribonucleic acid) [1], which is a hexagonal one-ring system containing two nitrogen atoms. It is also one of the pyrimidine derivatives of the important organic compounds in the preparation of many derivatives of biological importance [2]. As for chalcone compounds, they are an unsaturated α, β ketone group and are considered biologically important compounds. [3,4]

In this paper, a new group of pyrimidine derivatives containing a chalcone group was prepared. Chalcones are a major class of natural products found in the peels of fruits and vegetables, spices, tea, and soy-based foodstuffs and have been extensively studied for a wide range of biological, anti-fungal, anti-fungal, anti-bacterial, anti-inflammatory, antioxidant and anti-oxidant agents [5,6]. Changes in its composition have allowed a high degree of versatility that has proven useful in the development of a new class of drugs with improved efficacy and lower toxicity. On the other hand, many researchers believe that chalcone has an "imzportant anti-cancer effect" that has a significant impact on natural ingredients, as well as the anti-cancer group. The aromatic groups of chalcone can lead to significant changes in anticancer activity [7]. As the microwave has many advantages, including high yield, high selectivity, small amounts of by-products, moderate reaction conditions and shorter time, thus we get easy work and high purity. In 1986 by groups (Gedye and Giguere/Majetich) and became a basic technology in the synthesis of various heterocyclic compounds through cyclic reactions as well as their use in coupling reactions [8]. As heating or interaction by microwave is a very important process in view of the coupling of microwave rays directly with the molecules that are present in the reaction mixture [9], which leads to a rapid rise in temperatures and thus their reactions are faster, while traditional heating the temperature on the outer surface is higher than it is on the inside [10].

2. Experimental

2.1. Materials and Methods

All the used chemicals were obtained from commercial sources, with a purity range of 95–98%, that were used as received (without further purification). Melting points of all synthesized compounds were measured in open capillary tubes in a Gallen-Kamp MFB-600 melting point apparatus. FT-IR spectra measurements were recorded using FT-IR-8400S-Shimadizu spectrophotometer.^{1}H-NMR and ^{13}C-NMR spectra were recorded on VARIAN-INOVA 400 MHZ spectrophotometer (Germany), DMSO were used as solvents, and tetramethylsilane TMS as internal standard.

2.2. General Procedure for the Synthesis 1-)4dimethylamino)-2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethan-1-one (a)

Equivalent moles (1 mmol) of thiourea, 4-dimethylamino-2-hydroxybenzaldehyde and acetyl acetone were mixed in a 100 mL single-mouthed round flask to which 25 mL ethanol was added with some drops of hydrochloric acid as a catalyst. The mixture was scaled up and the reaction was followed by TLC and using a mobile phase of (methanol: dichloromethane) in a ratio of (9:1), after which the product was cooled and the solid product was filtered and then recrystallized from ethanol. [11]

2.3. General Procedure for the Synthetic Derivatives (b–g)

(0.33 mmol) (0.1 g) of pyrimidine and (0.09, 0.07, 0.048, 0.006, 0.052, and 0.055) g of (4-(diphenylamino) benzaldehyde), (4-benzyl oxybenzaldehyde), (iodine-3-carboxyaldehyde), (4-diphenylcarboxyaldehyde), (2-naphthaldehyde and (4-dimethylamino)-2-hydroxybenzaldehyde), were mixed respectively, in a single-mouth round flask 100 mL was added to it 5 mL ethanol and (0.04 g) of sodium hydroxide, then water and DMF were added to it in a ratio of (2:2) mL—the mixture was irradiated for 15–20 min under conditions (1 atmosphere, 200 watts, 80 °C)—to be followed The reaction was done by (TLC) and using a mobile phase of (ethyl acetate: n-hexane) in a ratio of (2:4) After the end of the reaction, the product was cooled and the solvent was evaporated using a rotary evaporator, and the rest was added to 30 mL of water and extracted using (3 × 30 mL) of acetate

The ethyl and the organic layer were dried using magnesium sulfate, the mixture was filtered, the solvent was evaporated, and the resulting product was recrystallized with ethanol [7,12].

3. Results and Discussion

Numerous studies have shown the importance of heterocyclic compounds and their derivatives, as they consist of more than 90% of pharmaceutical compounds. Therefore, researchers were interested in preparing these compounds to benefit from them in the pharmaceutical and medical fields, such as antibacterial, antifungal, antiviral, anticancer cells, and other therapeutic fields.

3.1. Identification of the Prepared Compounds

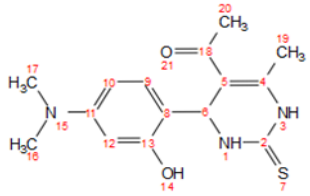
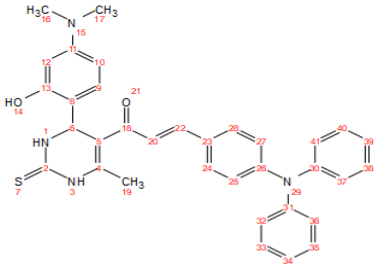
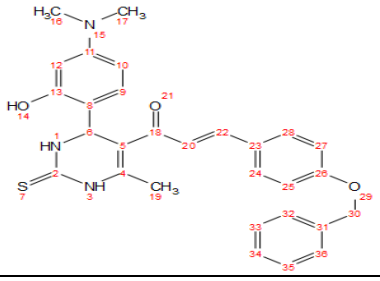
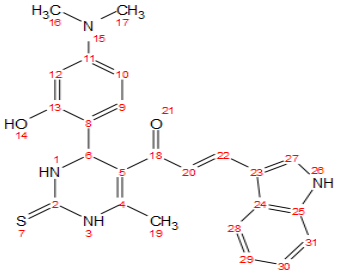
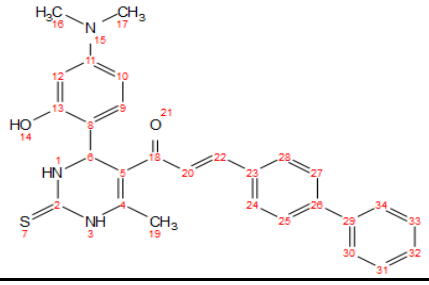
The compounds were prepared according to the preparation methods used in the work method, and the compounds were identified using the melting point technique as well as by following the spectroscopic methods represented by infrared spectra (IR) and proton nuclear magnetic resonance (^{1}H NMR spectra) and carbon (^{13}C NMR spectra) for all derivatives.as appearing in the following tables [13,14]:

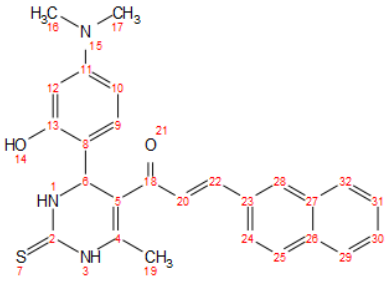
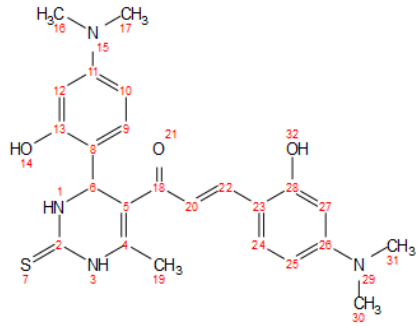
Table 1. spectral identification of derivatives.

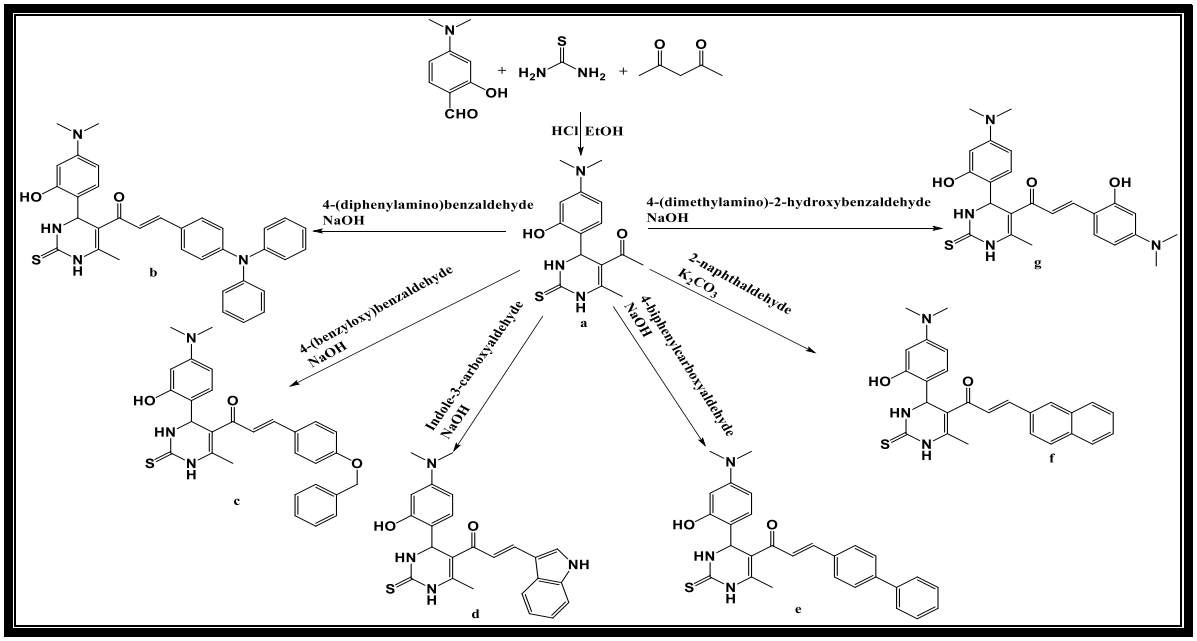
The Spectrum	The Group	The Derivatives						
		a	**b**	**c**	**d**	**e**	**f**	**g**
FT-IR (KBr) in cm−1	N-H&OH	3391	3378	3368	3380	3377	3383	3403
	C-H_{arom}	3080	3108,3069	3008	3058	3090	3090	3090
	C-H_{ali}	2963,2824	2924,2864	2967,2927	2924,2854	2969,2854	2960,2850	2968,2854
	C=O_{cha}	-	1639	1654	1650	1666	1650	1650
	C=$C_{cha.}$	-	1630	1628	1630	1627	1631	1630
	C=C $_{arm.}$	1597,1488	1594,1490	1554,1405	1584,1490	1566,1407	1560,1405	1569,1515
^{1}H-NMR (DMSO-*d6*, 400 MHz, δppm)	C19-H	2.34	2.38	2.29	2.26	2.37	2.37	2.35
	C16&17-H	2.93	2.93	2.85	2.82	2.85	2.95	2.89
	C6-H	5.82	5.84	5.83	5.90	5.85	5.77	5.78
	C-$H_{ar.}$ & C(20+22)-H	7.29–6.58	7.66–6.51	7.76–6.34	8.29–6.26	7.73–6.29	8.45–6.20	8.41–6.10
	N1-H	9.39	9.34	9.81	9.04	9.57	9.23	9.10
	N3-H	9.72	9.78	9.88	9.12	9.64	9.68	9.60
	O-H	10.81	10.26	10.67	11.09	10.14	10.00	10.65
	others	2.25 (C20-H)	-	5.01 (C30-H)	-	-	-	8.82 (C32-OH)
^{13}C-NMR (DMSO-*d6*, 100 MHz, δppm)	C-19	19.03	19.03	19.01	19.68	19.35	19.43	19.01
	C-(16+17)	39.36	40.63	39.83	39.67	39.56	39.91	39.84
	C-6	51.35	51.49	51.81	51.84	50.81	49.29	50.25
	C-5	112.91	112.69	112.91	112.63	113.40	113.60	112.35
	C-20	30.01	127.13	127.60	127.62	127.58	127.45	126.81
	C-22	-	147.28	145.33	136.36	145.68	145.34	144.99
	C-4	151.34	148.62	148.46	149.16	149.86	148.53	148.53
	$C_{ar.}$	157.11–99.62	159.68–99.83	158.48–100.47	155.28–98.56	155.52–99.55	155.96–99.20	157.23–97.88
	C-2	173.33	176.52	175.87	173.98	174.21	175.32	174.17
	C-18	189.44	185.32	185.41	185.69	185.71	186.37	184.59

	others	-	-	68.73 (C-30)	-	-	-	39.65 C-(30 + 31) 97.88 (C-30)

Table 2. physical properties of derivatives.

No.	Formula	m.p (oC)	Color	Rf	Yield (%)	Phase
a		190–191	Brown	0.54	89	solid
b		193–194	Brown	0.58	77	solid
c		198–200	blackish brown	0.61	79	solid
d		187–189	Red	0.67	82	solid
e		178–180	Brown	0.63	75	solid

f		165–167	blackish brown	0.77	85	solid
g		173–175	Red	0.69	81	solid



Scheme 1. Synthesis of chalcone derivatives.

3.2. Biological Activity

A study of the biological effectiveness of the prepared derivatives (a–g) was conducted on a type of gram-negative bacteria, *Escherichia Coli*. These bacteria were chosen because of their importance in the medical field, as they cause many serious diseases, as well as the nature of their resistance to antibiotics and therapeutic chemicals. It is noted that Table 3(1) shown that compound (b) shown a mediate inhibitory effect on gram-negative bacteria, *Escherichia Coli.* while compound (c) showed a weak inhibitory effect against negative bacteria, while compounds (d, f, and g) had a strong inhibitory effect on negative bacteria, *Escherichia Coli*, and it is believed that there is a relationship between the structural formula of the compound and its biological effectiveness. The compound's containment of heterocyclic rings works to increase the biological activity, in addition to that (OH, -N(Me)2) work to increase the biological effectiveness. The inhibitory activity of

the prepared compounds has been compared with the inhibitory effectiveness of the reference DMSO (as in the figures below). [15,16]

Table 3. shown the inhibition values for the prepared compounds.

no.	a	b	c	d	e	f	g
Inhibition zones (mm)	2	3	1	14	2	11	15

3.3. In Silico Study

In silico study of the derivatives (1–7) LD50 predicted computationally using by protox server and their study as anti-breast cancer by docking with (PDB:3eqm) protein by use (MOE 2015 program) as shown below:

3.3.1. LD50 Test by Protox 3.0 Online

The LD50 test determines the median lethal dose, which is the amount of a substance required to kill 50% of the test group (usually animals such as mice or rats). This test measures the acute toxicity of the substance; the lower the LD50 number, the more potent and lethal the substance is, as less of it is needed to cause death in half of the samples. The results are usually presented in milligrams of the substance per kilogram of body weight, which helps in comparing the relative safety of different products. ProTox 3.0 is a computational tool that predicts the oral toxicity of compounds by comparing their two-dimensional chemical structures with a database of known compounds, thereby estimating the dose that may be lethal to 50% of the tested animals. This approach aims to reduce the need for animal testing and provides a faster and less costly method to assess the potential acute toxicity of the compound.

The LD50 values of derivatives shown as following in below Table 4:

Table 4. shown the LD50 values by protox 3.0 for the prepared compounds.

The Derivative	a	b	c	d	e	f	g
LD50 (mg/Kg)	1700	1700	785	785	1700	1700	1700

3.3.2. Molecular Docking Study

Table 5 displays the results of the molecular docking and docking scores for each Ligand interaction with the (PDB:3eqm) receptor (Human Placental Aromatase Cytochrome P450 Protein) using (MOE 2015.10). The results show that chain A of (PDB:3eqm) receptor has the greatest binding affinity with (c) derivative having a general docking energy of about -10.1140 kcal/mol with a total of 2 sites of interactions [17].

Table 5. Binding Energies of synthetic derivatives on (PDB:3eqm).

The Derivative	Docking Score (kcal/mol)	Ranking	rsmd	Amino acid interaction
a	−7.2071	1	1.4506	SER 314, VAL 369, VAL 370
b	−9.5734	1	1.5638	MET 374
c	−10.1140	1	1.8279	ARG 115, ARG 375
d	−8.7276	2	1.0964	ARG 115, ARG 375, GLY 431, GLY 436,THR 310
e	−8.9375	1	1.7236	ARG 115, ARG 375
f	−8.4432	1	1.7314	ALA 438, ARG 115, THR 141, ARG 435, PHE 430
g	−9.1268	1	1.4235	ARG 115, ARG 375

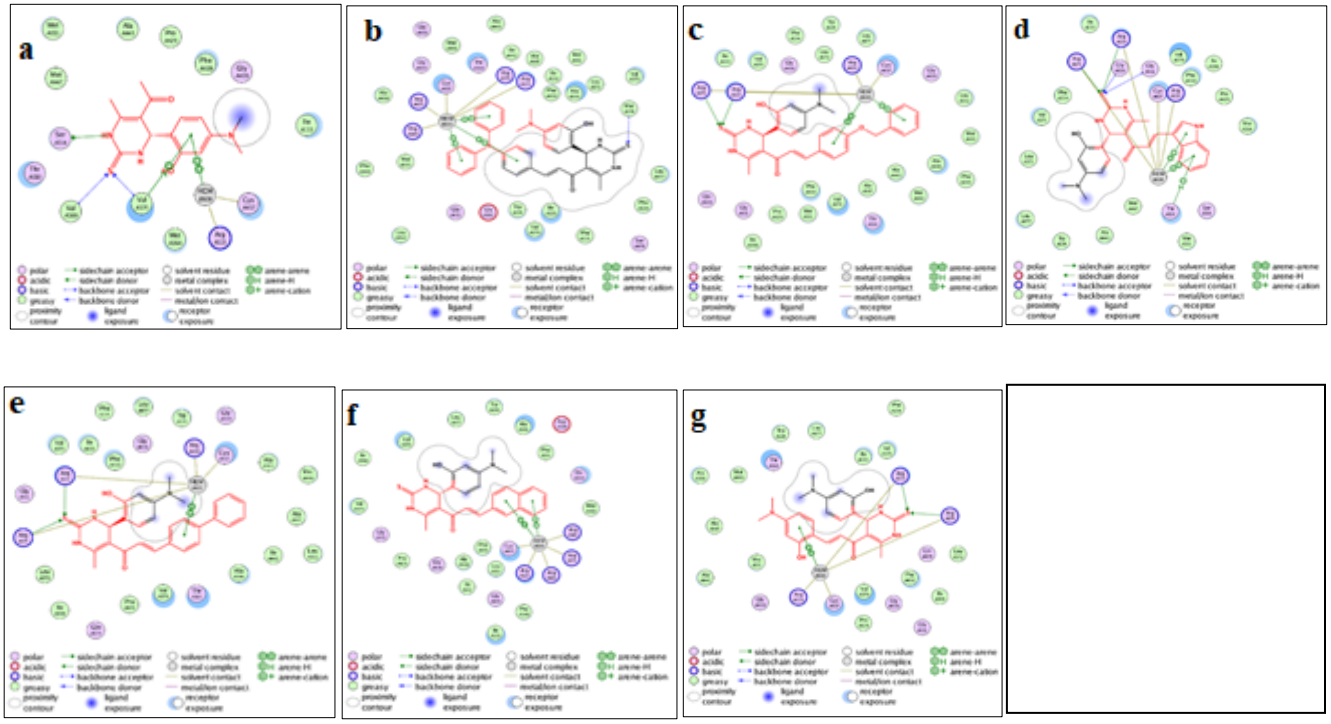


Figure 1. A two-dimensional diagram showing the binding sites of ligands (a-g) with the protein (PDB: 3eqm).

4. Conclusions

In this work, some derivatives containing the pyrimidine ring and the chalcone group were prepared and studied in terms of their structure as well as their effectiveness as antibacterial agents in the laboratory, and the lethal dose was studied using the protox 3.0 program. The results were very good in this regard. Additionally, their potential as breast cancer inhibitors was studied using molecular docking techniques by (MOE 2015.10) program, where molecular docking studies suggest strong binding affinity of some derivatives with the target protein, proposing them as potential breast cancer inhibitors.

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Conflicts of Interest:

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