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Synthesis, characterization, theoretical study and antibacterial studies of N(4-substitution phenylcarbamothioyl)biphenyl-4-carboxmide derivatives

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ABSTRACT

New compounds of N(4-substitution phenyl carbamothioyl) biphenyl-4-carboxamide derivatives have been prepared by first making biphenyl carbonyl isothiocyanate from ammonium thiocyanate and biphenyl carbonyl chloride, and then treating this products with primary amine to give products monothiourea, N- (phenylcarbanothioyl) biphenyl 4-carboxamide (1); N(p – tolylcarbmothoyl) biphelyl – 4 – carboxamide (2) and bisthiourea; N, Ń(1,4-phenylenebis (azanediyl) bis (thioxo methylene) dibiphenyl-4-carboxamide(3)and N,Ń(1,2-phenylene bis (azanediyl) bis (thioxo methylene) dibiphenyl-4-carboxamide (4). The structures of these compounds was characterized spectroscopy, theoretically and biological activity; the anti-bacterial activity indicated that compounds possessed a broad spectrum of activity.

Key words: thiourea, antibacterial activity, AM1and PM3semiemprical

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INTRODUCTION

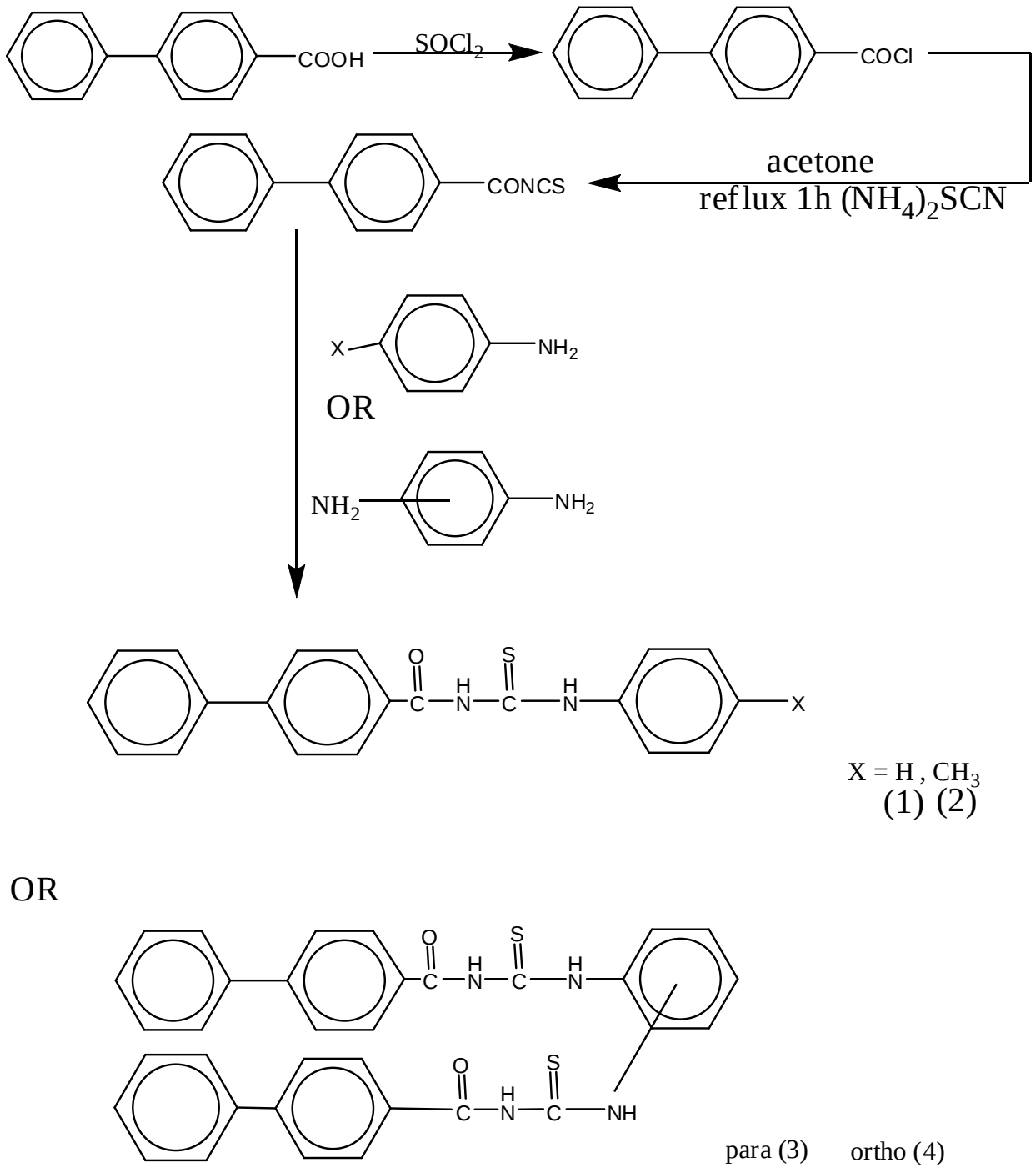
Thioureas compounds also known as thiocarbamide, are an organo sulfer compounds with formula $R_2SC(NH)_2$. It is structurally smaller to urea compounds except that the oxygen atom is replaced by a sulfur atom, but the properties of urea compounds differ significantly. Thiourea derivatives are playing an essential role in many fields, in industry, Its used as a corrosion inhibitory on mild steel in acid media [1].

Substituted thiourea are useful catalysts for organic synthesis, the phenomenon is called thioureaorgano catalysis [2].

Thiourea derivatives have biological properties such as antioxidant [3] antibacterial [4,5], antimicrobial [6], ant HlV activity [7,8], anti malarial [9] and anticancer [10].

Some Heterocyclic thiourea have been reported as new class of potent non-nucleoside inhibitors of human viruses type 1 reveres Ariansscriptas (NNRTIS) [11,12].

In the present paper, we report the synthesis, characterization, theoretical and antibacterial studies of some new mono thiourea compounds namely. N-(phenyl earbamothioyl) biphenyl-4-carboxamide (1), N (p-tolylcarbamothioyl) biphenyl- 4- carboxamide (2) and bisthiourea compounds namely N,Ń(1,4 – phenylenebis (azanediyl) bis (thioxomethylene) diphenyl -4- carboxamide (3) and N,Ń(1,2 – phenylenebis (azanediyl) bis (thioxomethylene) dibiphenyl 1,4 – carboxamide (4) as shown in Scheme 1.



Schem 1. The steps of formation products

MATERIALS AND METHODS

Preparation

New compounds of mono and bis thiourea were prepared in the study based on literatures [13-12]. The synthesis of these compounds consist of two parts, the first was prepared biphenyl -4- carbonyl chloride[18].

A solution of biphenyl- 4- carboxylic acid (10.g , 50.7 mmol) and N,N-dimethylforamide (DMF; 0.2ml) in thionyl chloride $SOCl_2$ (37.0 ml, 507 mmol) was strieed under reflux for 3h. After cooling at room temperature, the mixture was concentrated in vacuum to give biphenyl-4- carbonyl chloride as a colorless solid.

The second part, synthesis mono and bisthiourea of biphenyl -4- carbonyl chloride

(0.01 mol) from biphenyl-4-carbonyl chloride was added drop wise to a string a acetone solution 25ml of ammonium thiocyanat (0.01 mol) . The solution mixture was stirred at 50 ^{0}C for about 20 minutes. A solution of primary amine (0.01 mol) in dry a acetone was added and the reaction mixture was heated under reflux for 3 hours. The resulting solution was left to evaporate at room temperature. Crystallible solid was collected by filtration washed several time with cold ethanol and dried at room temperature to give product as described in Table 1.

Table 1: physical properties of prepared compounds

Comp. No	Colors	Yield	Mol. formula	Molecular weigh	Melting point°C
1	Brown	70	$C_{20}H_{16}N_2SO$	332.4211	182
2	Brown	70	$C_{21}H_{18}N_2SO$	346.4478	188
3	Brown	69	$C_{34}H_{26}N_4S_2O_2$	586.7299	199
4	Brown	65	$C_{34}H_{26}N_2S_2O_2$	586.7299	200

Physical measurements

IR spectra were recorded on a SHMADSU 8400 FT – IR spectrophotometer. Melting points were measured on Gallen Kemp melting point apparatus and were uncorrected.1HNR spectra were obtained CDCl3-d6 solvent using Bruker 300HZ, type advance Mltrasheild instrument in Central laboratories of the Institute of Earth and Environment Science of the University of Al al-Bayt, Jorden.

Theoretical calculations

AM1 and PM3 semi-empirical methods were preformed in the program hyperchem 8.01 were utilized to compete the properties of compounds (heat of formation ΔH, kcal.mol^{-1}), Homo orbital energies (E_{Homo}, ev), Lumo orbital energies (E_{Lumo}, ev), number of electron, total orbital and number of occupied level.

Biological activity

A filter disk assay was used to determinate the biological activity of the prepared compounds against strains of gram poisitive and gram negative bacteria which are (staphylococcus aureus and Escherichia coli) which were tasted using plate of muller – Hinton agar. The biological activity was defined as the clear zone of growth inhibition [19].

RESULTS AND DISCUSSION

FTIR spectra

The infrared spectra for all thioureas compound showed the expected frequencies of ʊc=o, ʊN–H, ʊC–N, at 1650 – 1630 cm^{-1}3367 – 3211 cm^{-} and 1446.5 – 1442.66 cm^{-1} respectively, the ʊc=s stretching vibration about 1115 – 1120 cm^{-1} are the close agreement with previously reported of the thiourea derivative [20 – 22]. Two strong peaks of aromatic double bond c=c stretching at 1558 – 1583 and 1544 – 1541 cm^{-1}. Table 2 showed the IR spectra for these compounds.

Table 2. IR values in cm^{-} for prepared compounds

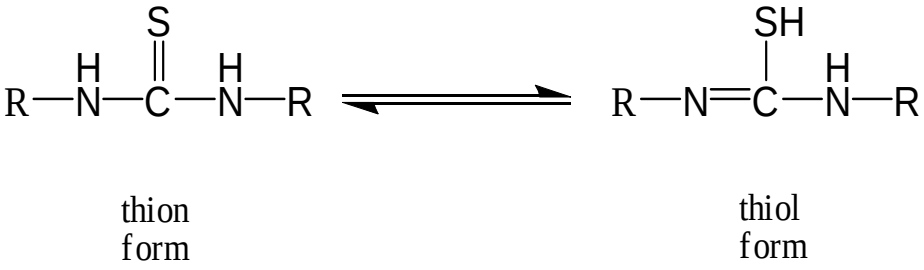
Comp. no	N-H	NH Ar	C=O	C=C	C-N	C=S
1	3473.56	3367.48	1645.17	1579.5 1529.4	1442.66	1115
2	3461	3365.55	1649.02	1583.45 1512.09	1442.66	1120
3	3508.21	3367.48	1649.02	1583.45 1512.09	1442.66	1115
4	3415.7	3211.26	1629.74	1498.58	1446.51	1115

^{1}HNMR

^{1}HNMR spectra of these compounds show similar peaks. The two singlet peaks related to thio amide protons (H, CS-NH) between11.5-12.5ppm and amide protons (H, CONH) chemical shift between 11.2-11.9ppm. The multiple peaks of aromatic protons (Ar-H) observed at 7-8.2 ppm. The substitution methyl protons appear as a single peak at 1.8ppm.

Electronic properties

The prepared compounds were exist in thion-thiol equilibrium due to the mobility of NH proton to mercapto to form thiol form Schem 2. [23]



Schem 2. Equilibrium between thion-thiol form

Theoretical studies on the tautomerisms using two semiemprical calculation methods (AMI and PM3) has shown that thion form was more stable than thiol form . Heat of formation of thion was smaller than thiol and this agreement with study of N-methyl- 4,5- phenyl mercaptoimidazole [23]. Table 3 show some of molecular information about the molecules studied . The ball and stick models of same molecules are shown in Figures (1-4) .

Table 3: Some electronic properties for prepared compounds

Comp. no	ΔH formation kcal /mole thion		ΔH/thiol		E_{Homo} ev	E_{Lomo} ev	No. of electron	Total orbital	No. of Occupied/ level
	AM1	PM3	AM1	PM3					
1	**89**	**92**	**100**	**103**	**-8.303**	**-1.211**	**118**	**112**	59
2	**92**	**89**	**102**	**105**	**-7.870**	**-1.700**	**124**	**118**	62
3	**150**	**155**	**163**	**167**	**-7.035**	**-5.903**	**206**	**149**	103
4	**150**	**154**	**160**	**163**	**-8.440**	**-2.349**	**206**	**149**	103

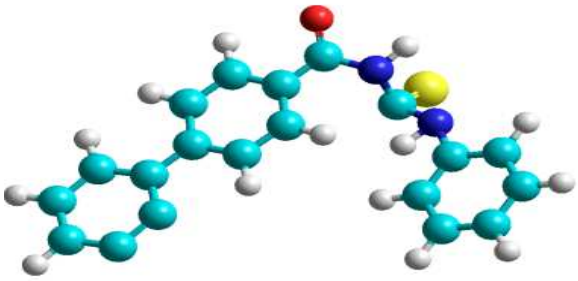
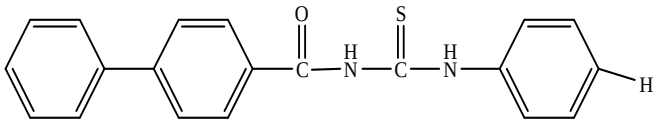
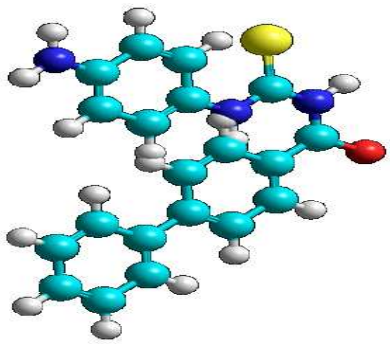


Fig.1. configuration of N- (phenylcarbanothioyl) biphenyl 4-carboxamide (1)





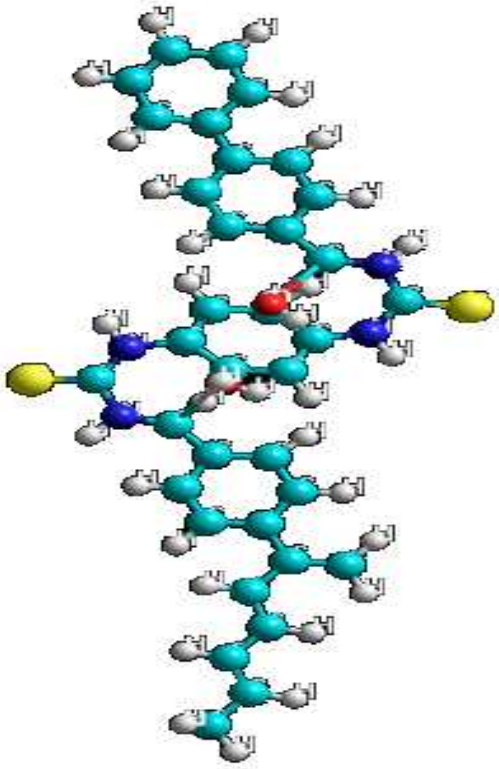


Fig.2. configuration of N-(p – tolylcarbmothoyl) biphelyl – 4 – carboxamide (2)

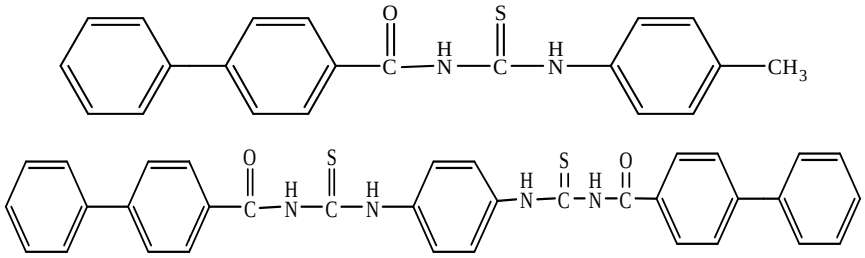


Fig.3. configuration of N, Ń-(1,4-phenylenebis (azanediyl)bis (thioxo methylene) dibiphenyl-4-carboxamide(3)

The biological activity

The results of the prepared compounds were shown in figures (5 and 6) . The prepared compounds in this study were shown very effective against gram negative strain (Escherichia coli) but less active against gram positive strain (Staphylococcus aureus).It has been postulated that cell membrane of (Escherichia coli) contains many condensed fat layers compared with (Staphylococcus aureus) [24] . The Chemicals and antibiotics or antiseptics face difficulty in penetrating these membranes and , therefore , their effectiveness is diminished , this may be justified due to the ionic combination between each complex and the phospholipids of the bacterial cell well, which led to destroy the cell membrane and then led to inhibit the microbial growth and may change the cell protein nature (Denaturation)and increase the permeability of the cell membranes [25] , as many types of antibacterial compounds [26].

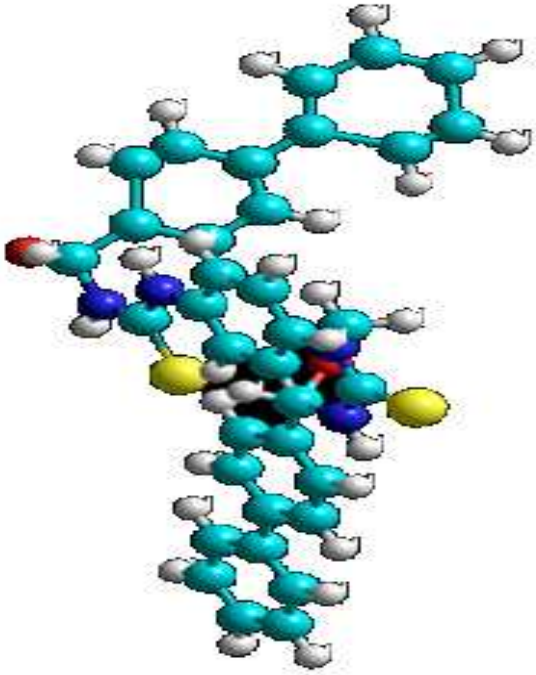
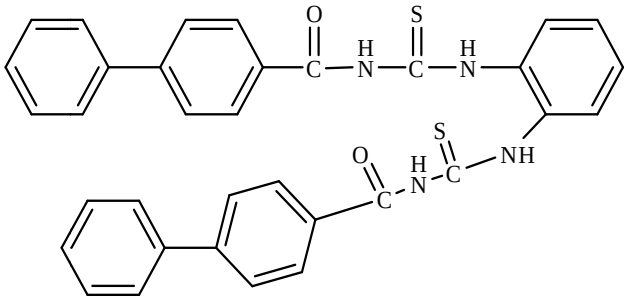


Fig.4.configuration of N,Ń(1,2-phenylene bis (azanediyl) bis (thioxo methylene) dibiphenyl-4-carboxamide (4)



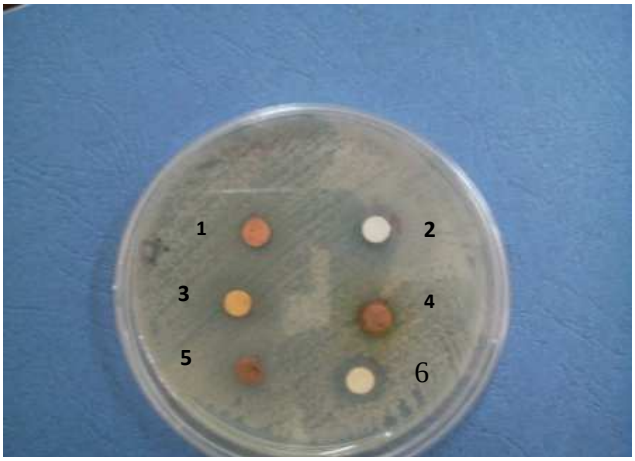


Fig 5: The antibacterial activity of prepared compounds against. *S. aureus*

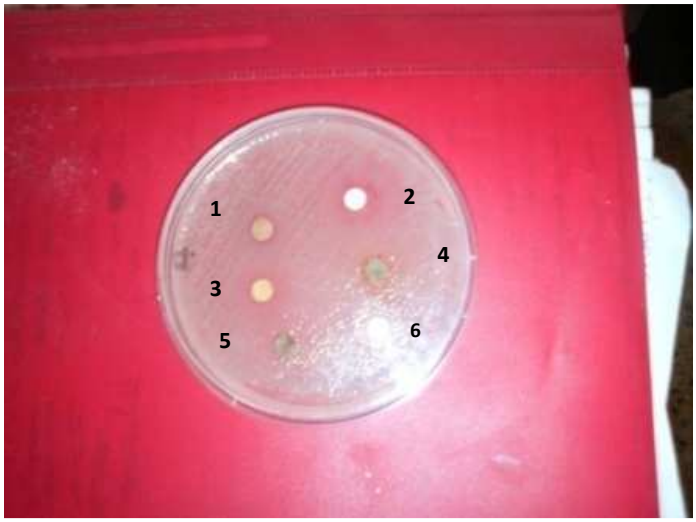


Fig6 : The antibacterial activity of prepared compounds against *E. coli*

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