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Synthesis, Characterization and Preliminary Antimicrobial Evaluation with DFT Study of New Thiazole Derivatives

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Abstract

Two compounds**,[**2-amino-4-(4-nitrophenyl)1,3-thiazole**],(4)** and [2-amino-4-(4-bromo phenyl)1,3-thiazole**],(5)**, were synthesized by refluxing thiourea **(1)** with each of *para*-ntirophenacylbromide **(2)** and *para*-bromophanacyl bromides **(3)** respectively**,** in dry methanol. Then, by reaction of compound **[5]** with 3,5-dinitrobenzoyl chloride in dimethylformamide **(DMF)** yielded compound **(6) .**On the other hand, reaction of compound **(4)** with chloroacetyl chloride in dry benzene afforded compound **(7)**, which is upon treatment with thiourea in dry methanol, afforded compound **(8)** . The characterization of the titled compounds were performed utilizing FTIR spectroscopy, [1]HNMR, CHNS elemental analysis and by measurements of their physical properties. The synthesized compounds had been screened for their, *in vitro* preliminary antimicrobial activity against four Gram positive bacteria (*Staphylococcus aureus, Micrococcus luteus, Bacillus subtilis* and *Bacillus pumilus*), and four Gram negative bacteria (*Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis* and *Klebsiella pneumoniae*)and three fungi species: (*Saccharomyces cerevisiae, Candida Tropicalis* and *Candida albicans*) using a minimum inhibitory concentration (MIC) of 100 µg\ml of a derivative in dimethylsulfoxide, by well diffusion method.

Compound **(6)** showed moderate antibacterial activity against some tested Gram positive bacteria (*Bacillus pumilus* and *Bacillus Subtilis*) and a moderate antifungal activity towards *Candida albicans*. Computational study was performed to calculate some of the thermodynamic parameters of synthesized derivatives by using density functional theory (DFT).

Keywords: Antimicrobial, Thiazole, DFT

تحضيرو تشخيص والتقييم الاولي المضاد للميكروبات مع دراسة نظرية الكثافة الوظيفية لمشتقات جديدة لحلقة الثيازول

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الخلاصة

حضر المركبان: [2-أمينو-4- (4-نايتروفينيل)- 1،3-ثيازول] **(4)** و [2-أمينو-4- (4-بروموفينيل) -1،3-ثيازول] **(5)** من تصعيد الثيوريا **(1)** مع كل من معوض نايترو فيناسيل بروماید**(2)** ومعوض برومو فيناسيل بروماید**(3)** على التوالي, باستعمال الميثانول الجاف. من ثم تم مفاعله المركب **(5)** مع 3،5-دينيتروبنزويل كلورايد في المذيب دايمثيل فورماميد لينتج المركب **(6)**. ومن ناحية أخرى تفاعل المركب **(4)** مع كلورو استيل كلورايد في البنزين الجاف انتج المركب **(7)** والاخير , بمفاعلته مع الثايويوريا في الميثانول الجاف انتج المركب**(8).**

تم تشخيص المركبات المحضره باستعمال مطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون والتحليل الدقيق للعناصر و كذلك قياس الخصائص الفيزيائية للمواد المحضره.

تم تقييم النشاط الاولي المختبري المضاد للميكروبات ضد أربع انواع من البكتريا الموجبه لصبغه غرام, وهي:(*المكورات العنقودية الذهبية، المكورات الدقيقة، العصوية الرقيقة و عصوية بوموليس*)، وكذلك ضد أربعة انواع من البكتيريا السالبة لصبغه غرام, وهي: (*الزائفة الزنجارية، الاشريكية القولونية ,المتقلبة الرائعة و الكليبسيلة الرئوية*) وثلاث انواع من الفطريات (*فطريات الخميرة و المبيضات الاستوائية والمبيضات البيض*) باستعمال 100مايكروغرام من المادة مذابة في ا مل من الدايميثيل سلفوكساید كأقل تركيز مثبط وذلك باستعمال طريقة الانتشار.

أظهر المركب **(6)** نشاط متوسط ضد بعض من البكتيريا الموجبه لصبغه غرام(*العصوية الرقيقة و عصوية بوموليس*)و نشاط معتدل ايضا مضاد للفطريات المبيضات البيض. تم في الاخير, اجراء دراسة حسابية لقياس بعض الـمعاملات الديناميكية الحرارية للمركبات المحضره باستعمال نظريه الكثافه الوظيفية.

الكلمات المفتاحية:- مضاد للميكروبات , ثيازول, نظريه الكثافه الوظيفية.

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Introduction

Thiazole is a five membered aromatic heterocyclic ring containing sulfur and nitrogen in its structure. Thiazole derivatives had received a great attention due to their remarkable reported different biological activities such as ,inhibitors of neuronal nitric oxide synthase[1], anti-cancer [2], antimicrobial [3-9], calcium-activated small conductance potassium channel blockers[10], antiulcerogenic[11], adenosine A3 receptor antagonists [12], antitumor [13], antifungal [14]and anti-inflammatory activities[15,16].

The thiazole ring moiety is an integral part of many potent biologically active pharmaceutical products such as pramipexole (dopamine agonist indicated for treating parkinson's disease) [17], meloxicam (NSAID drug, COX-2 inhibitor) [18] and in many third generation cephalosporins [19].Thiazole ring is also found naturally in the essential vitamin B_1 thiamin [20]. DFT calculations were used to study the quantitative structure-activity relationships (QSAR).

Materials and Methods

All chemicals and solvents used during synthesis were of analytical grade and used without further purification. Completion of reactions and the purity of compounds were ascertained by thin-layer chromatography (TLC), using Silica gel GF_{254} (type 60) pre-coated Aluminium sheets, Merck (Germany) exposed to UV-254nm light and the eluent used is ethyl acetate: *n*-hexane 4:6 for compounds **(4), (7)** and **(8),** and ethyl acetate: *n*-hexane 5:5 ,for compounds **(5)** and **(6)** to run TLC. Melting points were determined using Stuart SMP3 melting point apparatus in open capillary tubes, and are uncorrected. Fourier-Transform Infrared spectroscopy (FTIR), (KBr disc) (υ,cm^{-1}) were recorded using (Biotech engineering management FTIR-600, UK) at the University of Baghdad /College of Education for Pure Sciences Ibn Al-Haitham /central service laboratory .

Furthermore, The elemental microanalysis of the synthesized compounds was done using (Elemental vario MICRO cube instrument ,Germany) in the University of Mustansiriya-College of Pharmacy. ^{1}HNMR spectra were recorded on BRUKER model Ultra shield 300 MHz spectrophotometer with tetramethylsilane (TMS) as an internal standard, chemical shift were expressed as (δ=ppm) and coupling constant in (Hz), and it was run in Al al-Bayt University, Amman, Jordan. The synthetic method is depicted in scheme 1.

Chemical synthesis

General method for synthesis of parent nucleus (4and 5) [21]

A mixture of thiourea **(1)** (0.01 mol, 0.76g) and each of: 4-nitro phenacyl bromide **(2)** (0.005 mol, 1.22 g) or of 4-bromo phenacyl bromide **(3)**, (0.005 mol,1.38 g) were dissolved in 100 ml of dry methanol in a round bottom flask and refluxed for 3-4 h. After completion of reaction, as monitored using TLC, the mixture was cooled to room temperature then poured into cold water. The solid separated was collected by filtration. The residue obtained was dried, recrystallized from absolute ethanol.

2-amino-4-(4-nitro phenyl thiazole) **(4)**

Orange powder; yield 80%; m.p. 288-291°C; **IR** (KBr),(υ,cm^{-1}): 3398 and 3305 cm^{-1} *prim*. (NH_2) (str.); 3153 cm^{-1} Ar-(C-H) str, 1641 cm^{-1} (C=N) str ,1593&1325 cm^{-1} *asym*. and *sym*. (N=O) str of NO_2,1539 cm^{-1} (N-H) bend, 1502 cm^{-1} Ar(C=C)str,1410 cm^{-1} (N=O) bend, 1107 cm^{-1} (C-N) str,1038 & 845cm^{-1} in plane & out of plane Ar(C-H) bend, 717 cm^{-1} out of plane Ar-(C=C) bend.,663cm^{-1} (C-S) str.

2-amino-4-(4-bromo phenyl thiazole) **(5)**

Off white to pink powder; yield 73%; m.p. 181-184°C ; **IR**(KBr),(υ,cm^{-1}): 3429 and 3282 cm^{-1} *prim*. (NH_2) str, 3113 cm^{-1} Ar(C-H) str, 1633 cm^{-1} (C=N) str ,1533 cm^{-1} (N-H) bend,1473 cm^{-1} Ar(C=C) str,1198 cm^{-1} (C-N) str , 1038 & 906 cm^{-1} in plane& out of plane Ar(C-H) bend., 727 cm^{-1} out of plane Ar(C=C) bend., 669 (C-Br) str, 636 cm^{-1} (C-S) str.

General method for synthesis of (6) [22]

3,5-dinitrobenzoyl chloride (0.00078 mol,0.179 g) was added drop-wise to a stirring solution of compound **(5)** ,(0.00078 mol,0.2g) in dimethyl formamide (DMF). The mixture then refluxed for 4 h .after completion of reaction as monitored by TLC, The mixture was poured into distilled water to produce a precipitate which was collected by filtration. The residue was neutralized with 5% $NaHCO_3$ to *p*H7, and subsequently washed with water, Column chromatography was run using silica gel (60-120 mesh) and the mobile phase used; ethyl acetate: n-hexane (5:5) and recrystallized from aqueous methanol

N-(4-(4-bromophenyl)thiazol-2-yl)-3,5-dinitrobenzamide **(6)**

Light gray powder; yield 40%; m.p.165-168 °C ; **IR** (KBr),(υ,cm^{-1}):3410 cm^{-1} *sec*. amide (N-H) str., 3066 cm^{-1} Ar(C-H) str,1682 cm^{-1} (C=O) amide str, 1630 cm^{-1} (C=N) str,1572 cm^{-1} (N-H) amide bend., 1539&1346 cm^{-1} *asym*. &*sym*. (N=O)str, 1475cm^{-1} Ar(C=C)

str,1319 cm^{-1} (N=O) bend, 1288 & 908 cm^{-1} in plane& out of plane Ar(C-H) bend., 1070 cm^{-1} (C-N) str, 729 cm^{-1} out of plane Ar(C=C) bend. , 675 cm^{-1} for (C-S) str, 561 cm^{-1} for (C-Br) str.; **^{1}HNMR(300 MHz,acetone-d_6,δ= ppm)**: 11.25(1H,s,NHCO);9.15(2H,s,2Ar-H);8.65(1H,s,Ar-H);7.80(2H,d,Br-2Ar-H); 7.71(2H,d,Br-2Ar-H); 6.54(1H,s,H_5-Thiazole(THZ)); **CHNS** elemental microanalysis Calc., for ($C_{16}H_9BrN_4O_5S$) **Found**: C%42.635, H%2.136, N%12.098, S%7.095; **Calc**., C% 42.78,H% 2.02,N%12.47,S%7.14.

General method for synthesis of (7) *(23)*

A solution of compound **(4)** (0.005 mol, 1.10 g) in dry benzene (30 ml) was cooled to 0-5ºC in an ice bath. Chloroacetyl chloride (0.01 mol, 0.79 ml) dissolved in dry benzene (20 ml) was slowly added to the solution with vigorous stirring . When the addition was complete, the reaction mixture was stirred at room temperature for 30 min., then refluxed in a round bottom flask and a reflux condenser for 3 h. The reaction was monitored using TLC, and by using litmus paper which turns red indicative of HCl liberation. Then benzene was removed in rotary evaporator. The residue was neutralized with 5% $NaHCO_3$ to *p*H 7, and subsequently washed with water. The product was dried and recrystallized from methanol.

2-chloro-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide **(7)**

Bright Yellow powder; yield 82%; m.p. 214-217 ˚C ; **IR**(KBr)υ,cm^{-1}: 3354 cm^{-1} *sec*. amide (N-H) str,3105 cm^{-1} Ar(C-H) str, 3001&2947 cm^{-1} for *asym*. & *sym*. aliphatic (CH_2) str,1701 cm^{-1} (C=O) amide str ,1597&1444 cm^{-1} *asym.* & *sym.* (N=O) str,1549 cm^{-1} (N-H) amide bend., 1504 cm^{-1} Ar(C=C) str,1396 cm^{-1} (CH_2) bend.,1331 cm^{-1} (N=O) bend.,1151 cm^{-1}(C-N) str,1111&849 cm^{-1} in plane & out of plane Ar(C-H) bend.,849 cm^{-1} (C-Cl) str, 737 cm^{-1} out of plane Ar(C=C) bend., 634 cm^{-1} for (C-S) str.

; **^{1}HNMR(300 MHz,DMSO-d6,δ= ppm):**12.76(1H,s,NHCO); 8.31(2H,d,NO_2-2Ar-H);8.16 (2H,d,NO_2-2Ar-H);8.06(1H,s,H_5-THZ);4.43 (2H,s,$COCH_2$). ;**CHNS** elemental microanalysis Calc., for ($C_{12}H_{11}N_5O_3S_2$)**, Found**: C%44.66,H%2.853,N%14.13,S%10.428; **Calc**.,C%44.38,H% 2.71,N%14.11,S%10.77.

General method for synthesis of (8) *(24)*

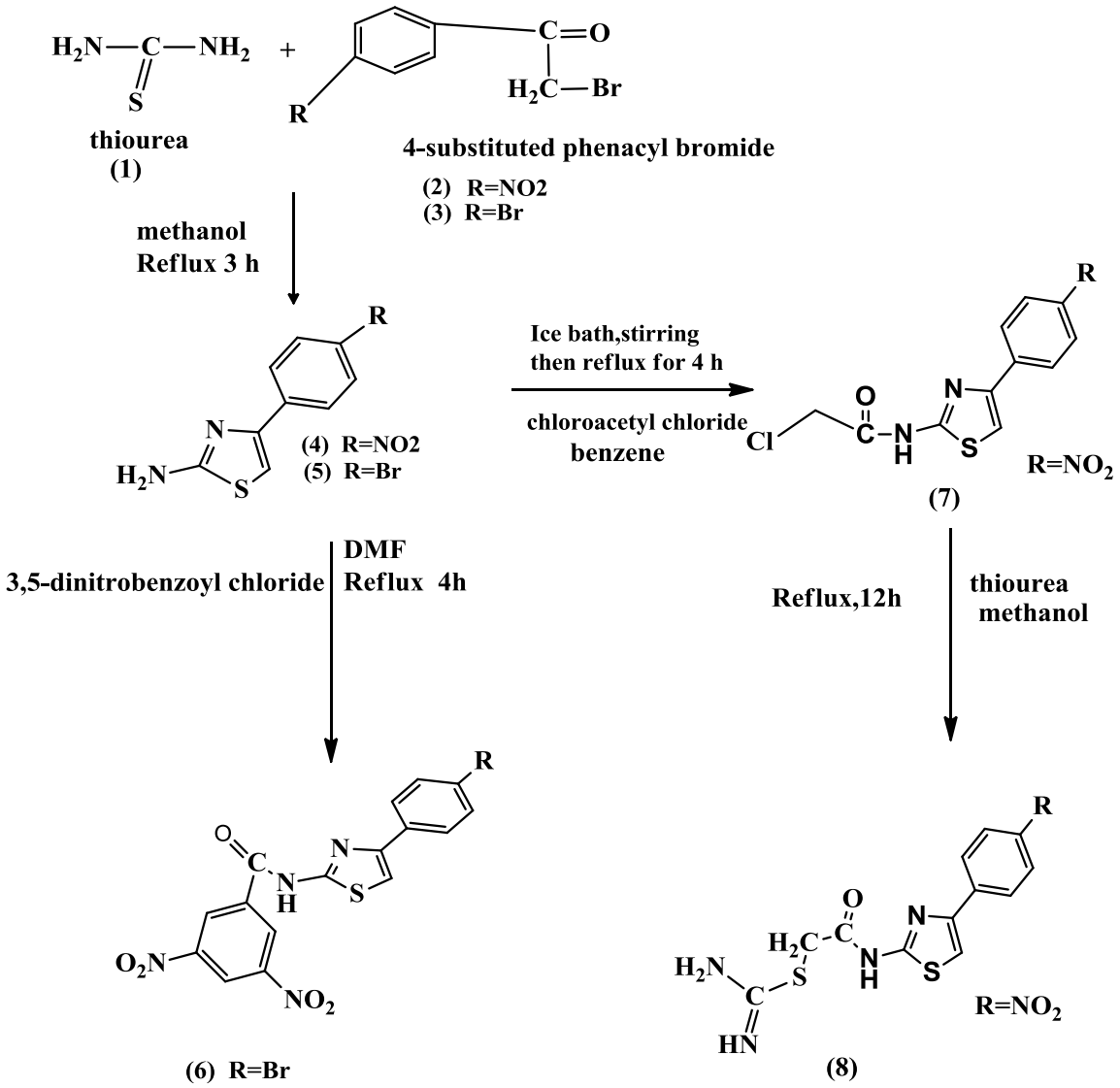
Equimolar amount of compound **(7)** (0.00117mol,0.35g) and thiourea (0.00117 mol,0.089g) in dry methanol was refluxed for 12 h .The solvent was removed in rotary evaporator .The residue was neutralized with 5% $NaHCO_3$ to *p*H 7,and subsequently washed with water ,filtered and dried. Column chromatography was run using silica gel (60-120 mesh) and the mobile phase used : ethyl acetate: *n*-hexane (4:6) to purify the titled compound, then recrystallized from aqueous methanol.

N-(4-(4-nitrophenyl)thiazol-2-yl)-2-thioureidoacetamide **(8)**

Light orange powder; yield 51%; m.p. 260 ˚C(decomposed); **IR**(KBr),(υ,cm^{-1}): 3398& 3303 cm^{-1} *prim*. (NH_2) str,3141 cm^{-1} *sec*. amide (N-H) str, 3116 cm^{-1} Ar(C-H) str,2981 & 2927 cm^{-1} *asym.&sym.* aliphatic (CH_2) str, 1641 cm^{-1} (C=O) amide str, 1593cm^{-1} (N-H) amide bend.; 1537&1325 cm^{-1} *asym.* &*sym*. (N=O) str of (NO_2), 1502 cm^{-1} (C=N) str. overlapped with Ar(C=C) str, 1038cm^{-1} (C-N) str.

; **^{1}HNMR(300 MHz, DMSO-d6,δ= ppm**): 12.80(1H,br,NHCO); 8.23(2H,d, 2Ar-H); 8.04 (2H,d, 2Ar-H); 7.40(2H,s,NH_2); 7.25(1H,s,H_5-THZ); 4.45(2H,s,CH_2),

; **CHNS** elemental microanalysis Calc. for ($C_{12}H_{11}N_5O_3S_2$), **Found**: C%42.300,H% 3.250, N%20.570, S%19.084 ;**Calc**., C%42.72,H%3.29,N%20.76,S% 19.01.



Scheme 1. Synthesis of titled thiazole derivatives.

Antimicrobial Screening

The antimicrobial activities of the synthesized derivatives were measured using well diffusion technique[25] with a comparison to cefotaxime sodium (cefot.) and sulfamethoxazole (sulf.) as standard antibacterial agents ,and miconazole as standard antifungal agent, using dimethylsulfoxide (DMSO) as solvent and as a control, and it was run in the ministry of health / National Center for Drug Control and Research (NCDCR) /Baghdad and in University of Baghdad /College of Education for Pure Sciences Ibn Al-Haitham /central service laboratory. The synthesized compounds had been screened for their *in vitro* preliminary antimicrobial activity against four Gram positive bacteria (*Staph.aureus, Micrococcus luteus, Bacillus subtilis* and *Bacillus pumilus*), four Gram negative bacteria (*Pseud.aeruginosa, E.coli, Proteus mirabilis* and *Klebsiella pneumoniae*) and three fungi (*Saccharomyces cerevisiae, Candida tropicalis* and *Candida albicans*), using a minimum inhibitory concentration (MIC) of 100 µg\ml of compound in DMSO as shown in tables **1** and **2**.

Results and Discussion

Chemistry

The synthesis of parent nucleus **(4) and (5)**, was carried out according to Hantzsch method, by refluxing *thiourea* **(1)** and *4-*

*substituted(4-Bromo or 4-nitro) phenacyl bromide***s (2)**and **(3)** in absolute methanol for 3 hours. They are characterized by FTIR, due to appearance primary amine ($\underline{NH_2}$) stretching at 3398 &3305 cm^{-1} for compound **(4)** and 3429&3282 cm^{-1} for compound **(5)**.

Compound **(6)** characterized by carbonyl amide ($\underline{C=O}$) stretching at 1682 cm^{-1},While ^{1}HNMR displayed ($\underline{NH}CO$) peak as *singlet* at δ=11.25 ppm, and the aromatic ring integrated for seven protons are displayed at their expected region (see exp. part).

Compound **(7)**, characterized by the appearance of ($\underline{C=O}$) amide stretching at 1701 cm^{-1} and a characteristic peak, as a *singlet* due to ($\underline{NH}CO$) δ=12.76ppm in addition to the aromatic protons displayed at their expected region.

Compound **(8)** recorded in the IR spectrum two characteristic absorption bands of primary amine (side chain), ($\underline{NH_2}$) stretching, at 3398 and 3303 cm^{-1}, while ^{1}HNMR spectrum displayed a *broad* peak at δ=12.80 ppm, , attributed to $\underline{NH}CO$, also prominent peak at δ= 7.40ppm as a *singlet* due to NH_2 of thiourea.

It must be noted that the H5-THZ recorded for the compound **(7)** and **(8)** as a *singlet* peak at δ= 8.06 and 7.25 ppm, respectively.

Antimicrobial activity

From the data illustrated in tables **1** and **2**, Compound **(6)** showed moderate antibacterial activity against some tested Gram positive bacteria (*Bacillus pumilus* and *Bacillus subtilis*), while compound **(8)** displayed no antimicrobial effect**.** In addition, compound **(6)** displayed moderate antifungal activity against *Candida albicans.*

Table 1. Antibacterial activity of the tested compounds.

Cpd. No.	Conc. µg/ml	*Staph. aureus*	*Micrococcus luteus*	*Bacillus pumilus*	*Bacillus subtilis*	*Pseud. aeruginosa*	*E.coli*	*Proteus mirabilis*	*Klebsiella pneumoniae*
		Zone of Inhibition (mm)							
(6)	100	_	_	11.3	12	_	_	_	_
(8)	100	_	_	_	_	_	_	_	_
Cefot.	100	50.11	59	41.5	45	32.5	53.2	27	28
Sulf.	100	24	29	32.4	20	25	27.8	27	23
DMSO	_	_	_	_	_	_	_	_	_

Table 2. Antifungal activity of the tested compounds.

Compound no.	Conc. µg/ml	*Saccharomyces cerevisiae*	*Candida tropicalis*	*Candida albicans*
		Zone of inhibition(mm)		
(6)	100	_	_	10.8
(8)	100	_	_	_
Miconazole	100	36.5	16	23.8
DMSO	_	_	_	_

(-)= No activity, slightly active (Inhibition Zone in between 5-10 mm), moderately active (Inhibition Zone in between 10-15 mm), highly active (Inhibition Zone More Than 15 mm). [26-28]

Computational Studies

Density function theory (DFT)

In order to explore the theoretical-experimental consistency, quantum chemical calculations were performed with complete geometry optimizations using standard Spartan 10 software. Geometry optimization was carried out by B3LYP / 6-31G* level of theory.

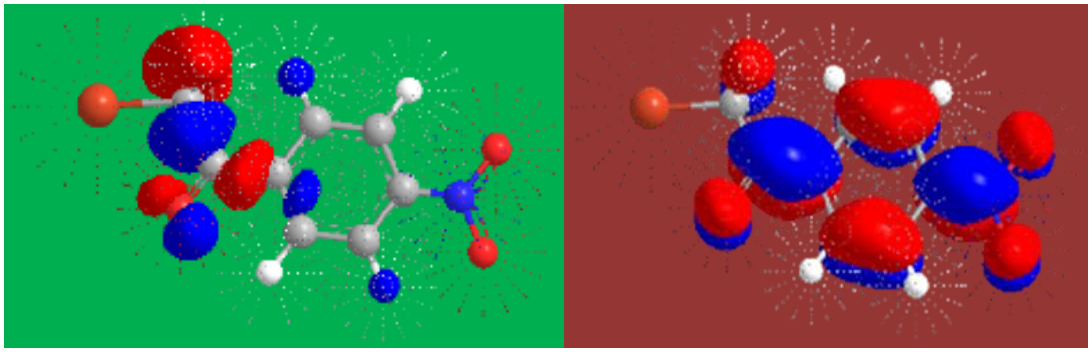
The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) play an important role in the molecule. These orbitals are sometimes referred to as the frontier molecular orbital.

Fig.**1** shows the frontier molecule orbital density distributions of the investigated compounds .The HOMO orbital is an electron donor and the LUMO orbital is the electron acceptor. The difference in energy between

HOMO orbital and LUMO orbital (energy gap) is a very effective property for characterizing the kinetic stability and chemical reactivity of the molecules. A molecule with a small LUMO-HOMO energy gap is chemically more reactive and kinetically less stable. On the contrary, a large LUMO - HOMO energy gap corresponds to high kinetic stability and low chemical reactivity [29].

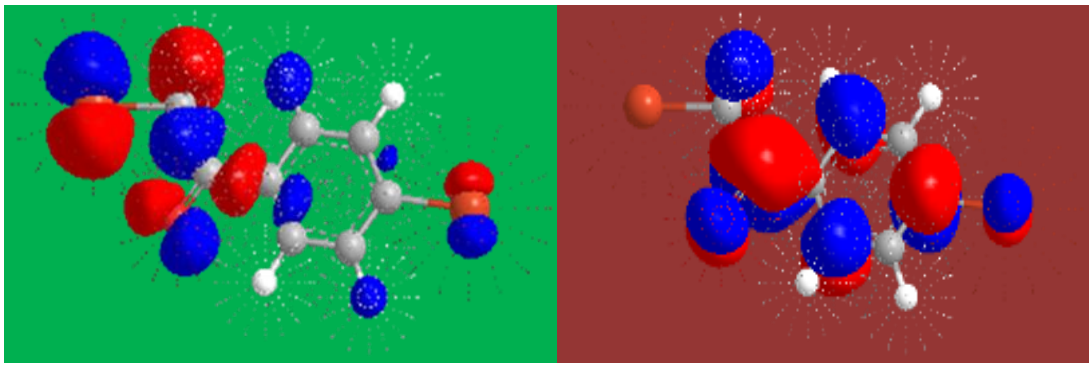
Structural and electronic properties

DFT calculations were performed for compounds (2 - 8). Optimized molecular structures of the most stable form are shown in Figure **1**.



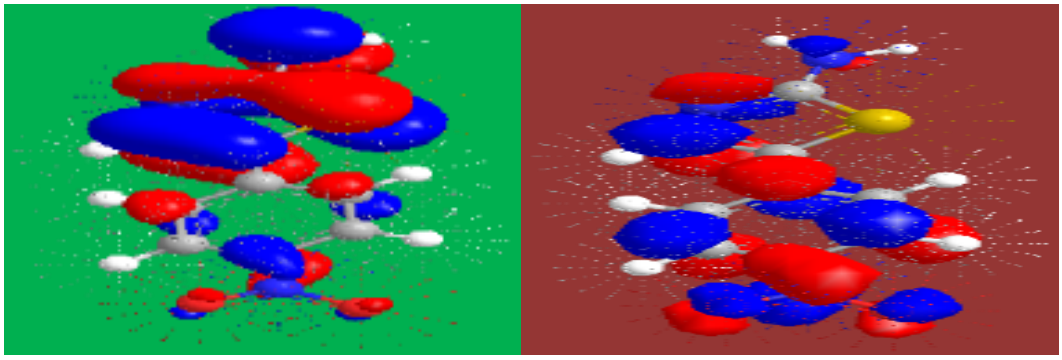
HOMO LUMO

Compound (2)



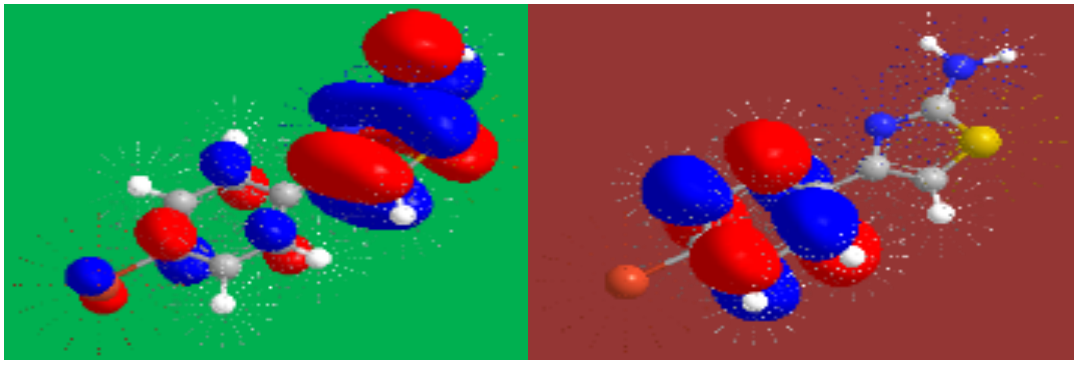
HOMO LUMO

Compound (3)



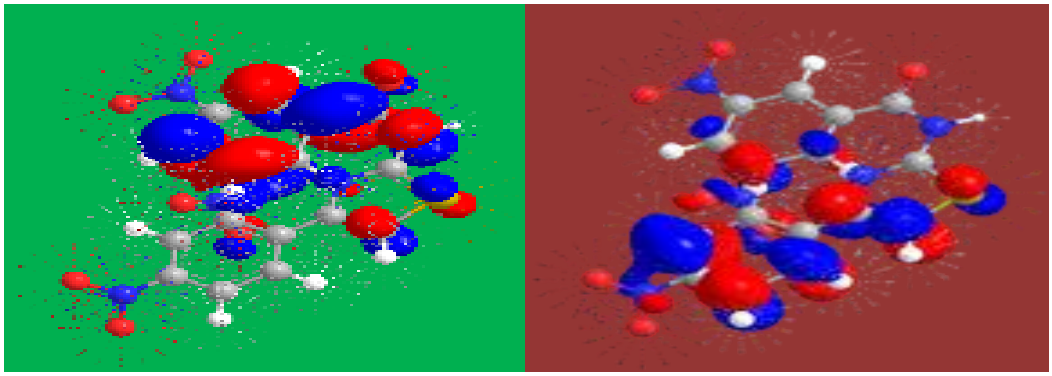
HOMO LUMO

Compound (4)



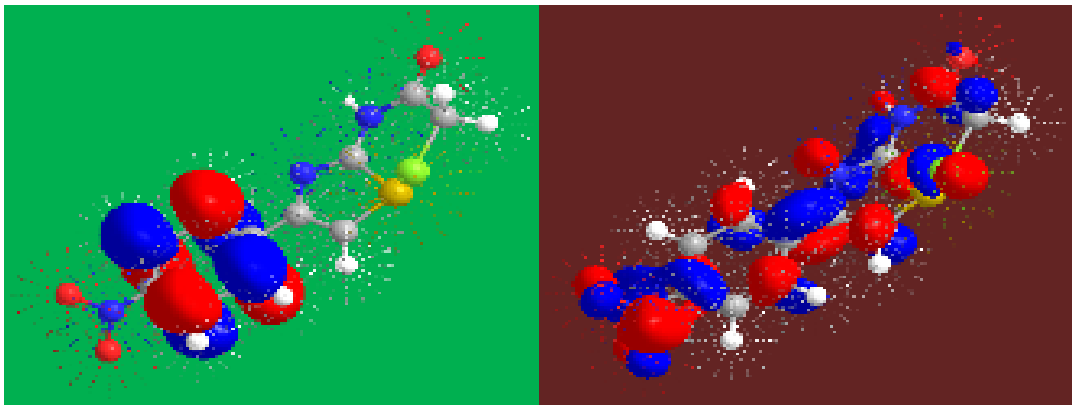
HOMO LUMO

Compound (5)



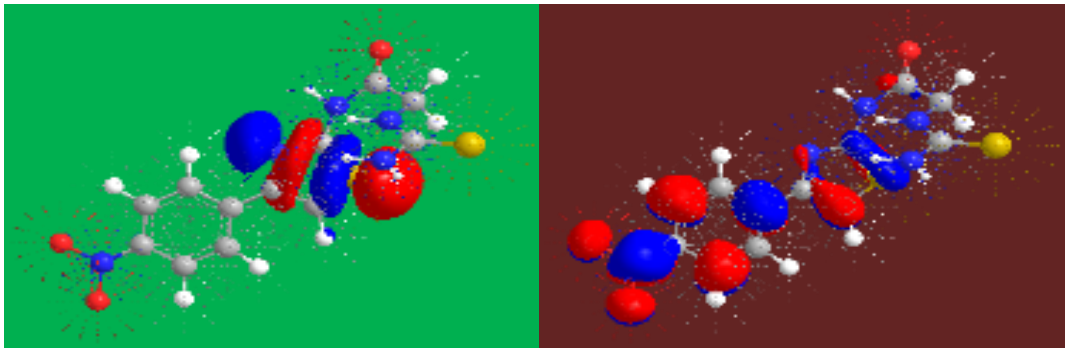
HOMO LUMO

Compound (6)



HOMO LUMO

Compound (7)



Compound (8)

Figure 1. Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) for compounds (2–8).

As shown in Table 3, the result of theoretical calculations reveals, that in the case of the compounds (**2-8**), the energy of highest occupied molecular orbital (EHOMO) are -10.804, -10.749, -8.339, -8.086, -2.264, -1.062 and -8.038 eV and the energy of the LUMO orbital (ELUMO) are -7.084, -4.120, -2.943, -1.227, 1.93, 0.474 and -4.826. Thus, the frontier orbital gap are about 3.72, 6.629, 5.396, 6.859, 4.194, 1.536 and 3.212 eV in the compounds **(2-8)**, respectively. As a result, the compound with less energy gap has more kinetic stability and less chemical reactivity than others, like compound **(7)**, whereas the compound with more energy gap has less kinetic stability and more chemical reactivity than others , for example, compound **(3)**.

The linkage between the molecular structures of compounds with its respective biological activities is central to the QSAR paradigm. Molecular descriptors play a crucial role in providing numerical description of the physicochemical properties of molecules. In order to properly account for these structural features, it is essential that suitable descriptors be chosen for QSAR investigation. Electronegativity (μ) essentially provides a measure of the asymmetric distribution of charges in a molecule [29] . It can be seen that compounds with the highest electronegativity were compound **2 > 3 > 8 >4> 5>7> 6** with values. It was observed that compound **(2)**. Such high value 8.944 is associated with the asymmetric distribution of electrons as afforded by the strong electron withdrawing nature of compound **(2)**.

log p provides a measure of a molecule's lipophilicity where high log p value indicates high lipophilicity, while low value suggests low lipophilicity. The results indicated that compounds having the highest lipophilicity were **5 > 3 > 2** with corresponding values of 3.51, 2.82 and 1.73, respectively. The compound **(5)**, set of a molecule possessed the highest lipophilicity.It can be observed that the energy gaps between HOMO and LUMO of compounds **(2-8)** is **5>3>4 >6 >2>8>7**. The larger the HOMO–LUMO energy gap, the harder and more stable/ less reactive the molecule, for example, compounds (**4**), (**5**) and (**8**).

Electrostatic potential charges and related quantum chemical properties

The distribution of the electronic density (electrostatic potential charges), related quantum chemical parameters . The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) play an important role in the molecule,HOMO/LUMO gap (Table 3, row 4) and the partition coefficients of the compounds (log p; Table 3, row 6)] were calculated for observed compounds.

Table 3. HOMO and LUMO, and electronic properties units for compounds (2-8) using DFT with B3LYP/6-B3LYP/6-31G* basis set.

Parameters	Compound (2)	Compound (3)	Compound (4)	Compound (5)	Compound (6)	Compound (7)	Compound (8)
Total Energy kcal/mol:	17.084	14.3827	5.9258	5.9262	10.6845	-3.3102	-2.9732
HOMO eV	-10.804	-10.749	-8.339	-8.086	-2.264	-1,062	-8.038
LUMO eV	-7.084	-4.120	-2.943	-1.227	1.93	0.474	-4.826
Energy gap eV	3.72	6.629	5.396	6.859	4.194	1.536	3.212
Electro negativity(μ)/ eV	8.944	7.435	5.641	4.657	0.132	0.294	6.432
Log P	1.73	2.82	-	3.51	-	-	-

Conclusion

In the present work new derivatives were synthesized starting from**,[**2-amino-4-(4-nitrophenyl) 1,3-thiazole**], (4)** and [2-amino-4-(4-bromophenyl) 1,3-thiazole**],(5)** using conventional method, the titled derivatives **(6)** and **(8)** were evaluated for their preliminary antimicrobial activity using well diffusion method. Compound **(6)** exhibited moderate antibacterial and antifungal activity against some Gram-positive bacteria (*Bacillus* pumilus , and *Bacillus subtilis*) and one fungal species (*Candida albicans*).

The titled thiazole derivatives were studied theoretically by using DFT calculations. the quantum chemistry calculations using the Density Function Theory, (DFT) method of biologically active molecules and can be used for a building of quantitative structure-activity relationship (QSAR) model in the future. Both experimental techniques and theoretical methods were used to determine the structural and spectroscopic properties of compound were in good result of each other.

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