Egypt. J. Chem. **Vol. 66** No. 11 pp. 611-619 (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis, DFT Calculations and Spectral Characterization of Novel Pyrimidine and Pyrazoline Derivatives

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Abstract

In this study, new pyrazole and pyridine derivatives bearing thiophene moieties have been prepared by condensing 1-(4-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one **1** with different nitrogen and carbon nucleophiles such as hydrazine, guanidine hydrochloride afforded compounds **2** and **3**. Reaction of hydrazine derivative **2** with carbon electrophile such as benzoyl chloride, chloroacetic acid and chloroacetyl chloride gave the corresponding pyrazol derivatives **4-6**. Condensation of pyrimidine derivative **3** with cyclohexanone and dichlorobenzaldehyde gave shiff`s base **7** and **8**. Elemental and spectroscopic evidence characterized all the newly synthesized compounds. The molecular electronic structures have been studied and computed with density function theory framework (DFT). We studied the electrophilicity of these compounds to determine the most active compound, which was compound **5**.

Keywords: Pyrazole, Pyrimidine, DFT, Thiophene, Electrophilicity, HOMO, LUMO.

1. Introduction

Compounds with Heterocyclic ring containing have piqued the interest of researchers due to their broad biological activities in the field of bioorganic and biomedical compounds, medicines and others [1-3]. Amongst these, pyrazoline, a nitrogen containing a five membered heterocyclic molecule is essential heterocyclic chemistry, this is evident from its extensive utilization as a pharmacophore and synthon [4]. Curiously, 2-pyrazoline, a substantial derivative of this heterocyclic molecule, has received a lot of attention due to its relatively greater stability and simultaneous monoimino feature. Several chemotherapeutic drug with a 2-pyrazoline moiety, have been explored for their anticancer [2], antibacterial [3] anti-inflammatory [5] antimalarial [2] and antiproliferative [6,7]. It has analgesic [5] antidepressant [8], and insecticidal properties [9,10]. 2-Pyrazolines are typically produced from aldehydes or ketones that contain actual or prospective α, β - unsaturation with substituted hydrazine under reflux conditions in the presence of a base [11-14]. As well as, A Pyrimidine nucleus is a necessary component of natural products such as nucleic acids and vitamin B1. Furthermore, several pyrimidine derivatives have significant medicinal value due to their biological activity as anti-HIV, antitubercular, and antidiabetic drug [15, 16]. In context of these discoveries and as a follow-up to of our previous research work [17-19]. Chalone, we present here in the synthesis of pyrazoline and pyrimidine derivatives from chalcone, the compounds were also, theoretically analyzed by density functional theory DFT and TD-DFT or time-dependent density (DFT). (TD-DFT) expands of the fundamental ideas of ground state density-functional theory DFT to address excitations or more broadly speaking time-dependent phenomena [19,20]. The computational chemistry show a great importance in new modern chemistry as a type of green chemistry because the calculations

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Receive Date: 26 January 2023, Revise Date: 20 February 2023, Accept Date: 26 February 2023

DOI: 10.21608/EJCHEM.2023.189866.7517

reduces the amount of chemical test to estimate the effect of synthesized materials. Materials for organic electronics are presently used in prominent applications, such as

Many of the challenges to improve and optimize these applications are material related and there is a nearly infinite chemical space that needs to be explored to identify the most suitable material candidates. Established experimental approaches struggle with the size and complexity of this chemical space. Herein, the development of simulation methods is addressed, with a particular emphasis on predictive multiscale protocols Throughout materials science and drug discovery, the application of computer-driven approaches has grown significantly. To rationally design any material from scratch is a multi-variable complex problem. computational chemistry was applied on drug synthesis [21- 26], anti-corrosion [[27-29].

1. **Experimental**

General

The infrared (IR) spectra were recorded on a Pye-Unicam SP-3-300 spectrophotometer (KBr disks) and expressed in wave number (cm^{-1}). All melting points were measured on a Gallenkamp apparatus and were uncorrected. ^{1}H-NMR spectra were run at 400 MHz, on a BrukerAvance III NMR spectrometer, TMS was used as an internal standard in deuterated dimethylsulphoxide (DMSO d6). Chemical shifts (d) are quoted in ppm. All coupling constant (J) values are given in hertz. Elemental analyses were performed on CHN analyzer, and all compounds were within ± 0.4 of the theoretical values. The reactions were monitored using thin layer chromatography sheets coated with UV fluorescent silica gel Merck 60 F254 plates and were visualized using UV lamp. Compound 1 was synthesized according to reported method in our published work [30].

Formation of 4-(5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-3-yl) phenol (2).

A mixture of chalcone 1 (2.30 gm; 0.01 mol) and hydrazine hydrate (2 mL) was refluxed for 8-10 h in ethanol (20 mL). After cooling, the reaction mixture was poured onto ice bath, the obtained precipitate was filtered out, dried, and recrystallized to get compound 2. Yield 83%; white crystal; mp 100-102℃ (EtOH); IR (cm^{-1}) ν: 3290 (NH), 2879 (CH aliphatic), 1606 (C=N); ^{1}H-NMR: 2.82 (d, d, 2H, CH_2 of pyrazole ring), 5.05 (d, d, 1H, CH of pyrazole ring), 6.77-7.47 (m, 7H, Ar-H), 9.67 (s, 1H, NH). Anal. Calcd for $C_{13}H_{12}N_2OS$ (244.31): C, 63.91; H, 4.95; N, 11.47; Found: C, 63.72; H, 4.84; N, 11.36.

Formation of 4-(2-amino-6-(thiophen-2-yl) pyrimidin-4-yl) phenol (3).

A mixture of chalcone 1 (2.30 gm; 0.01 mol) and guanidine hydrochloride (0.95 gm; 0.01 mol) in ethanolic sodium hydroxide solution (20 mL) was refluxed for 8 h. The reaction mixture was cooled, acidified with diluted hydrochloric acid and the resulting solid was filtered out, dried, and recrystallized to afford compound 3. Yield 76%; yellow crystal mp 180℃ (EtOH); IR (cm^{-1}) ν: 3290 (OH), 3200 (NH_2), 1636 (C=N); ^{1}H-NMR: 6.91 (s, 2H, NH_2), 6.89-8.01 (m, 7H, Ar-H), 7.65 (s, 1H, CH of pyrimidine ring), 10.43 (s, 1H, OH). Anal. Calcd for $C_{14}H_{11}N_3OS$ (269.32): C, 62.44; H, 4.12; N, 15.60; Found: C, 62.23; H, 4.19; N, 15.51.

General procedure for the synthesis of compounds (4), (5) and (6).

A mixture of 2 (2.44 gm; 0.01) and/or benzoyl chloride, chloroacetic acid and chloroacetyl chloride (0.01 mol) was refluxed for 8 h in ethanolic sodium hydroxide solution (20 mL). The reaction mixture was cooled, acidified with diluted hydrochloric acid and the resulting solid was filtered out, dried, and recrystallized to give compounds 4,5 and 6, respectively.

(3-(4-Hydroxyphenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) (phenyl)methanone (4). Yield 73%; brown crystal; mp 218-219℃ (EtOH); IR (cm^{-1}) ν: 3130 (OH), 2920 (CH aromatic), 2850 (CH aliphatic), 1695 (C=O), 1618 (C=N); ^{1}H-NMR: 4.31-4.33 (t, 2H, CH_2), 6.04- 7.98 (m, 12H, Ar-H). Anal. Calcd for $C_{20}H_{16}N_2O_2S$ (348.42): C, 68.95; H, 4.63; N, 8.04; found; C, 68.79; H, 4.55; N, 8.16.

2-(3-(4-Hydroxyphenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) acetic acid (5). Yield 68%; brown crystal; mp 65℃ (EtOH); IR (cm^{-1}) ν: 3350-3106 (OH broad), 2955 (CH aromatic), 2850 (CH aliphatic), 1719 (C=O), 1604 (C=N); ^{1}H-NMR: 5.03-5.09 (t, 2H, CH2), 6.76-7.99 (m, 7H, Ar-H), 9.89 (br.s, 1H, OH). Anal. Calcd for $C_{15}H_{14}N_2O_3S$ (302.35); C,

59.59; H, 4.67; N, 9.27; found C, 59.74; H, 4.60; N, 9.36.

2-Chloro-1-(3-(4-hydroxyphenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (6).
Yield 80%; brown crystal; mp 80℃ (EtOH); IR (cm^{-1}) ν: 3240 (OH), 2950 (CH aromatic), 2860 (CH aliphatic), 1734 (C=O), 1647 (C=N); ^{1}H-NMR: 3.60-4.07 (m, 2H, CH2), 6.76- 8.00 (m, 7H, Ar-H), 13.00 (s, 1H, OH). Anal. Calcd for $C_{15}H_{13}ClN_2O_2S$ (320.79): C, 56.16; H, 4.08; N, 8.73; found C, 56.31; H, 4.16; N, 8.63.

General procedure for the synthesis of compounds (7) and (8).
A mixture of 3 (2.69 gm; 0.01 mol) and/or cyclohexanone (1.05 mL; 0.01 mol) and 3,4-dichlorobenzaldehyde (1.75 gm; 0.01 mol) was refluxed for 3 h in ethanol (20 mL) with drops of piperidine. The reaction mixture was cooled, acidified with diluted hydrochloric acid and the resulting solid was filtered out, dried, and recrystallized to afford compound 7 and 8, respectively.

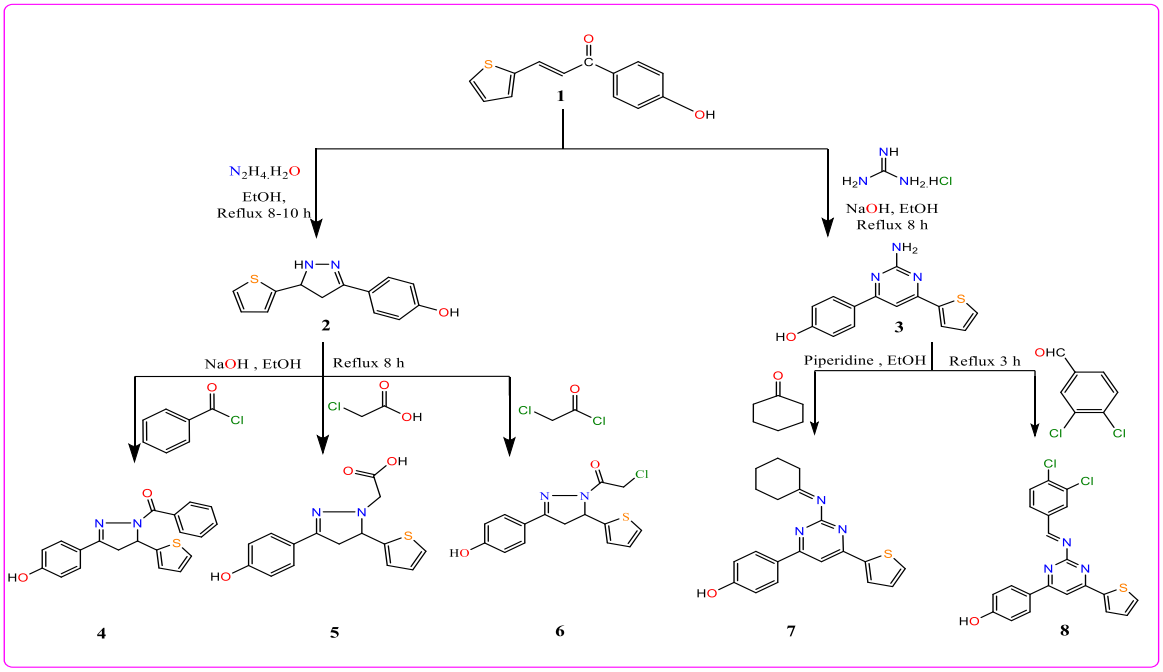
4-(2-(Cyclohexylideneamino)-6-(thiophen-2-yl) pyrimidin-4-yl) phenol (7).
Yield 70%; brown crystal; mp 260℃ (EtOH); IR (cm^{-1}) ν:3419 (OH), 3100 (CH aromatic), 2984(CH aliphatic); ^{1}H-NMR: 0.85-1.99 (m, 6H, CH-cyclohexane) 6.83-8.01 (m, 8H, Ar-H), 10.28 (s, 1H, OH). Anal. Calcd for $C_{20}H_{19}N_3OS$ (349.45); C, 68.74; H, 5.48; N, 12.02 found C, 68.59; H, 5.40; N,12.12.

(E)-4-(2-((3,4-dichlorobenzylidene) amino)-6-(thiophen-2-yl) pyrimidin-4-yl) phenol (8).
Yield 70%; Yellow crystal; mp 290℃ (EtOH); IR (cm^{-1}) ν:3347 (OH), 3046 (CH aromatic), 1660 (C=N); ^{1}H-NMR: 6.98-8.35 (m, 12H, Ar-H+ CH olefinic), 10.58 (s, 1H, OH). Anal. Calcd for $C_{21}H_{13}Cl_2N_3OS$ (426.32); C, 59.17; H, 3.07; N, 9.86; found C, 59.02; H, 3.15; N,9.76.

3. Results and Discussion

3.1. Chemistry

The aim of the present study is to develop an efficient protocol with good to excellent yield. The formation of all these new heterocyclic derivatives were fully characterized by means of spectroscopic techniques such as FTIR, ^{1}HNMR and elemental analysis that were in full agreement with their proposed structures. As an example, in the IR spectrum of compound **2** showed band at 1606 cm^{-1} accounts for the formation of C=N bond. The appearance of CH_2 proton at 2.82 ppm in the ^{1}HNMR spectra of compound **2**, confirmed the formation of the pyrazole ring, in addition to the appearance of signals at δ 5.05 for compound **2** attributed to CH proton of pyrazole ring. The IR spectrum of compound 3 showed a strong characteristic band at 1636 cm^{-1} and 3164 cm^{-1} due to the C=N and NH_2 group of pyrimidine ring. The appearance of NH_2 proton at 6.91 ppm in the ^{1}HNMR spectra of compound **3**, confirmed the formation of the Pyrimidine ring, in addition to the appearance of signal at δ 7.65 for compound **3** attributed to CH proton of Pyrimidine ring .The IR spectra of compounds 4-6 showed bands at 1696, 1719, and 1734 cm^{-1} attributed to C=O groups, respectively. In addition, showed a bands attributed to C=N at 1618, 1604 and 1647 cm^{-1} For compounds **4-6**, respectively. The H NMR of **4** exhibited a triplet and doublet signals at 4.31-4.33 ppm and 6.04-6.08 ppm attributed to CH and CH_2 protons of the pyrazole ring.



Compound **5** exhibited a triplet signal at 5.03-5.09 ppm attributed to CH_2 However, the CH_2 of acetyl chloride in compound **6** exhibited a multiplet signal at 3.60- 4.07 ppm. The IR spectra of 7-8 showed bands at 1644 and 1660 cm^{-1} attributed to C=N groups, respectively. the appearance of multiple at δ 0.85-1.99 ppm for compound 7 attributed to CH_2 protons of cyclohexane, in addition to the appearance of a broad signal at δ 10.28 attributed to OH proton. The ^{1}HNMR spectrum of compound 8 showed a signal at δ 6.98-8.35 ppm attributed to aromatic protons and CH-olefinic.
All the target compounds **1-8** were characterized using spectral data such as ^{1}HNMR, Mass, as well as IR spectroscopy. Moreover, the purity of the previously mentioned derivatives was confirmed by elemental analysis.

3.2. Molecular Reactivities.

Studying the chemical reactivity theory is part of history as far back as the introduction of such fundamental concepts as acid, base, Lewis acid, and Lewis base. It pervades almost all of chemistry. The most relevant indices defined within the conceptual DFT [31] for the study of the organic reactivity are discussed elsewhere. Molecular reactivity indices [19] such as chemical potential (μ) hardness (η), and electrophilicity (ω), were computed from the energies of frontier orbitals and defined as follows:

(1) Chemical potential is defined as

$$\mu=(E_{HOMO}+E_{LUMO})/2 \quad (1)$$

(2) Hardness is given by

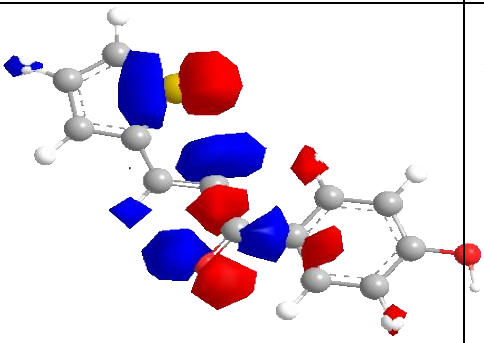
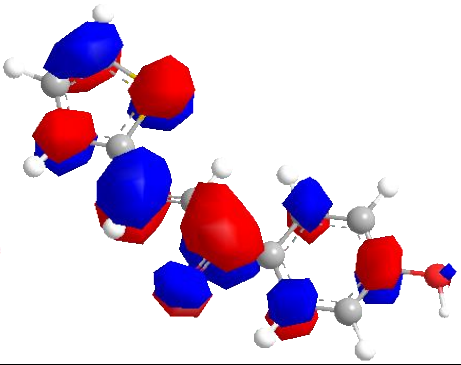
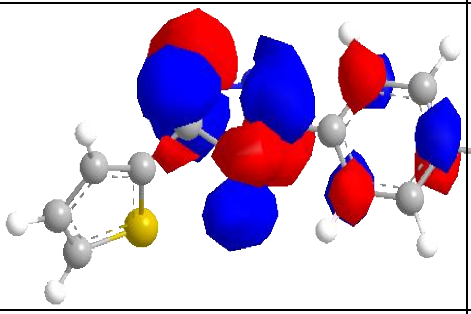
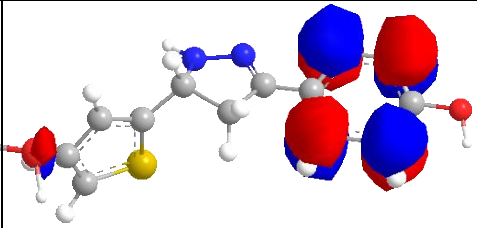
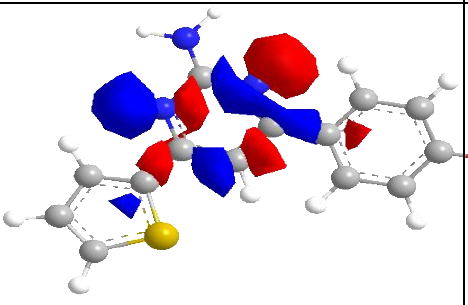
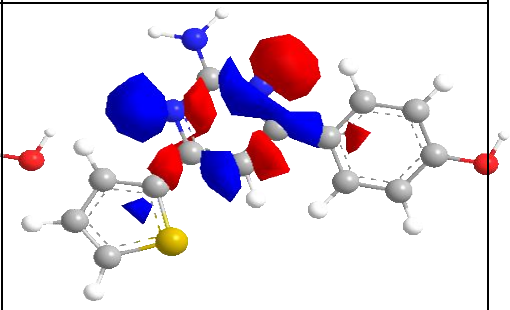
$$\eta=(E_{LUMO}-E_{HOMO})/2 \quad (2)$$

The chemical hardness **η** can be thought as a resistance of a molecule to exchange electron density with the environment.

(3) *Electrophilicity* **($\omega = \mu^2/(2*\eta)$):** Parr (in 1999) defined the electrophilicity index [19] , measures a molecule's ability to act as an electron sink the higher its value, the stronger the ligand's electron sink property. The
electrophilicity index provides a magnitude of the energy stabilization of a molecule when it gains an extra amount of electron density during the interaction. The electrophilicity index comprises the tendency of an electrophile to earn an excessive amount of electron density, given by the chemical potential **μ** and the resistance of a molecule to exchange electron density during an interaction, provided by the hardness **η**. Therefore, a suitable electrophile is characterized by an excessive **μ** value and a little **η** value. The electrophilicity index rendered a powerful apparatus for studying the reactivity of organic molecules [19].

(4) *Nucleophilicity (N):* Domingo and his coworkers [19] suggested that nucleophilicity of compounds (N) can be studied using DFT calculations, it depends on the HOMO energy of the compound and can be calculated using the following equation **N= E_{HOMO}**

(ev) + 9.12(ev), where -9.12 is the energy of the HOMO of tetracyanoethylene (TCE). Thus, this nucleophilicity scale is referred to tetracyanoethylene (TCE) taken as a reference, because it exhibits the lowest HOMO energy in a large series of molecules investigated [19]. Nucleophilicity parameter could be employed to explain the reactivity of these new compound towards electrophiles.

Comp. No	HOMO- LUMO	
	HOMO	LUMO
1		
2		
3		
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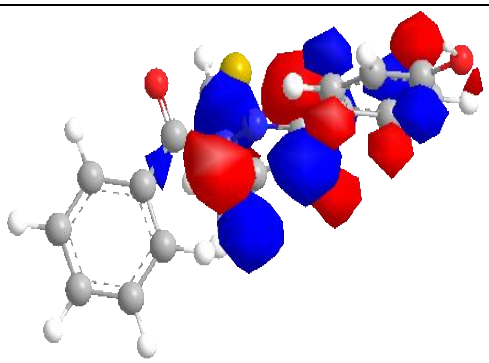
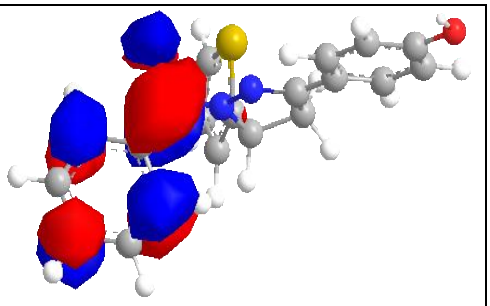
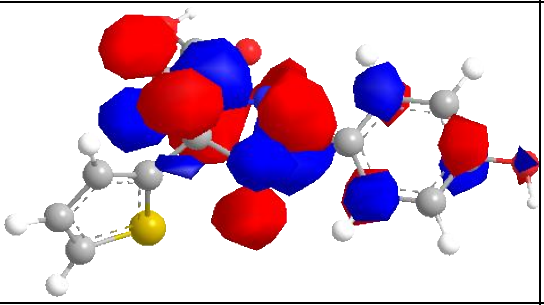
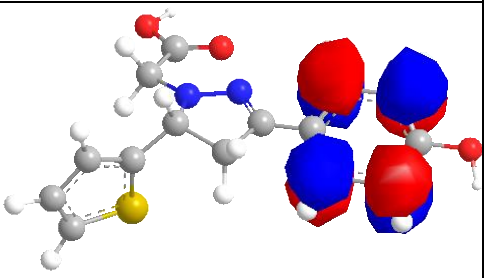
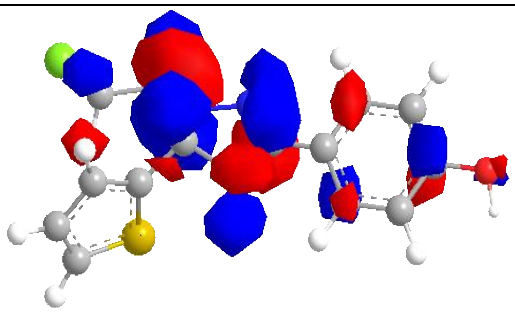
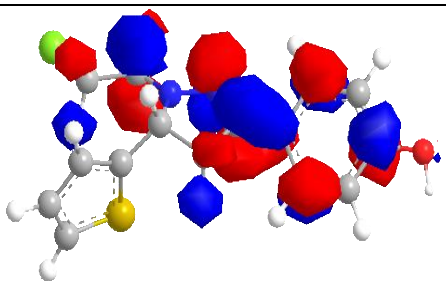
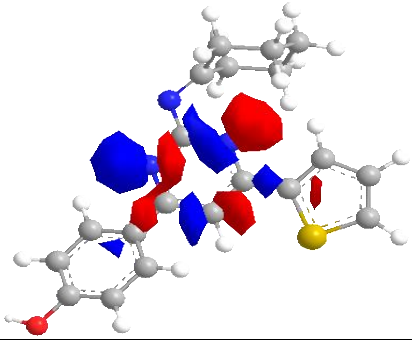
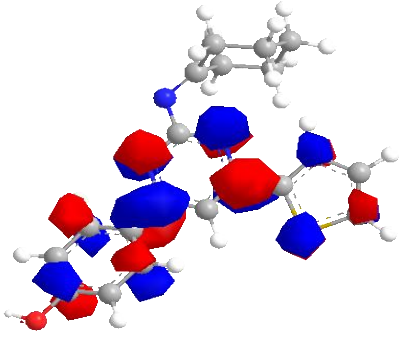
4		
5		
6		
7		

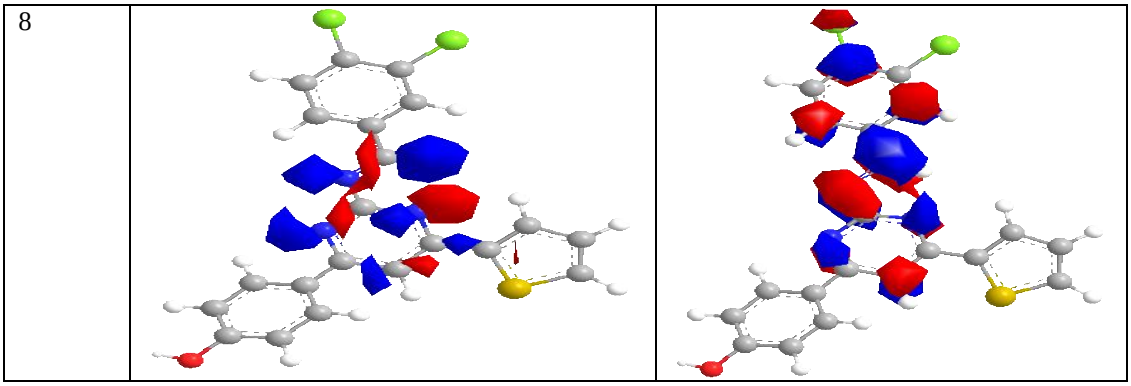


Fig. 1: HOMO-LUMO frontier orbital of the newly synthesized thiophene derivatives (Red color represent positive phase while the blue the blue color points to the negative one).

Table 1: Reactivity indices* sorted according to nucleophilicity

Comp. No	HOMO	LUMO	μ	η	ω	N	S
1	-10.938	-5.708	-8.323	2.615	13.24	-1.818	0.191
2	-7.749	-1.074	- 4.411	3.337	2.915	1.371	0.149
3	-8.833	-3.024	-5.92	2.904	6.034	0.287	0.172
4	-7.124	-4.882	-6.001	1.121	16.062	1.996	0.446
5	-6.940	-1.072	-4.006	2.934	2.734	2.18	0.170
6	-9.228	-2.019	-5.623	3.6045	1.792	-0.108	0.139
7	-8.829	-2.816	- 5.822	3.006	5.63	0.291	0.166
8	-7.639	-4.624	- 6.131	1.507	12.47	1.481	0.332

Inspection of figure 1 and Table 2 reveals the reactivates of the new molecules; compound **5** is the most susceptible molecule to electrophilic attack due to its large N value of 2.18 eV.

Conclusions

In this paper we reported the synthesis of new pyrazole and pyridine derivatives bearing thiophene moiety have been prepared by condensing 1-(4-hydroxyphenyl)-3-(thiophen-2-yl) prop-2-en-1-one with hydrazine hydraite, guanidine hydrochloride. hydrazine derivative react with carbone electrophile such as benzoyl chloride, chloroacetic acid and chloroacetyl chloride gave the corresponding pyrazol derivatives. gave shiff`s base prepared by condensation of pyrimidine derivative with cyclohexanone and dichlorobenzaldehyde all the newly synthesized compounds were evidenced and characterized by elemental and spectroscopic data. the structures were studied using DFT to prove that compound 5 is the most active compound.

Conflicts of interest

The authors declared no conflict of interest.

Formatting of funding sources

The authors declared no funding

Acknowledgments

We dedicate this work to our Colleague Maher Ahamed El-Hashash who passed away few months before the end of this study.

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