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Synthesis, Characterization and Computational Study of Some New Heterocyclic Derived from 1-(biphenyl-4-yl)-3-(furan-2-yl)prop-2-en-1-one

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Abstract

An efficient and practical synthesis of pyrazole, isoxazole and pyrmidine derivatives structures was achieved through cyclization of hydrazine hydrate , hydroxylamine hydrochloride, urea and thiourea with α,β-unsaturated ketones (chalcones) using glacial acetic acid or alkaline media as catalyst under thermal condition. The synthesized compounds were characterized by means of their IR- and NMR-spectral data, and elemental analysis. The structural and electronic properties of eight para- substituted phenyl selenobenzoates have been investigated theoretically by performing semi-empirical molecular orbital theory at the level of PM3 of theory and Density Functional theory at the B3LYP/3-21G levels of theory. The optimized structures, relative binding energies, atomic charges, position of HOMO and LUMO of the molecules are obtained.

Key words : chalcone, pyrmidine,isoxazole

Introduction

Chalcones are products of condensation of simple or substituted aromatic with simple or substituted acetophenones in presence of alkali. Chalcone constitute an impartment group of natural products and some of them possess a wide range of biological activities such as antimicrobial [1], anticancer[2], antitubercular [3] and antiviral [4] etc.

Chalcones and the corresponding heterocyclic analogs are valuable intermediates in organic synthesis [5] and exhibit a multitude of biological activities[6]. From a chemical point of view, an important feature of chalcones and their heteroanalogs is the ability to act as activated unsaturated systems in conjugated addition reactions of carbanions in the presence of basic catalysts [7,8]. This type of reaction may be exploited with the view of obtaining highly functionalized cyclohexene derivatives [9], but is more commonly used for the preparation of 3,5-diaryl-6-carbethoxycyclohexenones *via* Michael addition of ethyl acetoacetate. The mentioned cyclohexenones are efficient synthons in building spiranic compounds[10] or intermediates in the synthesis of fused heterocycles such as benzoselenadiazoles and benzothiadiazoles,[11] benzopyrazoles and benzisoxazoles[12,13] or carbazole derivatives[14]. Density-functional theory (DFT) is currently the method of choice for the study of structural, electronic, and dynamical properties in materials science. The reason for this lies both in the ability of DFT schemes to treat models of relatively large sizes compared to other firstprinciples methods, and in the degree of accuracy that can be achieved for diverse systems in a systematic fashion [15].

In this work we have synthesized and characterized some of new hetrocyclic chalcone Derivatives. The synthesis compounds have been studied theoretically by semi-empirical molecular orbital theory at the level of PM3 of theory and Density Functional theory at the B3LYP/3-21G levels of theory.

Experimental methods

1. General

Melting points were uncorrected. NMR spectra were acquired with a Bruker Ultra Shield (^{1}H : 300 MHz) (University of AL-al-Bayt,Jordan). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. The elemental analyses were performed by using Euro Vector EA3000A (University of AL-al-Bayt, Jordan).

1.1. Synthesis of 1-(biphenyl-4-yl)-3-(furan-2-yl)prop-2-en-1-one (3)

An ethanolic solution of 4-phenylacetophenone (0.01mol) and furfural (0.01 mol) in presence of catalytic amount of 40% KOH was stirred for 3 h at room temperature. It was then poured over crushed ice and the product formed was crystallized from ethanol. Yield (87%), m.p. (70-72)^{o}C,. CHN analysis for $C_{19}H_{14}O_2$; C 83.19; H 5.14; N 0.00 Found C 83.10; H 5.12; N 0.00, FT-IR spectra (KBr pellet) ν(cm^{-1}) 1693 (C=O) 1580 (CH=CH,stretching), δ_H(CDCl$_3$) (8.255-8.264) ppm (1H,d,1), (8.065-8.074) ppm (2H,d,9,13), (7.902-7.907) ppm (1H,d,5), (7.755-7.769) ppm (2H,d,10,12), (7.565-7.574) ppm (1H,d,6), (7.402-7.407) ppm (1H,d,3), (7.218-7.281) ppm (5H,m,14,15,16,17,18), (6.525-6.650) ppm (1H,t,2).

1.2. Synthesis of 4-(biphenyl-4-yl)-6-(furan-2-yl)-1,„2-dihydropyrimidine-2-thiol (4)

A mixture of Chalcone (1) (0.02mol), thiourea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was reflux overnight. The precipitate obtained was filtered, washed and recrystallized from ethanol. Yield (71%), m.p. (180-182)^{o}C,. CHN analysis for $C_{20}H_{14}N_2OS$; C 72.70 ; H 4.27; N 8.48 Found C 72.60; H 4.27; N 8.41, FT-IR spectra (KBr pellet) ν(cm^{-1}) 2820 (C–H stretching of aliphatic), 1573 (C=C stretching) , 1602 (C=N stretching), 1272 (C–N stretching of pyrmidine ring), 2400 (SH stretching), δ_H(CDCl$_3$) (8.255-8.264) ppm (1H,d,1), (7.518-7.581) ppm (5H,m,3,13,14,15,17), (7.318-7.381) ppm (5H,m,19,20,21,22,23), (6.525-6.650) ppm (1H,t,2), 5.000 ppm (1H,s,11), 3.400 ppm (1H,s,8).

1.3. Synthesis of 4-(biphenyl-4-yl)-6-(furan-2-yl)-1,„2-dihydropyrimidine-2-ol (5)

A mixture of Chalcone (1) (0.02mol), urea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was reflux overnight. The precipitate obtained was filtered, washed and recrystallized from ethanol. Yield (76%), m.p. (200-202)^{o}C,. CHN analysis for $C_{20}H_{14}N_2O_2$; C 76.42; H 4.49; N 8.91 Found C 76.40; H 4.47; N 8.90, FT-IR spectra (KBr pellet) ν(cm^{-1}) (3250-3600) (OH stretching), 2825 (C–H stretching of aliphatic), 1580 (C=C stretching),1610 (C=N stretching), 1272 (C–N stretching of pyrmidine ring), δ_H(CDCl$_3$) (8.255-8.264) ppm (1H,d,1), (7.718-7.781) ppm (5H,m,3,13,14,15,17), (7.218-7.281) ppm (5H,m,19,20,21,22,23), (6.525-6.650) ppm (1H,t,2), 4.811 ppm (1H,s,11), 4.000 ppm (1H,s,8). .

1.4. Synthesis of 3-(biphenyl-4-yl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole (6)

A mixture of Chalcone (1) (0.02 mol), hydrazine hydrate (0.02 mol) and glacial acetic acid (10 ml) in ethanol (25 ml) was refluxed overnight. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from ethanol. Yield (82%), m.p. (170-172)^{o}C,. CHN analysis for $C_{19}H_{16}N_2O$; C 79.14; H 5.59; N 9.72 Found C 79.10; H 5.58; N 9.71, FT-IR spectra (KBr pellet) ν(cm^{-1}) 3330 (NH stretching of pyrazoline ring), 2800 (C–H stretching of aliphatic), 1593 (C=N stretching of pyrazoline ring), 1276 (C–N stretching of pyrazoline ring), δ_H(CDCl$_3$) (8.065-8.074) ppm (2H,d,11,15), (7.755-7.764) ppm (2H,d,12,14), (7.565-7.574) ppm (1H,d,1), (7.218-7.281) ppm (5H,m,17,18,19,20,21), 7.065 ppm (1H,s,6), (6.211-6.481) ppm (2H,m,2,3), (4.625-4.725) ppm (1H,t,5), (3.927-3.937) ppm (2H,d,9,9$^{\backslash}$)

1.5.Synthesis of 3-(biphenyl-4-yl)-5-(furan-2-yl)-4,5-dihydroisoxazole (7)

A mixture of Chalcone (1) (0.02mol), hydroxylamine hydrochloride (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was reflux overnight. The precipitate obtained was filtered, washed and recrystallized from ethanol. Yield (87%), m.p. (178-180)^{o}C,. CHN analysis for $C_{19}H_{15}NO_2$; C 78.87; H 5.23; N 4.84 Found C 78.83; H 5.21; N 4.83, FT-IR spectra (KBr pellet) ν(cm^{-1}) 2830 (C–H stretching of aliphatic), 1540 (C=C stretching) , 1625 (C=N stretching), 1274 (C–N stretching of isoxazolidine ring), 1100 (C-O-C stretching of isoxazole ring), 820 (N-O stretching of isoxazole ring), δ_H(CDCl$_3$) (8.065-8.074) ppm

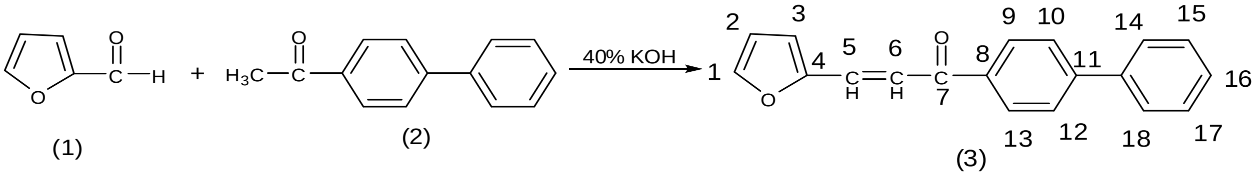
(2H,d,11,15), (7.755-7.764) ppm (2H,d,12,14), (7.565-7.574) ppm (1H,d,1), (7.218-7.281) ppm (5H,m,17,18,19,20,21), (6.211-6.481) ppm (2H,m,2,3), (4.625-4.725) ppm (1H,t,5), (3.927-3.937) ppm (2H,d,9,$9^{\backslash}$)

2. Computational methods

All theoretical calculations in this work were performed using the computational methods implemented in the GAUSSIAN09 package [16]. Geometry optimization of the studied compounds was done by performing the semi-empirical molecular orbital theory at the level PM3. The electronics properties of the studied compounds have been studied by performing the Density Functional theory at the B3LYP/3-21G levels of theory. The hybrid Becke 3-Lee–Yang–Parr (B3LYP) exchange correlation functional was applied for DFT calculations [17]

Result and discussions:

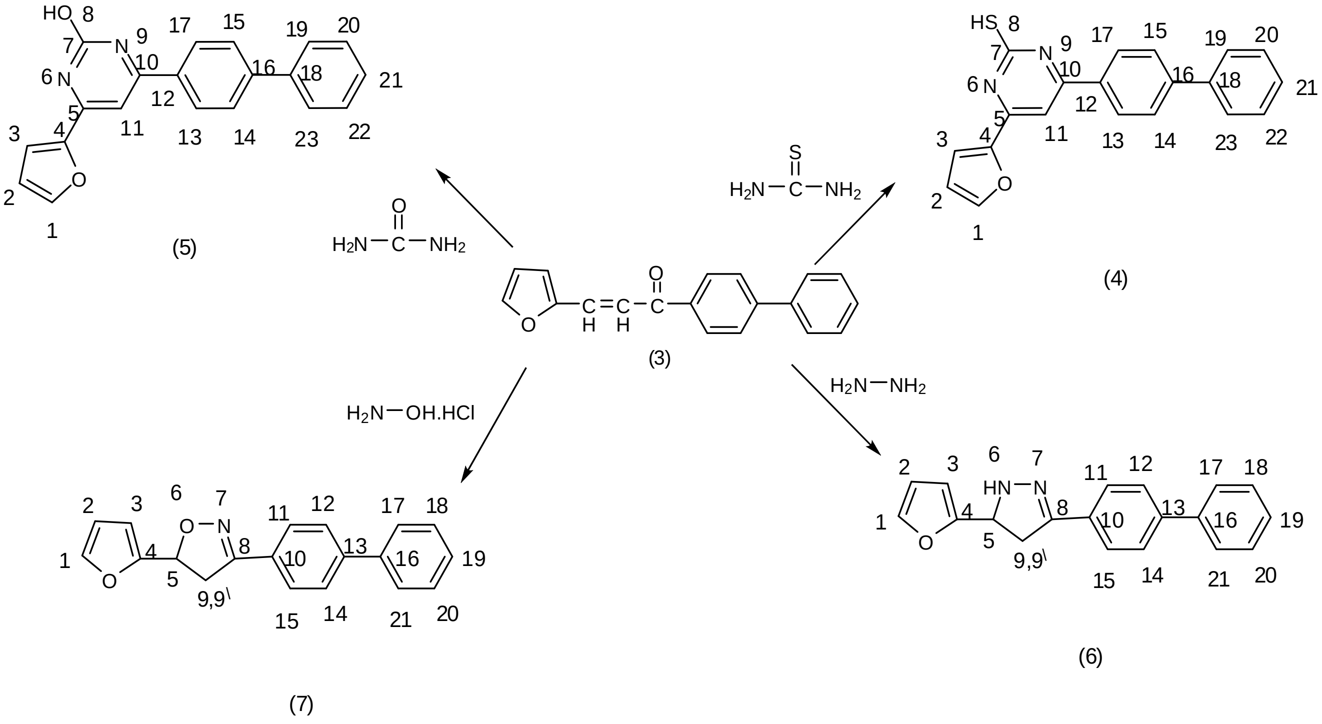
Treatment of furfural (1) with 4-phenylacetophenone (2) in boiling ethanol gave chalcone (3)**,** after purification by recrystallization from ethanol, pure compounds as shown in (scheme 1) in (87)% yield. Then treatment of chalcones (3) with thiourea, urea, hydraszine hydrate and hydroxylamine hydrochloride in boiling ethanol gave pyrmidine derivatives (4,5), pyrazine (6) and isoxazoline compounds (7), after purification by recrystallization from ethanol, pure compounds as shown in (scheme 2) in (71-87)% yield. The structures of these products were established from their elemental analysis, FT-IR,C.H.N and ^{1}H NMR spectra.



Scheme (1)

All the IR spectra of pyrmidine derivatives (4,5), pyrazine(6) and isoxazoline(7) showed a peak at (1593-1625) cm^{-1} which appeared due to (C=N) stretching of pyrmidine derivatives, pyrazine and isoxazoline rings , and showed a peak at (1272-1276) cm^{-1} which appeared due to (C-N) stretching of pyrmidine derivatives, pyrazine and isoxazoline rings, and showed peak at (1540-1580) cm^{-1} which appeared due to (C=C stretching of aromatic ring), the C-H stretching aliphatic showed peak within the range (2800-2830) cm^{-1}. The SH stretching showed peak within the range 2400 cm^{-1}, while the OH stretching showed peak within the range (3250-3600) cm^{-1}. The NH stretching of pyrazoline ring showed peak within the range 3330 cm^{-1}. The C-O-C stretching of isoxazole ring showed peak within the range 1100 cm^{-1}. While the N-O stretching of isoxazoline ring showed peak within the range 820 cm^{-1}.

The ^{1}H NMR spectra of chalcone, pyrmidine derivatives (4,5), pyrazine (6) and isoxazoline (7) rings compounds as shown in Scheme 2. All the ^{1}H NMR spectra of pyrazoline ring were characterized [17,18] by the presence of protons of at δ= (7.565-8.264) ppm doublet appeared to proton in position 1 of furan ring, while the proton in position 2 of furan ring showed triplet signals within the range(6.525-6.650) ppm in compound (4,5), and multiplet signals within the range (6.211-6.481) ppm, the other proton in 3 position of furan ring showed doublet signal within the range (7.402-7.407) ppm in compound (3), while this proton showed multiplet signals within the range (6.211-7.781) ppm in compounds (4,5,6,7). The proton 5 of chalcone (3) showed doublet signal within the range (7.902-7.907) ppm, while the other proton in 6 position of chalcone (3) showed doublet signal within the range (7.565-7.574) ppm. The proton of pyrmidine ring 11 showed singlet signals within the range (4.811-5.000) ppm. The proton of pyrazoline ring 6 showed singlet signal within the range 7.065 ppm, and showed triplet signals within the range (4.625-4.725) ppm appeared to proton in 5 position, while the protons in 9,$9^{\backslash}$ position showed doublet signals within the range (3.927-3.937) ppm. The proton of isoxazoline ring showed triplet signals within the range (4.625-4.725) ppm appeared to proton in 5 position, while the protons in 9,$9^{\backslash}$ position showed doublet signals within the range (3.927-3.937) ppm. The proton of OH group in compound (5) showed singlet signals within the range 4.000 ppm. While the proton of SH group in compound (4) showed singlet signals within the range 3.400 ppm. The protons of aromatic rings in chalcone (3) showed doublet signals within the range (8.065-8.074) ppm due to protons in positions 9,13 and showed doublet signals within the range (7.755-7.764) ppm due to protons in positions 10,12. While the other aromatic protons in 14,15,16,17,18 showed multiplet signals within the range (7.218-7.281) ppm. The protons of aromatic rings in pyrmidine derivatives (4,5) showed multiplet signals within the range (7.518-7.781) ppm due to protons in positions 13,14,15,17 , and showed multiplet signals within the range (7.218-7.381) ppm due to protons in positions 19,20,21,22,23. The protons of aromatic rings in pyrazoline and isoxazoline rings (6,7) showed doublet signals within the range (8.065-8.074) ppm due to protons in positions 11,15 and showed doublet signals within the range (7.755-7.764) ppm due to protons in positions 12,14. While the other aromatic protons in 17, 18, 19, 20,21 showed multiplet signals within the range (7.218-7.281) ppm.



Scheme (2)

Computational Study

The optimized structures of the studied molecules are shown in Fig 1. The PM3 geometry optimizations yield planar structures for the (4, 5) molecules and a non-planar structures in molecules (6 and 7). The general geometries of molecule 3and 4 are very similar. As for O-H and S-H which substituted to pyrimidine ring, we see that bond distance of C-O and S-H are 1.344Å and 1.77Å respectively. While O-H and S-H bonds of the same groups are 0.518 Å and 1.314Å respectively. The others moieties of the two molecules (naphthalene , pyrimidine and furan rings) gave similar bond lengths. Concerning 6 and 7 molecules, the two molecules are non-planar .The 6 molecule has pyrazole moiety, while the 7 molecule has isoxazole moiety. The N-N bond distance of the pyrazole ring is 1.394Å, whereas the O-N bond distance of isoxazole is 1.398Å. Also, the others moieties of the two molecules (naphthalene and furan rings) gave similar bond lengths.

The total energy, highest occupied and the lowest unoccupied molecular orbital (HOMO and LUMO, respectively) energies and the energy band gap (LUMO–HOMO energy difference, ΔE) and the dipole moment, μ (in Debyes) for the studied molecules are given in Table 4. As shown in this table, the molecules need energy vary from 0.1628 to 0.2955 au to reach to excited state. The calculated magnitudes of dipole moment vary from 2.2788 to 3.2788 Debyes according to PM3 calculations. While the calculated values according to DFT calculations vary from 2.7579 to 3.1978 Debyes. The calculated dipole moments by the two methods indicate that the studied molecules are pole. This means that these molecules are polar and they may interact with its environmental, especially other polar molecules.

The spatial distributions of HOMO LUMO are shown in Fig. 2. In general the 4 and 5 molecules gave similar HOMO and LUMO orbitals; also the same thing has been seen for 6 and 7 orbitals. According to DFT calculation, in the of molecule 4 and 5 the HOMO orbital is mainly localized on the naphthalene and pyrimidine rings, while the LUMO orbital is localized mainly on the naphthalene , pyrimidine and furan rings. This means that the two molecules may be more active in the excitation state. However, in the molecule 6 and 7 the HOMO orbital is mainly localized on naphthalene and pyrazole rings in molecule number 6 and localized on naphthalene and isoxazole rings in molecule number 7. In contrast, the LUMO orbital located on the same rings in 6 and 7 molecules. This means that these molecules have the same reactivity in the ground and excited states. These indications reveal useful information about the reactivity of such molecules and give good information about the active sites in the molecules and clarify the sites of molecules which undergo nucleophilic substitution or electrophilic substitution reactions.

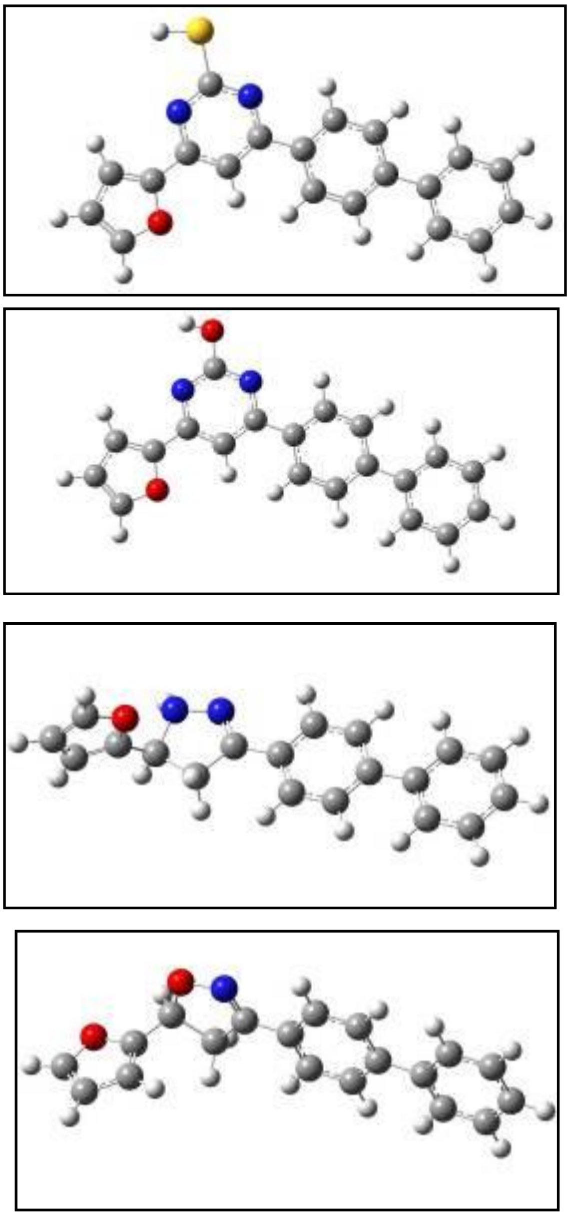
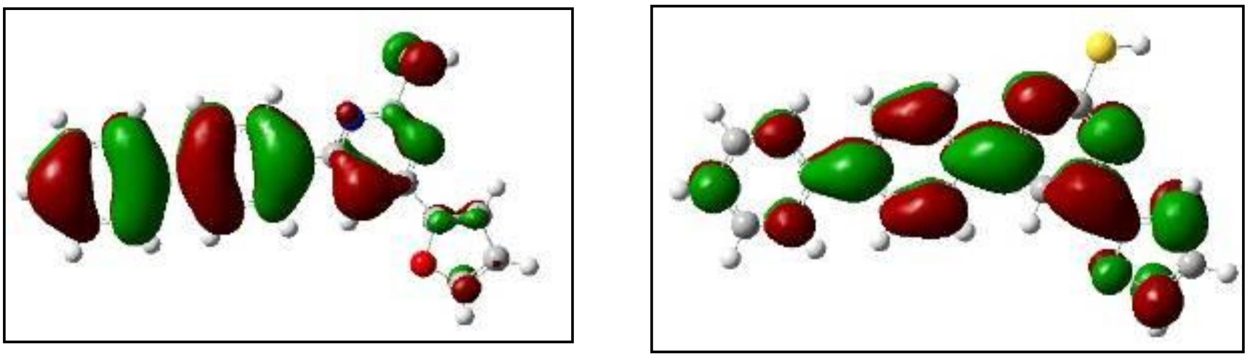
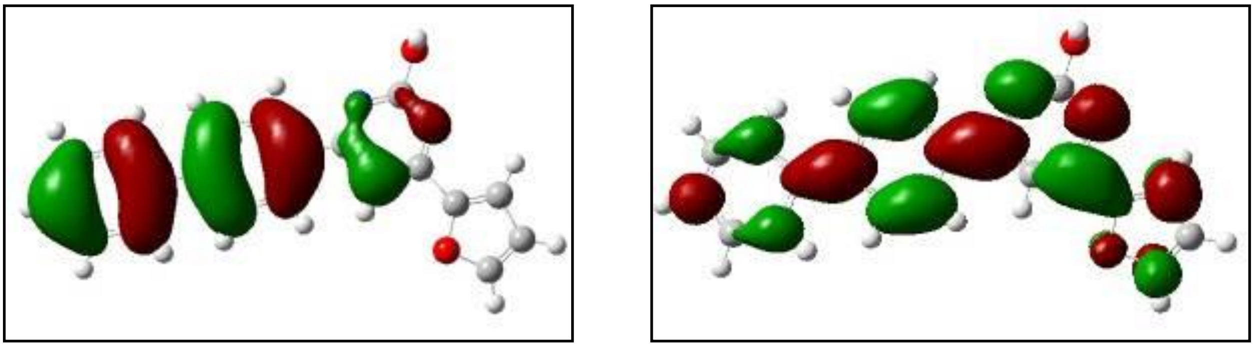


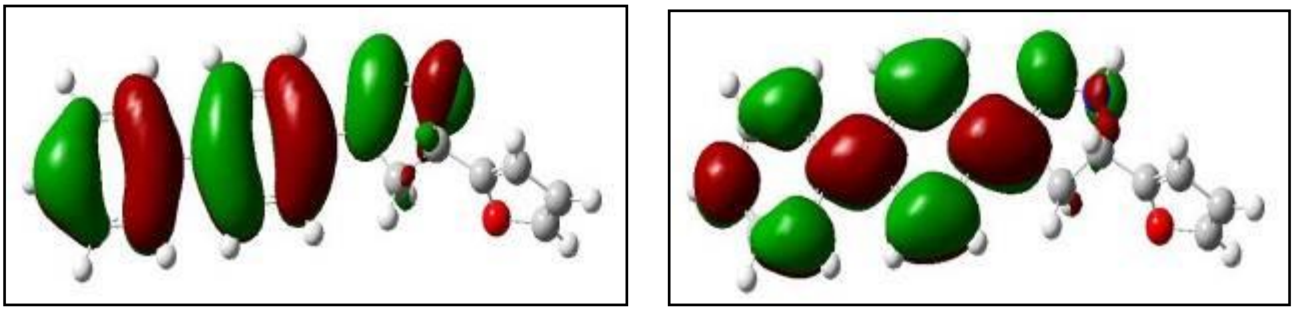
Fig. 1. The optimized structure of the studied molecules 4, 5,6 and 7, optimization has been performed by PM3 method.



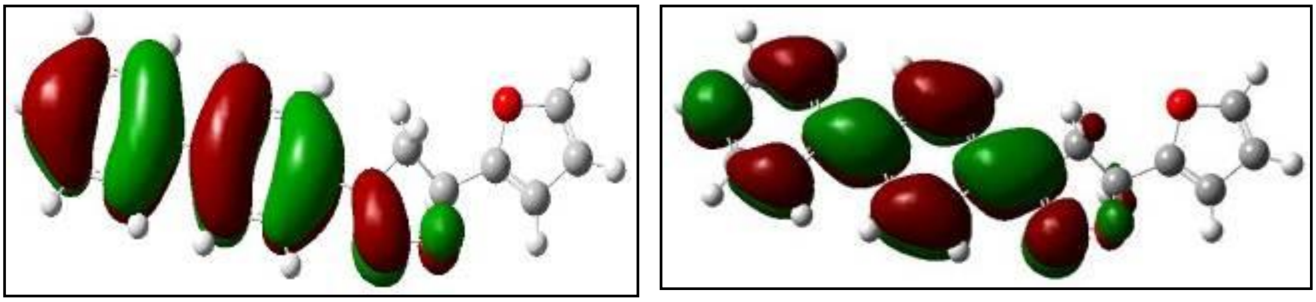
HOMO (4) **LUMO (4)**



HOMO (5) **LUMO (5)**



HOMO (6) **LUMO 6)**



HOMO (7) **LUMO (7)**

Fig. 2. 3D HOMO and LUMO plots of the studied molecules (DFT results).

Table1. The Total energy, MO energy of the lowest, highest, HOMO, LUMO, levels, ΔE (in au) and the dipole moment, $\boldsymbol{\mu}$ (in Debyes) for the studied molecules

Mol.	Method	Total energy	HOMO	LUMO	ΔE	μ
4	PM3	0.1435	-0.3278	-0.0438	0.2838	3.0945
	B3LYP/3-21G	-1346.18	-0.2265	-0.0637	0.1628	3.1418
5	PM3	0.0583	-0.3269	-0.0425	0.2844	2.5634
	B3LYP/3-21G	-1018.36	-0.2995	0.0626	0.2369	2.9270
6	PM3	o.1334	-0.3156	0.0269	0.2887	2.3968
	B3LYP/3-21G	-907.36	-0.2889	0.0809	0.2080	2.7579
7	PM3	0.1030	-0.3271	0.0316	0.2955	3.2788
	B3LYP/3-21G	-927.06	-0.3021	0.0711	0.231	3.1978

Conclusion

In conclusion, a rapid, high yield, simple, practical, economic, readily available system, and convenient procedure for the synthesis of heterocyclic derived from 1-(biphenyl-4-yl)-3-(furan-2-yl)prop-2-en-1-one and computational study, has been developed. The theoretical study indicates that these molecules are polare and active molecule and they may interact with its environment strongly in solution. The indications of the theoretical study reveals useful information about the reactivity of such molecules and give good information about the active sites in the molecules and clarify the sites of molecules which undergo nucleophilic substitution or electrophilic substitution reactions.

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