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*Research Article*

# SYNTHESIS , CHARACTERIZATION AND COMPUTATIONAL STUDY OF SOME NEW 5-(FURAN-2-YL)-3-PHENYL-4,5-DIHYDROISOXAZOLE DERIVATIVES FROM CHALCONE COMPOUNDS

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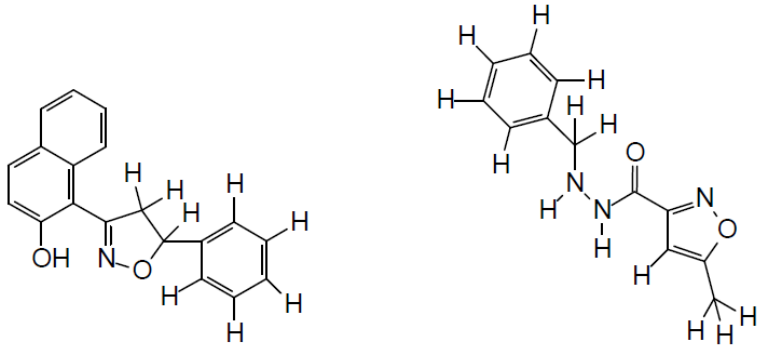
**ABSTRACT**

An efficient and practical synthesis of six compounds of isooxazoline derivatives was achieved through cyclization of hydroxyl amine hydrochloride with α,β--unsaturated ketones (chalcones) using glacial acetic acid as catalyst under thermal conditions. These compounds were characterized by using elemental analysis, FT-IR spectroscopy and $^{1}$H-NMR spectroscopy.

**Keywords:** isoxazoline, chalcone, hetrocyclic.

## INTRODUCTION

Compounds with isoxazoline structures are known to possess a wide spectrum of activities like antifungal, anticancer, antiviral and insecticidal and are also important precursors for different natural products[1-4]. Prodrug- based monoamine oxidase (MAO) inhibitors having hydrazide, hydrazine and amine moiety such as isocarboxazide[5], phenelzine[6] and meclobemide[7,8] show prominent antidepressant activity in laboratory animals and human. Additionally, tranylcypromine-like MAO inhibitors are mechanism based inactivators and they are metabolized by MAO with one electron of the nitrogen pair and to generate an imine, the other residing on a methylene carbon (R-C=NH2+). The structures of the synthesized 2-isoxazoline derivatives are very similar to those of isocarboxazid (Fig. 1).



**(3)** **Isocarboxazid**

**Fig. 1: Structures of 3-(2''-hydroxy naphthalene-1''-yl)-1,5-diphenyl-2-pyrazolines (3) and Isocarboxazid**

Earlier studies on some 1,3,5-triphenyl- 2-pyrazolines, 3-(2''-hydroxy naphthalene-1''-yl)-1,5-diphenyl-2-pyrazolines, 1-thiocarbamoyl- 3,5-diphenyl-2-pyrazolines and bicyclic pyrazolines revealed monoamine oxidase inhibitory activity in behavioural despair test[9-13]. Hence, some new 5-(furan-2-yl)-3-phenyl-4,5-dihydroisoxazoles have been synthesised.

**EXPERIMENTAL**

Melting points were uncorrected. FT.IR-8400, SHIMADZU. 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 analysis was performed by using Euro Vector EA3000A (University of AL-al-Bayt, Jordan).

**1. Synthesis of isoxazoline derivatives (2a-e)**

**General procedure:** To a stirred solution of chalcone (**1a–e**) ( which was prepared as mentioned in the literature)[14] (1.0 mmol) in 10 ml EtOH (96 %) was added to hydroxylamine hydrochloride (2.0 mmol) and glacialaceticacid (2.5 ml) at room temperature. The reaction mixture was heated to reflux overnight. The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 8:2). The EtOH was removed under reduced pressure and the residue was recrystalized from EtOH to afford the pure products (**2a–e**).

**5-(furan-2-yl)-3-phenyl-4,5-dihydroisoxazole (2a)**

5-(furan-2-yl)-3-phenyl-4,5-dihydroisoxazole (2a) was prepared from the reaction of 3-(furan-2-yl)-1-phenylprop-2-en-1-one (1a) with hydroxylamine hydrochloride and gave a 71% yield with a m.p. (188-190)$^o$c. The CHN analysis for $C_{13}H_{11}NO_2$ ; C 73.23; H 5.20; N 6.57 Found C 73.20; H 5.20; N 6.56, FT-IR spectra (KBr pellet) υ(cm$^{-1}$) 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching of isoxazoline ring), 1595 (C=C stretching of aromatic ring), 1219 (C–N stretching of isoxazoline ring), $\delta_H$($CDCl_3$) (7.912-7.921) ppm (1H,d,1); (7.518-7.581) ppm (5H,m,8,9,10,11,12); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

**5-(furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (2b)**

5-(furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (2b) was prepared from the reaction of 3-(furan-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (1b) with hydroxylamine hydrochloride and gave a 73% yield with a m.p. (198-200)$^o$c. The CHN analysis for $C_{14}H_{13}NO_3$ ; C 69.12; H 5.39; N 5.76 Found C 69.10; H 5.39; N 5.75, FT-IR spectra (KBr pellet) υ(cm$^{-1}$) 3022 (C–H stretching of aromatic ring), 2883 (C–H stretching of aliphatic), 1619 (C=N stretching of isoxazoline ring), 1594 (C=C stretching of aromatic ring), 1216 (C–N stretching of isoxazoline ring), $\delta_H$($CDCl_3$) (7.912-7.921) ppm (1H,d,1); (7.455-7.465) ppm (2H,d,8,12); (7.259-7.269) ppm (2H,d,9,11); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); 4.111 ppm (3H,s,10); (3.350-3.360) ppm (2H,d,7,7\)

**3-(4-bromoxyphenyl)-5-(furan-2-yl)- 4,5-dihydroisoxazole (2c)**

3-(4-bromoxyphenyl)-5-(furan-2-yl)- 4,5-dihydroisoxazole (2c) was prepared from the reaction of 3-(furan-2-yl)-1-(4-bromophenyl)prop-2-en-1-one (1c) with hydroxylamine hydrochloride and gave a 78% yield with a m.p. (205-207)$^o$c. The CHN analysis for $C_{13}H_{10}BrNO_2$ ; C 53.45; H 3.45; N 4.79 Found C 53.41; H 3.43; N 4.78, FT-IR spectra (KBr pellet) υ(cm$^{-1}$) 3023 (C–H stretching of aromatic ring), 2884 (C–H stretching of aliphatic), 1622 (C=N stretching of isoxazoline ring), 1596 (C=C stretching of aromatic ring), 1217 (C–N stretching of isoxazoline ring), $\delta_H$($CDCl_3$) (7.912-7.921) ppm (1H,d,1); (7.709-7.719) ppm (2H,d,8,12); (7.402-7.412) ppm (2H,d,9,11); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

**5-(furan-2-yl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole (2d)**

5-(furan-2-yl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole (2d) was prepared from the reaction of 3-(furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (1d) with hydroxylamine hydrochloride and gave a 82% yield with a m.p. (204-206)$^o$c. The CHN analysis for $C_{13}H_{10}N_2O_4$ ; C 60.47; H 3.90; N 10.85 Found C 60.45; H 3.90; N 10.84, FT-IR spectra (KBr pellet) υ(cm$^{-1}$) 3021 (C–H stretching of aromatic ring), 2881 (C–H stretching of aliphatic), 1625 (C=N stretching of isoxazoline ring), 1597 (C=C stretching of aromatic ring), 1212 (C–N stretching of isoxazoline ring), $\delta_H$($CDCl_3$) ( 8.321-8.331) ppm (2H,d,9,11); (8.111-8.121) ppm (2H,d,8,12); (7.912-7.921) ppm (1H,d,1); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

**5-(furan-2-yl)-3-(4-aminophenyl)-4,5-dihydroisoxazole (2e)**

5-(furan-2-yl)-3-(4-aminophenyl)-4,5-dihydroisoxazole (2e) was prepared from the reaction of 3-(furan-2-yl)-1-(4-aminophenyl)prop-2-en-1-one (1e) with hydroxylamine hydrochloride and gave a 70% yield with a m.p. (197-199)$^{o}$c. The CHN analysis for $C_{13}H_{12}N_2O_2$ ; C 68.41; H 5.30; N 12.27 Found C 68.40; H 5.28; N 12.25, FT-IR spectra (KBr pellet) υ(cm$^{-1}$) 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1620 (C=N stretching of isoxazoline ring), 1590 (C=C stretching of aromatic ring), 1210 (C–N stretching of isoxazoline ring), $\delta_H$($CDCl_3$) ( 8.321-8.331) ppm (2H,d,9,11); (8.111-8.121) ppm (2H,d,8,12); (7.912-7.921) ppm (1H,d,1); (6.211-6.481) ppm (2H,m,2,3); 5.500 ppm (2H,s,10); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

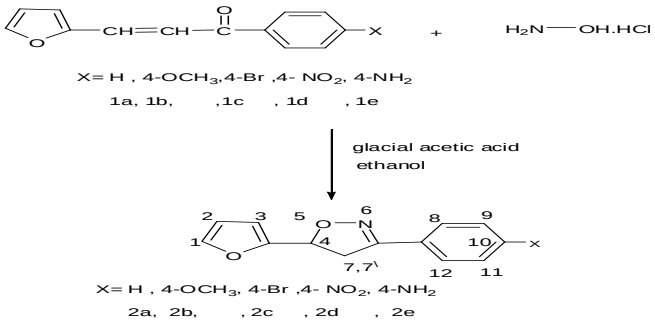
## 2. Computational methods

All theoretical calculations in this work were performed using the computational methods. Geometry optimization of the studied compounds was done by performing the semi-empirical molecular orbital theory at the level PM3[15].

## RESULTS AND DISCUSSION

Treatment of chalcone derivatives **(1a-e)** with hydroxylamine hydrochloride in boiling ethanol gave isoxazoline derivative compounds, after purification by recrystallization from ethanol, pure isoxazoline derivative compounds in (70-82)% yield were obtained, as shown in (scheme 1). The structures of these products were established from their elemental analysis, FT-IR,C.H.N and $^1$H NMR spectra. The FT-IR spectra of pyrazoline compounds were characterized by the disappearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1672-1710) cm$^{-1}$. These facts confirmed the correct expected chemical structure of these compounds. All the IR spectra of isoxazoline derivatives showed a peak at (1614-1625) cm$^{-1}$ which is related to (C=N) stretching of isoxazoline ring , a peak at (1210-1219) cm$^{-1}$ which appeared due to (C-N) stretching of isoxazoline ring and a peak at (1590-1597) cm$^{-1}$ which appeared due to (C=C stretching of aromatic ring). While, the C-H stretching aromatic rings showed a peak within the range (3020-3024) cm$^{-1}$ and the C-H stretching aliphatic showed a peak within the range (2880-2885) cm$^{-1}$. The N-H stretching showed a peak within the range (3330-3338) cm$^{-1}$.

All the $^1$H NMR spectra of isoxazoline ring were characterized[16-18] and showed triplet signals within the range (4.625-4.725) ppm which appeared to proton in (4) position because of the interaction with two protons in (7 and 7\) position, while the two protons in (7 and 7\) position showed doublet signals within the range (3.350-3.937) ppm because of the interaction with protons in (4) position. These peaks confirmed the correct expected chemical structure of isoxazoline compounds. The proton in position (1) of furan ring showed doublet signals at (7.900-7.921) ppm, while the other two protons in positions (2 and 3) of furan ring showed multiplet signals within the range (6.211-7.281) ppm. The protons of aromatic rings in compound (2a) showed multiplet signals within the range (7.518-7.581) ppm which appeared to five protons in (8,9,10,11 and 12). While the compounds (2b,2c,2d and 2e) including AB system in $^1$H NMR spectra therefore showed doublet signals within the range (7.455-8.121) ppm which appeared to the two protons in (8 and 12) positions. The other two protons in positions (9 and 11) showed doublet signals within the range (7.259-8.331) ppm. The $OCH_3$ protons showed singlet signal for three protons at 4.111 ppm. The $NH_2$ protons showed singlet signal for two protons in the region δ= 5.500 ppm.




**Scheme (1)**

**Computational Study**

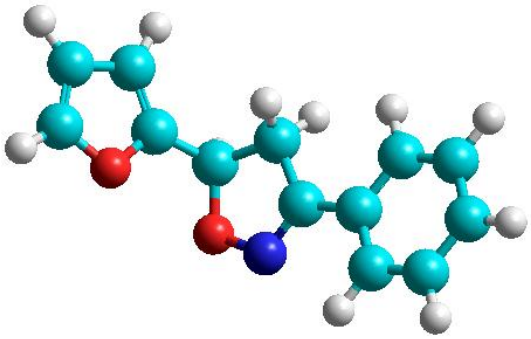
The optimized structures of the studied molecules are shown in Fig 1. The PM3 geometry optimizations yield planar structures for the synthesis compounds. The general geometries of molecule all compounds are very similar.

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 1. The calculated dipole moment indicates that the studied molecules are pole. This means that these molecules may interact with its environmental, especially other polar molecules.

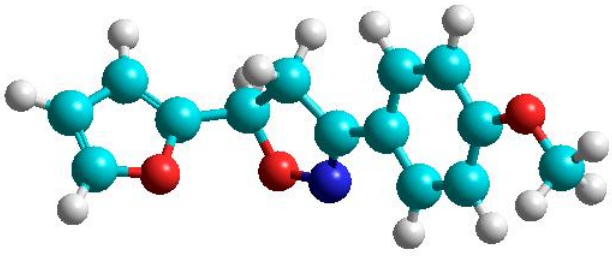
The spatial distributions of HOMO LUMO are shown in Fig. 2. In general the all molecules gave similar HOMOand LUMO orbitals.

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

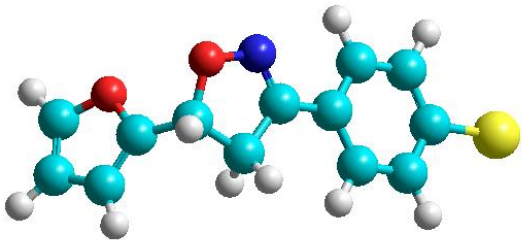
| Mol. | Method | Total energy | HOMO | LUMO | ΔE | μ |
|---|---|---|---|---|---|---|
| H | PM3 | -90.239823759 | -9.386246 | -0.5119647 | -9.8982107 | 3.271 |
| OCH3 | PM3 | -106.516514028 | -9.007346 | -0.4265804 | -9.4339264 | 2.614 |
| Br | PM3 | -102.661835395 | -9.454806 | -0.7566164 | -10.2114224 | 3.065 |
| $NO_2$ | PM3 | -117.118397343 | -9.688211 | -1.567412 | -11.255623 | 5.901 |
| $NH_2$ | PM3 | -96.779744133 | -8.626534 | -0.4503611 | -9.0768951 | 4.061 |



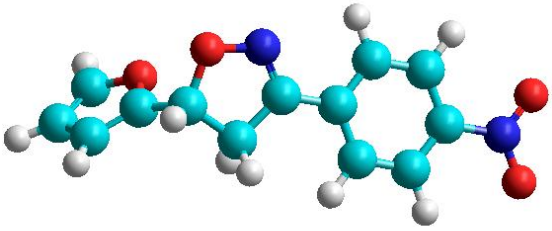
**Geometry optimization (H)**



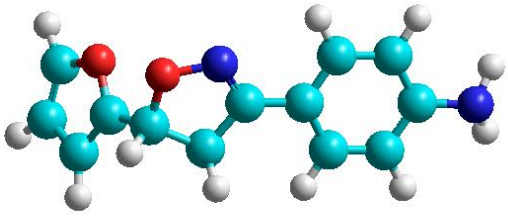
**Geometry optimization ($OCH_3$)**



**Geometry optimization (Br)**

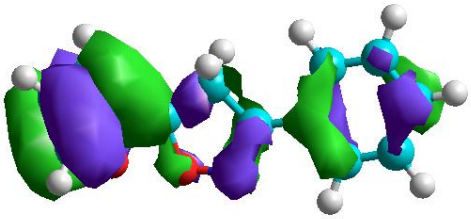


**Geometry optimization ($NO_2$)**

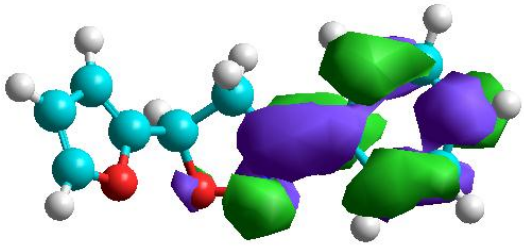


**Geometry optimization ($NH_2$)**

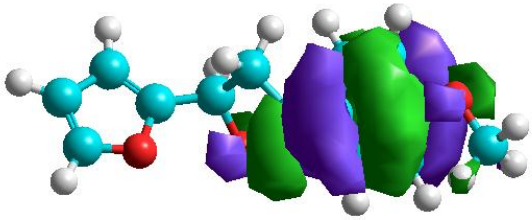
**Fig. 1: The optimized structure of the studied molecules optimization has been performed by PM3 method.**



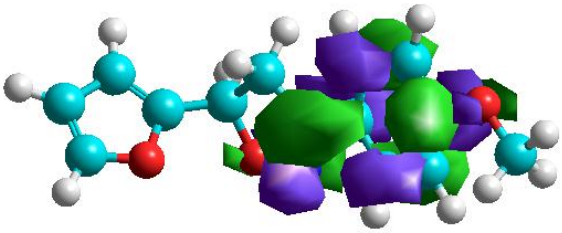
**HOMO (H)**



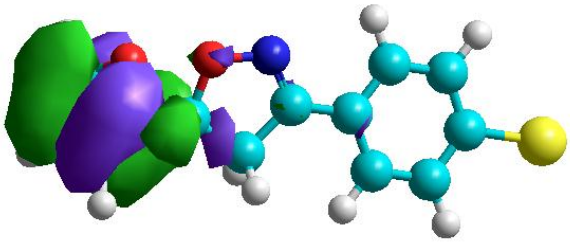
**LUMO (H)**



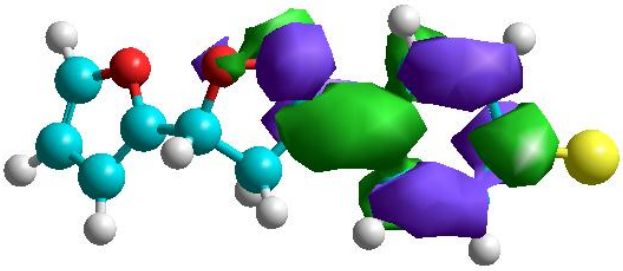
**HOMO ($OCH_3$)**



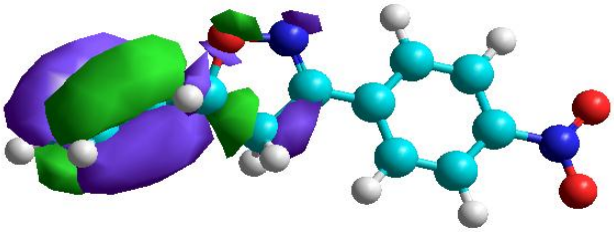
**LUMO ($OCH_3$)**



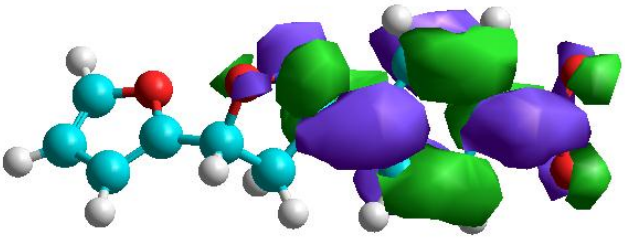
**HOMO (Br)**



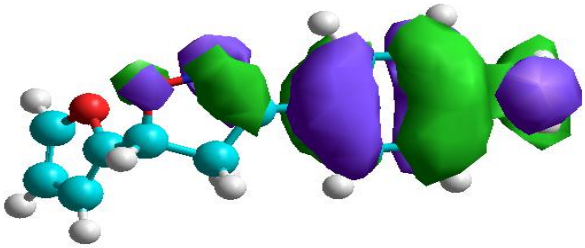
**LUMO (Br)**



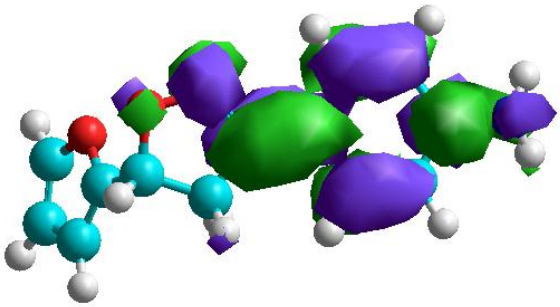
**HOMO ($NO_2$)**



**LUMO (NO2)**



**HOMO ($NH_2$)**



**LUMO ($NH_2$)**

**Fig. 2: 3D HOMO and LUMO plots of the studied molecules**

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