International Journal of Modern Agriculture, Volume 9, No. 4, 2020
ISSN: 2305-7246

SYNTHESIS AND DFT QUANTUM CHEMICAL CALCULATIONS OF PYRAZOLE SCAFFOLD PYRIMIDINE DERIVATIVES

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Abstract

In this study, a suitable procedure for the preparation of pyrazolo[1,5-c]pyrimidin-7(1H)-one derivatives is described.. The structures of the synthesized compounds (2a, b) were characterized by elemental analysis, FT-IR, 1H and 13C-NMR spectroscopic techniques. In addition to experimental study in order to find molecular properties, quantum-chemical calculations of the new pyrazolo[1,5-c]pyrimidin-7(1H)-one derivatives (2a, b) were carried out by using DFT/B3LYP method with the 6-311G(d,p) and 6-311++G(2d,2p) basic sets.

Key words: Synthesis; DFT; Quantum chemical calculations.

Introduction

In the recent years pyrimidine and pyrazole derivatives have attracted much interest because of the their biological and pharmacological properties. Pyrimidines have been used in synthesis for long years due to their structural diversities and medicinal properties such as antibacterial [1], anticancer [2], antitumour [3] and anti-inflammatory [4] activities. Similarly, pyrazolopyrimidines show very important biological properties such as antitumor [5], anti-inflammatory [6], antiviral [7] and antifungal [8] activity. N-Amino-pyrimidine-2-one derivatives such as 1-amino-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrimidin-2(1*H*)-one (**1a**) and 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidin-2(1*H*)-one (**1b**) appeared to be an important starting compound in synthetic organic chemistry. In recent years, the reactions of N-amino-pyrimidine-2-one derivatives (**1a**, **b**) with anhydrides [9], isothiociyanate [10], 1,3-dicarbonyl compounds [11] and acyl chlorides [12] have been made in different solvents and at different temperatures. Moreover, transition metal complexes of N-amino-pyrimidine-2-one derivatives (**1a**, **b**) have been studied [13].

Optimization of synthesized molecules was performed using DFT/B3LYP method with 6-311G(d,p) and 6-311++G(2d,2p) basis sets of Gaussian program [15]. The basis set 6-311++G(2d,2p) is known as one of the basic sets that gives more reliable results in terms of the determination of geometries and electronic properties of a broad range of organic molecules [16]. Quantum chemical parameters for synthesized molecules (**2a**, **b**) such as the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), HOMO-LUMO energy gap (ΔE), chemical hardness (η), chemical softness (σ), electronegativity (χ), chemical potential (μ), dipole moment (DM) like for gas and solvent phase of neutral molecules were calculated and discussed. Optimization of molecules with different basic sets and discussion of the results are widely used [17-33].

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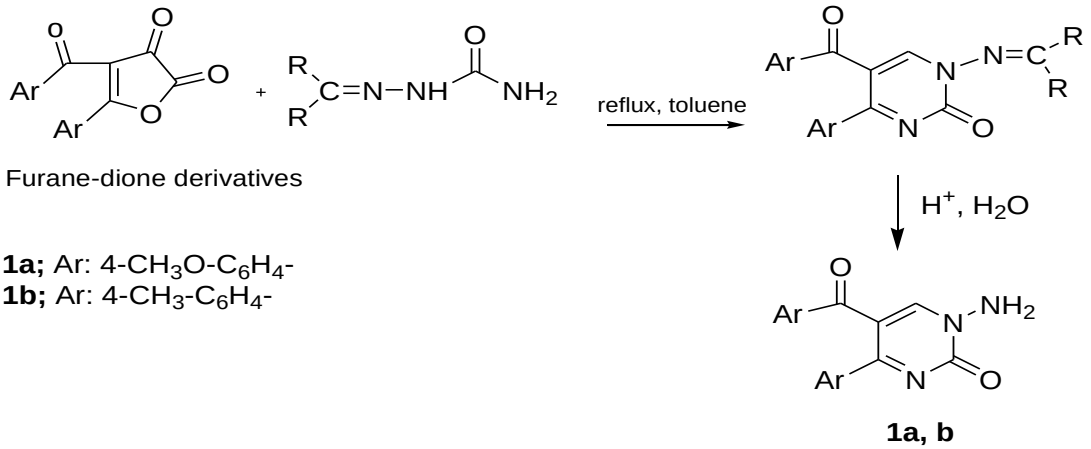

Furane-dione derivatives

1a; Ar: 4-CH_3O-C_6H_4-
1b; Ar: 4-CH_3-C_6H_4-

1a, b

Scheme-1: The mechanism for the formation of the products **1a**, **b**.

Experimental

General materials and instruments

Chemicals and all solvents were commercially available and used without further purification. Melting points were determined on the digital melting point apparatus (Electrothermal 9100) and are uncorrected. The compounds were routinely checked for their homogeneity by TLC using DC Alufolien Kieselgel 60 F254 (Merck) and Camag TLC lamp (254/366 nm). Microanalyses were performed on a Leco CHNSO-932 Elemental Analyser and the results agreed favourably with the calculated values. The FT-IR spectra were recorded on a Shimadzu Model 8400 FT-IR spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker 400(100) MHz Ultra Shield instrument. The chemical shifts were reported in ppm from tetramethylsilane as an internal standard and are given in δ (ppm).

*Synthesis of pyrazolo[1,5-c]pyrimidin-7(1H)-one derivatives (**2a**, **b**)*

*5-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)carbonyl]-2-methylpyrazolo[1,5-c]pyrimidin-7(1H)-on (**2a**)*

Compound **1a** (0.35 g, 1 mmol) and *α*-chloracetone (0.11 mL, 1.3 mmol) were refluxed in 30 mL xylene for 10 hours. The solvent was evaporated. The remaining oily residue was then treated with petroleum ether and stirred for 24 hours. The product **2a** which precipitated was filtered off and washed with ethanol and allowed to dry on P_2O_5; 60% yield; m.p. 225-227 ^oC; FT-IR ν (cm^{-1}): 3072 (aromatic C-H stretch.), 2921 (CH_3O-), 1737-1647 (C=O carbonyl's), 1598-1550 (C=C and C=N), 740-660 (pyrimidine ring skeleton vib.); ^{1}H-NMR (400 MHz, DMSO): δ= 9.01 (s, 1H, NH), 8.88-6.88 (m, 9H, Ar-H), 3.82-3.73 (s, 6H, $2CH_3O$-), 2.36 ppm (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO): δ= 191.97, 164.10 (C=O), 160.38-114.08 ppm (aromatic carbons), 56.09-55.65 ($2CH_3O$-), 11.73 ppm (CH_3-). Elemental analysis (%) for $C_{22}H_{19}N_3O_4$, Found (Calc.): C= 67.63 (67.86); H= 4.86 (4.92); N= 10.67 (10.79).

Computational details

In the section, optimization of synthesized molecules was performed with Gaussian program [15] by using DFT/B3LYP method. Molecular properties of compounds, related to the reactivity and selectivity, were estimated using the Koopmans's theorem relating the energy of the E_{HOMO} and the E_{LUMO}. Electronegativity (χ) is calculated using from E_{HOMO} and E_{LUMO}:

$$\chi \cong -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \qquad (1)$$

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Chemical hardness (η) that measures the resistance of an atom to a charge transfer [34] can be calculated with the below equations by using E_{HOMO} and E_{LUMO} [16]:

$$\eta \cong -\frac{1}{2}(E_{HOMO} - E_{LUMO}) \qquad (2)$$

Chemical potential (μ) can be calculated with the below equations by using electronegativity (χ) or E_{HOMO} and E_{LUMO} [16]:

$$\mu = -\chi \cong \left(\frac{E_{HOMO} + E_{LUMO}}{2}\right) \qquad (3)$$

Electron polarizability as called chemical softness (σ) that describes the capacity of an atom or group of atoms to receive electrons [34] and it can be found by using chemical hardness (η) or E_{HOMO} and E_{LUMO}:

$$\sigma = \frac{1}{\eta} \cong -\left(\frac{2}{E_{HOMO} - E_{LUMO}}\right) \qquad (4)$$

The global electrophilicity index (ω) is a useful feature for reactivity descriptor that can be used to compare the electron-donating abilities of molecules [35]. Global electrophilicity index can be found by using the electronegativity and chemical hardness parameters with below equation:

$$\omega = \frac{\chi^2}{2\eta} \qquad (5)$$

A high value describes a good electrophile while a small value describes a good nucleophile [36].

Results and discussion

Main reasons of our interest in N-aminopyrimidine derivatives (**1a**, **b**) are related to their being important materials in the synthesis of heterocyclic compounds, structural diversities and medicinal properties. Hence, in our study, 5-(4-methoxyphenyl)-4-[(4-methoxyphenyl)carbonyl]-2-methylpyrazolo[1,5-c]pyrimidin-7(1*H*)-on (**2a**) and 5-(4-methylphenyl)-4-[(4-methylphenyl)carbonyl]-2-methylpyrazolo[1,5-c]pyrimidin-7(1*H*)-one (**2b**) were synthesized by the cyclization, involving the reaction of N-aminopyrimidine derivatives (**1a**, **b**) with α-chloracetone in xylene under reflux for 8 h (**Scheme 2**) (for details see Experimental). The reactions of N-aminopyrimidine-2-one derivatives (**1a**, **b**) with α-chloracetone yielded pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) in moderate yields (60-71%). The synthesized compounds were characterized by using ^{1}H and ^{13}C-NMR, and FT-IR spectroscopic methods, and elemental analysis.

The proposed mechanism for the formation of pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) are depicted in **Scheme 3**. On treatment of α-chloracetone with N-aminopyrimidine-2-one derivatives (**1a**, **b**), the reaction started by a nucleophilic attack of the nitrogen atom single pair electrons of N-aminopyrimidine-2-one derivatives (**1a**, **b**) to the carbonyls' carbon of α-chloracetone [37]. Then, schiff base occurs at first step by the condensation reactions of N-aminopyrimidine-2-one derivatives (**1a**, **b**) and α-chloracetone. The cyclization reactions of (**1a**, **b**) to (**2a**, **b**), via elimination of a molecule of hydrogenchloride occur by refluxing in xylene. The formation mechanism of the compounds **2a**, **b** from 1a, b with α-chloracetone can be seen in **Scheme 3**.

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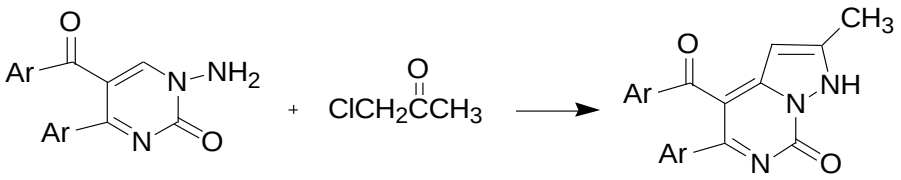

1a; Ar: 4-CH_3O-C_6H_4-
1b; Ar: 4-CH_3-C_6H_4-

2a; Ar: 4-CH_3O-C_6H_4-
2b; Ar: 4-CH_3-C_6H_4-

Scheme-2: The mechanism for the formation of the products **2a**, **b**.

The product **2a** was obtained in 60 % yield by treating (**1a**) with α-chloracetone and by refluxing them in 30 mL xylene for 10 hours. The FT-IR spectra are excellent evidences of compound **2a** structure. The C=O absorption bands were observed at 1737 and 1647 cm^{-1}, respectively. Important structural information of compound **2a** can be obtained from its ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum of (**2a**), contains three singlet peaks at 3.82, 3.73, 2.36 ppm representing the methoxy and methyl groups respectively. Chemical shift value for the proton at -NH- in pyrazol rings of the compound (**2a**) was observed at 9.01 ppm. The peaks between 8.88-6.88 ppm are thought to represent the aromatic protons. The ^{13}C-NMR signals were found to be at 191.97 (benzoyl, C=O), 164.10 (pyrimidine, C=O), 160.38-114.08 (aromatic C), 56.09-55.65 ($2CH_3O$-), 11.73 ppm (CH_3-). Finally, the elemental analysis and spectroscopic data confirm the molecule structure of **2a**.

The reaction of compound **1b** with α-chloracetone led to the formation of the corresponding of 5-(4-methylphenyl)-4-[(4-methylphenyl)carbonyl]-2-methylpyrazolo[1,5-c]pyrimidin-7(1*H*)-on (**2b**) in moderate yields (71%) (**Scheme 1**). The information about spectra of molecule **2b** was given in the experimental section and confirmed the structure of molecules **2b** with elemental analysis data.

Molecular structure

E_{HOMO}, E_{LUMO}, ΔE, DM, MV, TNC, η, σ, μ, χ, ω, SEZPE were calculated for the pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) with the DFT/B3LYP method using 6-311G(d,p) and 6-311++G(2d,2p) basic sets for gas phase and solvent phase (ethanol) of neutral molecules, as shown in **Figs. 1** and **2**, and **Table 1**.

E_{HOMO} is associated with electron donating ability and E_{LUMO} electron accepting ability of a molecule. High E_{HOMO} is essential for reaction with nucleophiles of molecule while low E_{LUMO} is essential for reaction with electrophiles [38]. E_{HOMO} values of **2a**, **b** molecules were found by using 6-311++G(2d,2p) basic set for gas phase -5.87, -6.02 eV and for solvent phase -5.96, -6.16 eV, respectively (**Fig. 1**). According to these results, the electron donating trends for study molecules for gas and solvent phase can be written as: **2b**>**2a**. The same trend can be written in 6-311G(d,p) basic set for gas and solvent phase (see **Fig. 1**). E_{HOMO} values in **2a** molecule is lower than other molecule **2b**, for the gas phase and solvent phase for the two basic sets. This is due to the methoxy group attached to the phenyl ring of **2a** molecule. As is known, the methoxy group is an electron attracting group. E_{LUMO} values of **2a**, **b** molecules were found by using 6-311++G(2d,2p) basic set for gas phase -1.76, -1.88 eV and for solvent phase -1.97, -2.09 eV, respectively (**Fig. 1**). E_{LUMO} values in **2a** molecule is lower than other molecule **2b**. The electron accepting trends for study molecules for gas and solvent phase can be written as: **2a**>**2b**. The same trend can be written in 6-311G(d,p) basic set for gas and solvent phase (see **Fig. 1**). The energy gap (ΔE), chemical hardness and chemical softness are closely related to chemical properties. ΔE value is smaller when the basis set of atomic orbitals are magnified due to the changing of HOMO, usually to a more negative energy and decreasing in energy of LUMO [39]. More stable molecules have large ΔE value and less stable molecules have small ΔE value. ΔE values of **2a**, **b** molecules were found by using 6-311++G(2d,2p) basic set for gas phase 4.11, 4.14 eV and for solvent phase 3.99, 4.07 eV, respectively (**Fig. 1**). **2b** molecule is found more stable than other molecule for gas and solvent phase due to the fact that a large ΔE value is observed (**Fig. 1**).

International Journal of Modern Agriculture, Volume 9, No. 4, 2020
ISSN: 2305-7246

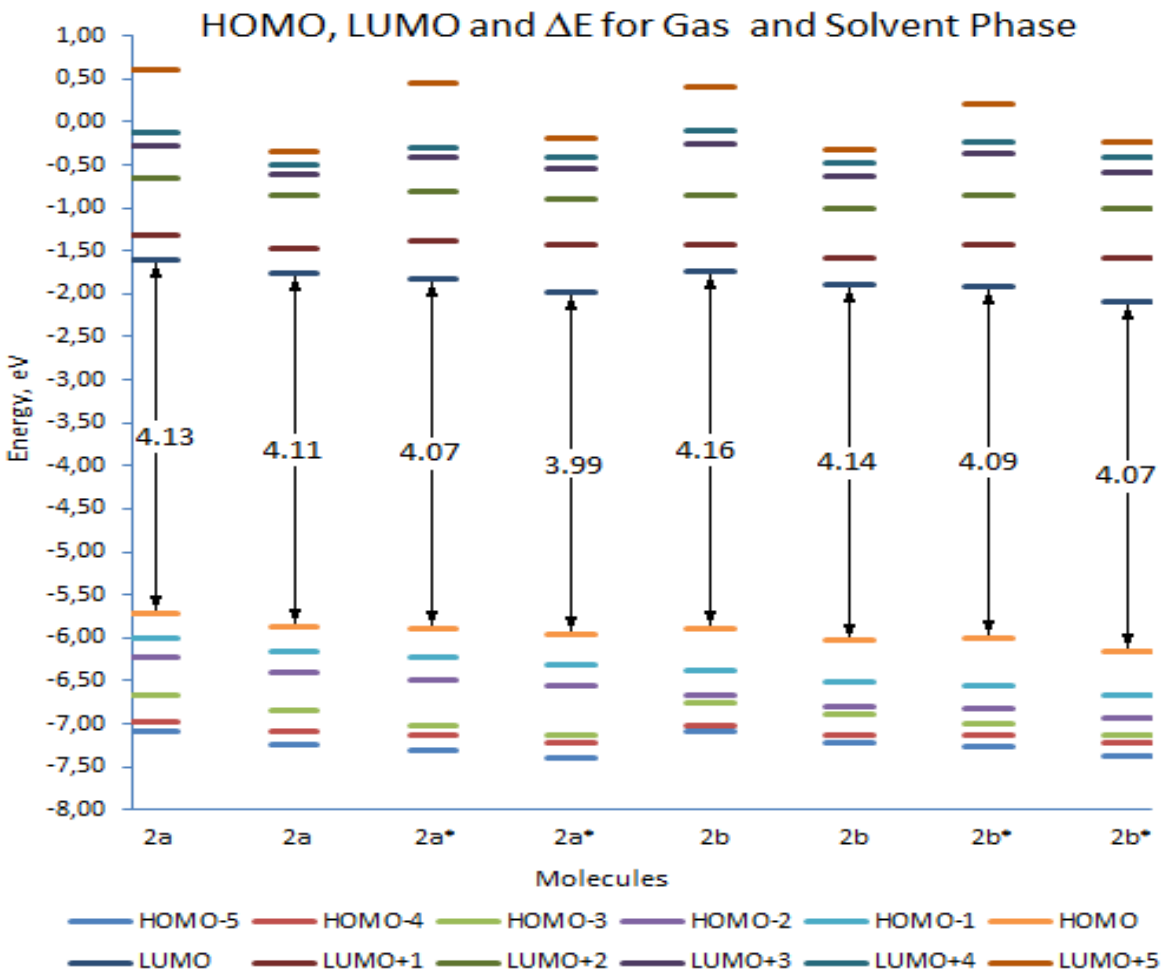

Fig. 1: The calculated HOMO, LUMO and ΔE parameters for neutral molecules for gas and solvent phase (*) by using DFT B3LYP/6-311G(d,p) and 6-311++G(2d,2p) basic sets (the results are given for the same numbered molecule, left to right first with 6-311G(d,p) and second with 6-311++G(2d,2p) basic set.

The hardness (η) that chemical hardness is a measure of the stability of chemical species [40], and softness (σ) are widely used in chemistry for explaining stability of compounds. The hardness is just half the energy gap between the E_{HOMO} and E_{LUMO} (see **eq. 2**). η values of **2a**, **b** molecules were found by using 6-311++G(2d,2p) basic set for gas phase 2.05, 2.07 eV and for solvent phase 1.99, 2.03 eV, respectively (**Fig. 2**). This condition can also see in the SEZPE energies of the molecules (**Table 1**).

If a compound has a large energy gap, it is called hard and other wise is called soft [41]. Softness is a indication of the polarizability, and soft molecules give more easy electrons to an electron acceptor surface or molecule [16]. The calculated softness values are given in **Fig. 2**. According to softness values, electron donating trend of compounds can be written as: **2b**>**2a** for gas and solvent phase.

The average values of the HOMO and LUMO energies have been defined as the chemical potential (μ). The negative of the chemical potential was known as the electronegativity (χ) (see **eq. 3**). Electronegativity, chemical hardness and chemical potential help to determine the chemical properties of molecules [12]. Electronegativity that represents the power to attract the electrons of chemical species is a useful quantity in the prediction of inhibitive performance of molecules [16]. The electronegativity values were found 3.82, 3.95 for

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ISSN: 2305-7246

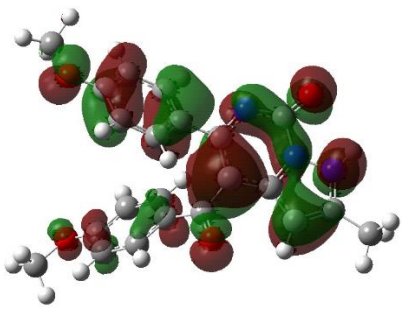
gas phase and 3.97, 4.12 eV for solvent phase of **2a**, **b** molecules with 6-311++G(2d,2p) basic set, respectively. The electronegativity value of **2b** is more than other molecule for gas and solvent phase (**Fig. 2**)

Table-1: The calculated some chemical parameters for gas and solvent phase of the non-protonated compounds using B3LYP method 6-311G(d,p) and 6-311++G(2d,2p) basic sets.

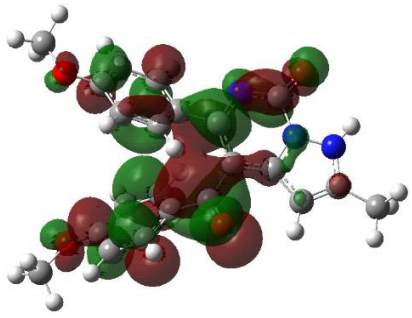
Molecule	**Method, B3LYP**	**DM, Debye**	**MV, cm^3/mol**	**TNC, e**	**ω, eV**	**SEZPE, eV**
2a	6-311G(d,p)	3.564	270.585	-2.905	3.244	-35779.206
2a	6-311++G(2d,2p)	4.036	313.314	-3.062	3.548	-35781.056
2a*	6-311G(d,p)	5.453	288.814	-3.031	3.666	-35780.174
2a*	6-311++G(2d,2p)	6.884	289.558	-3.432	3.944	-35782.760
2b	6-311G(d,p)	3.647	248.704	-2.285	3.491	-31685.432
2b	6-311++G(2d,2p)	3.952	255.671	-3.192	3.774	-31686.993
2b*	6-311G(d,p)	5.361	192.973	-2.426	3.854	-31686.252
2b*	6-311++G(2d,2p)	6.131	281.660	-3.289	4.177	-31687.854

*Solvent phase: ethanol

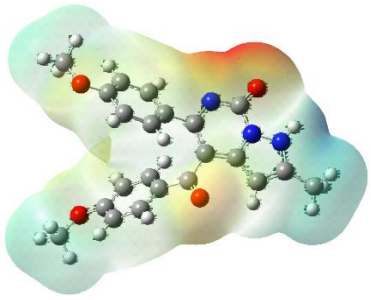
The results of other calculations: dipole moment (DM), global electrophilicity (ω), sum of the total negative charge (TNC) and sum of electronic and zero-point energies (SEZPE) can be seen in **Table 1**.



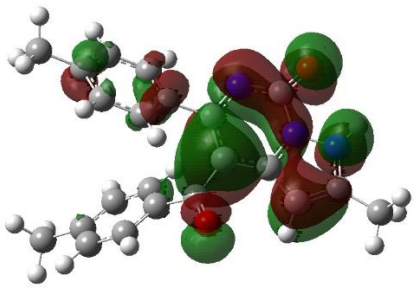
2a-HOMO



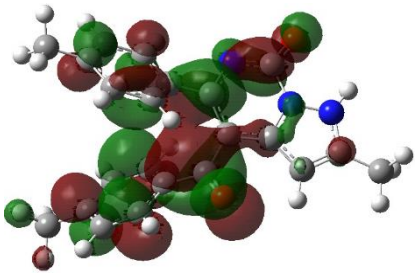
2a-LUMO



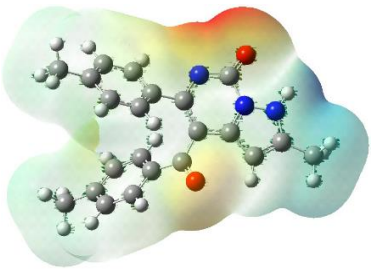
2a-Total Density



2b-HOMO



2b-LUMO



2b-Total Density

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ISSN: 2305-7246

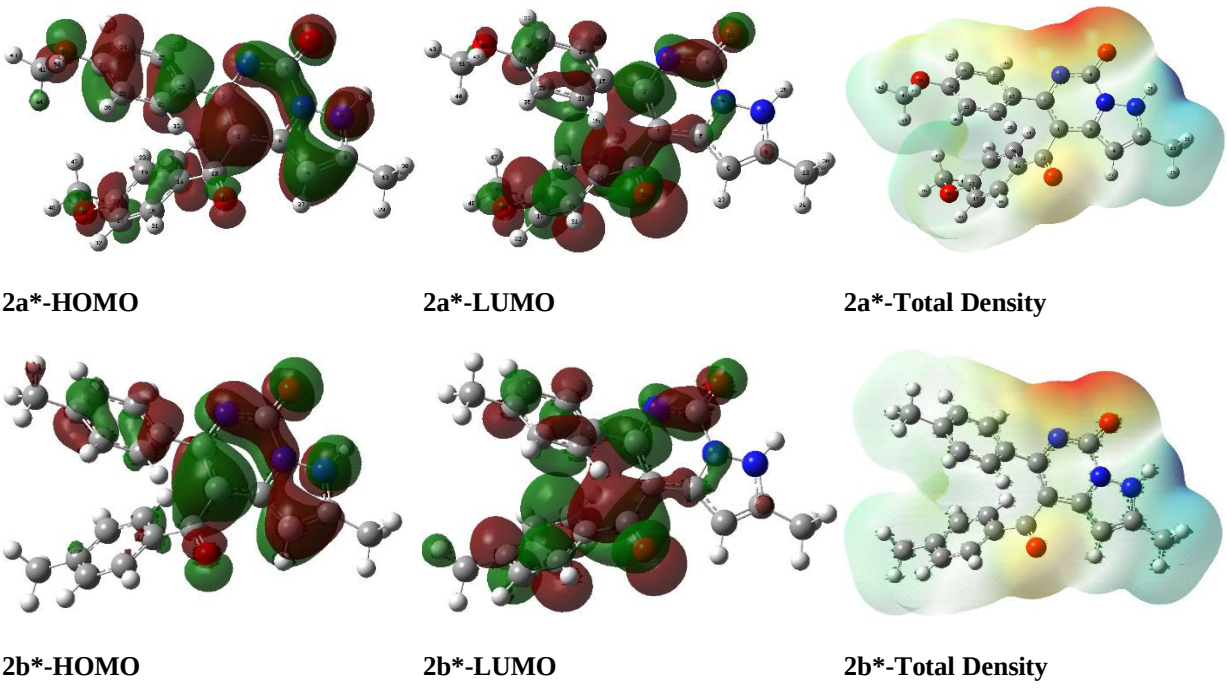

Fig. 3: The optimized molecular structures for gas and solvent (*) phase. HOMOs, LUMOs and total density of the non-protonated molecules by using DFT/B3LYP/6-311++G(2d,2p) basic set.

A typical electron density distribution of total electronic charge (TNC) values calculated by using 6-311G(d,p) and 6-311++G(2d,2p) basic sets. TNC values are lower in gas phase than in solvent phase. SEZPE for **2a** molecule containing one methoxy group is higher than **2b** molecule containing one methyl group (see **Table 1**).

The optimized molecular structures HOMOs, LUMOs and total electron density are also given in **Fig. 3**. This figure shows that there is much more electron density in the vicinity of oxygen atoms for all studied molecules.

The HOMO and LUMO orbitals contribution of the atoms for **2a**, **b** molecules are shown in **Table 2**. The HOMO and LUMO orbitals were calculated by using AOmix program [42, 43] after optimization with DFT/B3LYP method 6-311G(d,p) basic set for gas and solvent phase. HOMO orbitals for 6-311G(d,p) basic set at gas phase consist of + 10.6% 3PZ(C1) + 8.2% 4PZ(C1) + 4.8% 2PZ(C1) - 2.3% 3PZ(C9) + 2.3% 3PZ(N7) - 2.2% 4PZ(C9), + 12.7% 3PZ(C1) + 9.2% 4PZ(C1) + 5.7% 2PZ(C1) + 3.7% 3PZ(O12) + 3.1% 4PZ(O12) - 3.0% 3PZ(N3) for **2a**, **b** respectively.

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Table-2: HOMO and LUMO population for gas and solvent phase of neutral molecules by using AOmix method after from B3LYP/6-311G(d,p) basic set.

Mol.	**HOMO**
2a	+ 10.6% 3PZ(C1) + 8.2% 4PZ(C1) + 4.8% 2PZ(C1) - 2.3% 3PZ(C9) + 2.3% 3PZ(N7) - 2.2% 4PZ(C9)
2a*	+ 7.6% 3PZ(C1) + 5.7% 4PZ(C1) + 3.5% 2PZ(C1) + 2.9% 4PY(C1) + 2.7% 3PY(C1) - 2.6% 3PY(C15)
2b	+ 12.7% 3PZ(C1) + 9.2% 4PZ(C1) + 5.7% 2PZ(C1) + 3.7% 3PZ(O12) + 3.1% 4PZ(O12) - 3.0% 3PZ(N3)
2b*	+ 11.6% 3PZ(C1) + 8.5% 4PZ(C1) + 5.2% 2PZ(C1) - 3.8% 3PZ(C9) - 3.6% 4PZ(C9) + 3.2% 3PZ(N7)
	LUMO
2a	+ 4.8% 3PZ(C2) - 3.8% 3PZ(C10) - 3.0% 3PY(C10) + 3.0% 4PY(C16) + 2.8% 4PZ(C2) + 2.7% 3PZ(O11)
2a*	+ 5.3% 3PY(C10) + 4.2% 4PY(C10) - 3.7% 3PZ(C2) - 3.5% 3PY(O11) + 2.7% 3PX(C10) - 2.6% 4PY(C16)
2b	+ 4.7% 3PZ(C2) - 4.0% 3PZ(C10) + 3.0% 3PZ(O11) + 2.8% 3PY(C10) + 2.7% 4PZ(C2) - 2.6% 4PZ(C10)
2b*	+ 4.3% 3PZ(C2) + 3.8% 3PY(C10) - 3.7% 3PZ(C10) + 3.2% 4PY(C10) - 2.9% 4PY(C16) - 2.6% 3PY(O11)

*in the presence of solvent (ethanol)

Their LUMO consist of + 4.8% 3PZ(C2) - 3.8% 3PZ(C10) - 3.0% 3PY(C10) + 3.0% 4PY(C16) + 2.8% 4PZ(C2) + 2.7% 3PZ(O11), + 4.7% 3PZ(C2) - 4.0% 3PZ(C10) + 3.0% 3PZ(O11) + 2.8% 3PY(C10) + 2.7% 4PZ(C2) - 2.6% 4PZ(C10), respectively. HOMO and LUMO orbitals results for non-protonated gas and solvent phase of molecules can be seen from **Table 2**. As seen from **Table 2**, HOMO orbitals of **2a**, **b** molecules for gas phase consist of mainly C1 carbon atom, and their LUMO orbitals of all molecules for gas and solvent phase can be seen mainly at C2 and C10 carbon atoms.

Conclusions

In this study, the new pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives **2a**, **b** were synthesized from the cyclocondensation reaction of N-Amino-pyrimidine-2-one derivatives**.** The chemical structures of synthesized compounds (**2a**, **b**) were determined by the FT-IR, ^{1}H and ^{13}C-NMR spectroscopic data and elemental analysis. Further investigation of were carried out by using DFT/B3LYP method with basic sets of the 6-311G(d,p) and 6-311++G(2d,2p). Quantum chemical features such as HOMO, LUMO, HOMO-LUMO energy gap, chemical hardness, chemical softness, electronegativity, etc. values for gas and solvent phase of neutral molecules were calculated and discussed. According to quantum chemical calculation results, the electron donating trends for **2a**, **b** molecules for gas and solvent phase can be written as: **2b**>**2a**. According to energy gap (ΔE) results, **2b** molecule is found more stable than **2a** molecule for gas and solvent phase. The HOMO populations of **2a**, **b** molecules for gas and solvent phase consist of mainly C1 carbon atom, and LUMO populations can be seen mainly at C2 and C10 carbon atoms.

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