Synthesis and DFT Quantum Chemical Calculations of Novel Pyrazolo[1,5-c]pyrimidin-7(1*H*)-one Derivatives

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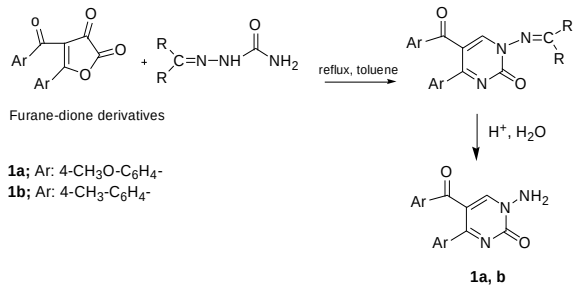
Summary: In this study, a convenient procedure for the preparation of pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives is described. The new pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) were synthesized from the cyclocondensation reaction of the compounds 1-amino-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrimidin-2(1*H*)-one (**1a**) and 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidin-2(1*H*)-one (**1b**) with α-chloroacetone. The structures of the compounds (**2a**, **b**) were characterized by elemental analysis, FT-IR, ^{1}H-NMR and ^{13}C-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(1*H*)-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. Quantum chemical features such as HOMO, LUMO, HOMO-LUMO energy gap, chemical hardness, chemical softness, electronegativity, chemical potential, dipole moment etc. values for gas and solvent phase of neutral molecules were calculated and discussed.

Keywords: Aminopyrimidine; Pyrazolo[1,5-c]pyrimidin-7(1*H*)-one Derivatives; Synthesis; DFT; Quantum chemical calculations.

Introduction

In the recent years pyrimidines and pyrazoles have attracted much interest due to the biological and pharmacological properties. Pyrimidines have been used in synthesis for many years due to their importance about structural diversities and medicinal properties such as antibacterial [1], anticancer [2], antitumor [3] and anti-inflammatory [4] activities. Similarly, pyrazolopyrimidines exhibit 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], isothiocyanate [10], 1,3-dicarbonyl compounds [11] and acyl chlorides [12] have been reported in different solvents and at various temperatures. Moreover, transition metal complexes of N-amino-pyrimidine-2-one derivatives (**1a**, **b**) have been studied [13].

In this study, N-Aminopyrimidine-2-one derivatives (**1a**, **b**) were synthesized in two steps from furan-2,3-diones [14] (Scheme-1). The new pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) were prepared in 60-71% yields via the cyclocondensation reaction of N-aminopyrimidine-2-one derivatives (**1a**, **b**) with α-chloroacetone according to (Schemes-2 and 3). These compounds have been elucidated both experimentally and theoretically. In experimental studies, the molecules were characterized by FT-IR, ^{1}H and ^{13}C-NMR spectroscopies.



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

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]. 6-311++G(2d,2p) basis set is

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known as one of the basis sets that gives more accurate results in terms of the determination of electronic and geometries properties for a wide range of organic compounds [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), softness (σ), electronegativity (χ), chemical potential (μ), dipole moment (DM), global electrophilicity (ω), sum of the total negative charge (TNC) and sum of electronic and zero-point energies (SEZPE) for gas and solvent phase of neutral molecules were calculated and discussed. Recently, optimization of molecules with different basic sets and discussion of the results are widely used [17-36]. Arshad at al. have been synthesized and characterized by various spectroscopic techniques including FT-IR, UV-vis, ^{1}H-NMR, ^{13}C-NMR spectroscopy, the structure and density functional theory (DFT) study was unequivocally confirmed by single crystal X-ray diffraction studies of *N*-[3-anthracen-9-yl-1-(4-bromo-phenyl)-allylidene]-N-benzenesulfonohydrazine [37]. Nisa at al. are investigated acceleration of the electrocyclization of 1,3,5-hexatriene to 1,3-cyclohexadiene through early transition metal catalysis of through quantum mechanical methods [38].

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 tetramethyl silane 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-chloroacetone (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 °C; 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).

5-(4-Methylphenyl)-4-[(4-methylphenyl)carbonyl]-2-methylpyrazolo[1,5-c]pyrimidin-7(1H)-on (**2b**)

Compound **1b** (0.32 g, 1 mmol) and α-chloroacetone (0.10 mL, 1.3 mmol) were refluxed in 30 mL xylene for 8 hours. The solvent was evaporated. The remaining oily residue was then treated with petroleum ether and stirred for 24 hours. The product **2b** which precipitated was filtered off and washed with ethanol and allowed to dry on P_2O_5; 71% yield; m.p. 243-245 °C; FT-IR ν (cm^{-1}): 3066 (aromatic C-H stretch.), 2920 (CH_3-), 1737-1647 (C=O carbonyl's), 1581-1483 (C=C and C=N), 744-667 (pyrimidine ring skeleton vib.); ^{1}H-NMR (400 MHz, DMSO): δ= 9.05 (s, 1H, NH), 8.90-7.12 (m, 9H, Ar-H), 2.26-2.37 ppm (s, 9H, $3CH_3$-); ^{13}C-NMR (100 MHz, DMSO): δ= 192.92, 153.72 (C=O), 146.40-118.48 (aromatic carbons), 21.26 ($2CH_3$-), 11.73 ppm (CH_3-). Elemental analysis (%) for $C_{22}H_{19}N_3O_2$, Found (Calc.): C= 74.07 (73.93); H= 5.41 (5.36); N= 11.86 (11.76).

Computational details

The quantum chemical study of the title compound has been performed within the density functional theory with Becke's three parameter hybrid exchange functional with Lee–Yang–Parr correlation functional (B3LYP) employing 6-311G(d,p) and 6-311++G(2d,2p) basis sets. All quantum chemical calculations are performed using computer software Gaussian-03, Revision D.01 [15].

Molecular properties, related to the reactivity and selectivity of the compounds, were estimated following the Koopmans's theorem relating the energy of the HOMO and the LUMO. Electronegativity is estimated using the following the equation from E_{HOMO} and E_{LUMO}:

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

Chemical hardness (η) measures the resistance of an atom to a charge transfer [39], chemical hardness, chemical potential (μ) and electronegativity (χ) can be calculated with the help of the following equations from E_{HOMO} and E_{LUMO} [16]:

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

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

Electron polarizability, called chemical softness (σ), describes the capacity of an atom or group of atoms to receive electrons [39] and it is estimated by using chemical hardness (η) or E_{HOMO} and E_{LUMO}:

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

The global electrophilicity (ω) is a useful reactivity descriptor that can be used to compare the electron-donating abilities of molecules [40]. Global electrophilicity index is estimated by using the electronegativity and chemical hardness parameters through the equation:

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

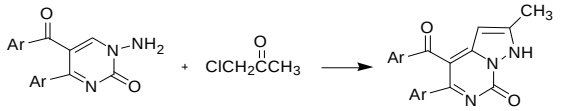
A high value of electrophilicity describes a good electrophile while a small value of electrophilicity describes a good nucleophile [41].

Results and Discussion

Structural analysis

Main reasons of our interest in N-aminopyrimidine derivatives (**1a**, **b**) are related to their being important materials in the synthesis of heterocyclic compounds and their importance about 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-chloroacetone 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-chloroacetone yielded pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) in moderate yields (60-71%). The prepared compounds were characterized by means of ^{1}H-NMR, ^{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-chloroacetone with N-aminopyrimidine-2-one derivatives (**1a**, **b**), the reaction should start by a nucleophilic attack of the nitrogen atom lone pair electrons of N-aminopyrimidine-2-one derivatives (**1a**, **b**) to the carbonyls' carbon of α-chloroacetone [42]. Then, schiff base occurs at first step by the condensation reactions of N-aminopyrimidine-2-one derivatives (**1a**, **b**) and α-chloroacetone. It is noteworthy that the reactivity of α-haloketones is due to the inductive effect of the carbonyl group which enhances the polarity of the carbon-halogen bond [43]. The cyclization reactions of (**1a**, **b**) to (**2a**, **b**), via elimination of a molecule of hydrogen chloride occur by refluxing in xylene. In the light of this, based on the proposed reaction pathway, we showed in detail the reaction pathway of **1** with α-chloroacetone as outlined in Scheme-3.



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-chloroacetone 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 (**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 pyrazolo rings of the compound (**2a**) was observed at 9.01 ppm. The multiple 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 data along with spectroscopic data confirm the structure of (**2a**).

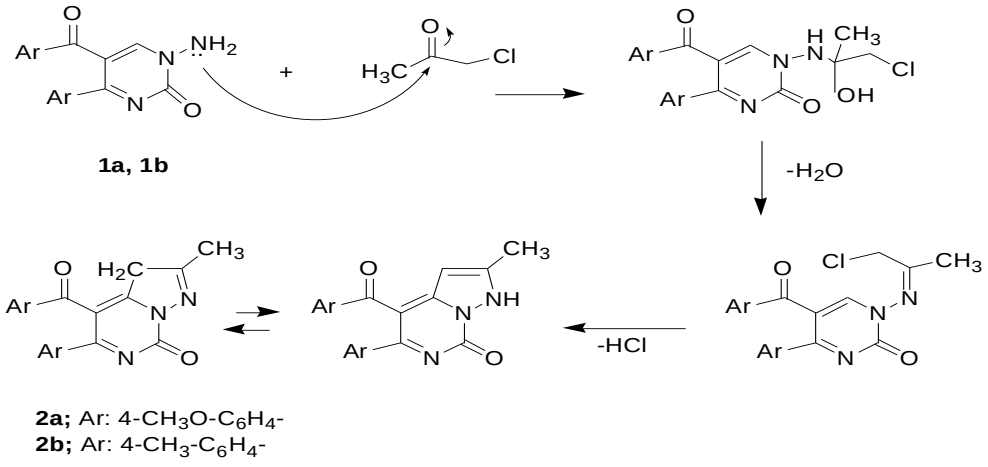
In a similar way, the reaction of (**1b**) with α-chloroacetone led to the formation of the corresponding of 5-(4-methylphenyl)-4-[(4-methylphenyl) carbonyl]-2-methylpyrazolo[1,5-c]pyrimidin-7(1*H*)-on (**2b**) in moderate yields (71%) (Scheme-1). The information about spectra of (**2b**) was given in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

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, Fig. 1 and 2, and Table-1.

E_{HOMO} is associated with electron donating ability of a molecule, and E_{LUMO} is associated with 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 [44]. 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 another 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 (Fig. 1).

HOMO-LUMO energy gap (ΔE), chemical hardness and 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 [45]. 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).



Scheme-3: Mechanistic proposal for the formation of **2a** and **2b**.

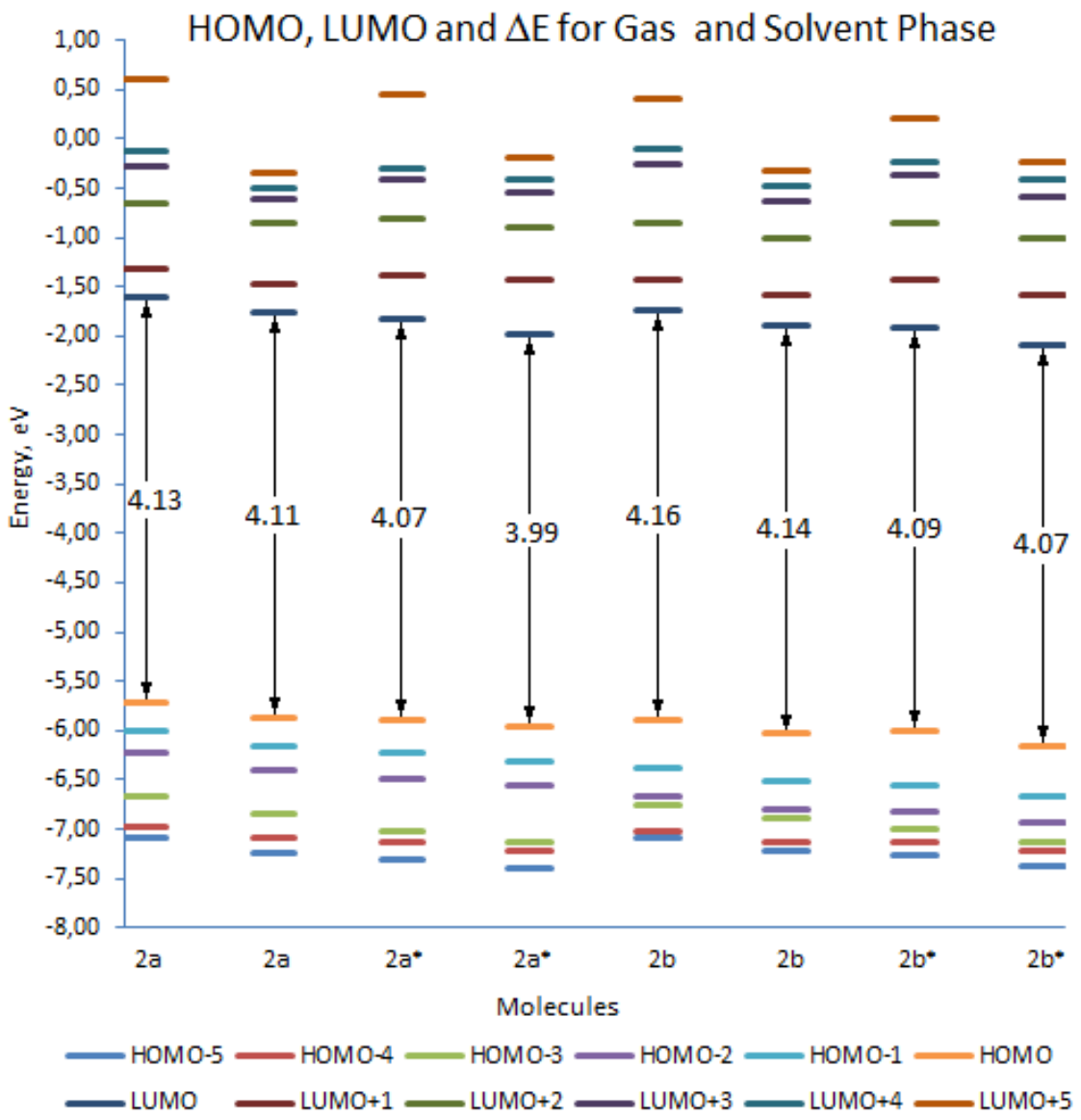


Fig. 1: The calculated HOMO, LUMO and ΔE parameters for neutral molecules for gas and solvent phase (*) using B3LYP/6-311G(d,p) and 6-311++G(2d,2p) methods (the results are given for the same numbered molecule, left to right first with 6-311G(d,p) and second with 6-311++G(2d,2p) basic sets).

The hardness (η) and softness (σ) are widely used in chemistry for explaining stability of compounds. According to Maximum Hardness Principle [46], chemical hardness is a measure of the stability of chemical species. 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 molecule has a large energy gap, it is called hard and other wise is called soft [47]. Softness is a measure of the polarizability and soft molecules give more easily electrons to an electron acceptor molecule or surface [16]. The calculated chemical hardness and softness values are given in Fig. 2. According to softness values, electron donating trend of studied chemical compounds may be written as: **2b**>**2a** for gas and solvent phase.

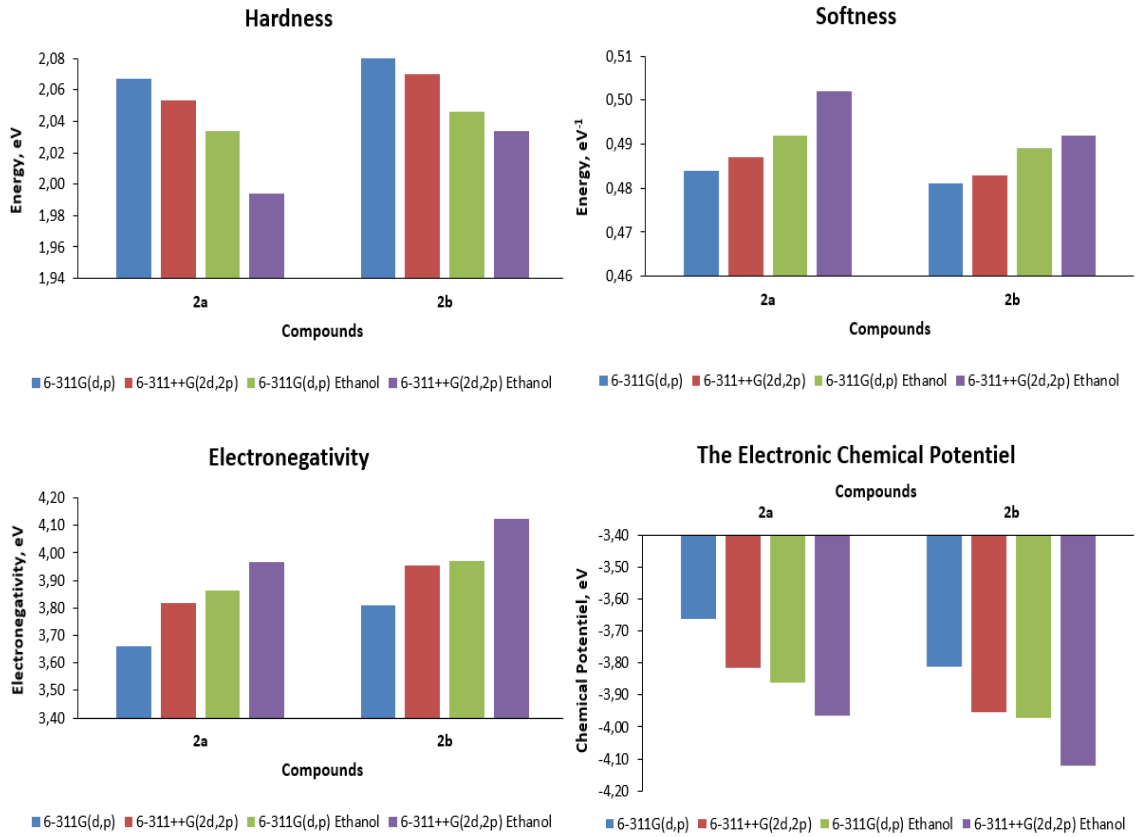


Fig. 2: The calculated quantum chemical parameters for the non-protonated for gas and solvent phase compounds using B3LYP method 6-311G(d,p) and 6-311++G(2d,2p) basic sets.

The average values of the HOMO and LUMO energies have been defined as the chemical potential (μ). The chemical potential was defined as the first derivative of the total energy with respect to the number of electrons. The negative of the chemical potential was known as the electronegativity (χ) (see **eq. 3**). Chemical potential, electronegativity and hardness are descriptors for the predictions about 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 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).

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.

Table-1: The calculated quantum 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

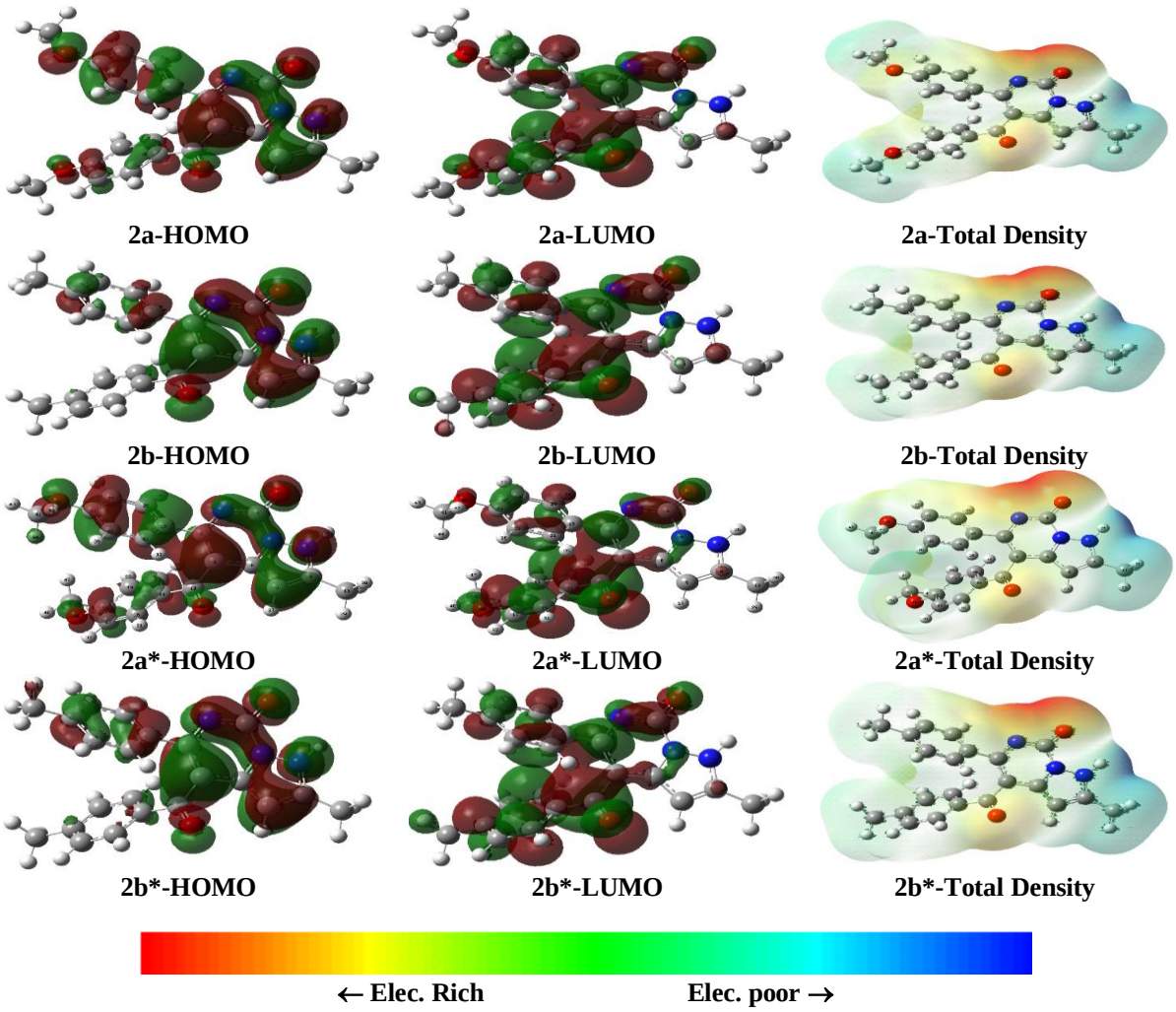


Fig. 3: The optimized molecular structures for gas and solvent (*) phase. HOMOs, LUMOs and total density of the non-protonated inhibitor molecules using DFT/B3LYP/6-311++G(2d,2p) basic set.

A typical electron density distribution of total electronic charge (TNC) values calculated with the 6-311G(d,p) and 6-311++G(2d,2p) basis 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 (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 with AOmix program [48, 49] 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.

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 result 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.

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.

Molecule	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)

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 **1a**, **b** with α-chloroacetone. Mechanistic proposal for the formation of **2a**, **b** was given in **Scheme-3**. The structures of these newly synthesized compounds (**2a**, **b**) were determined from the FT-IR, ^{1}H and ^{13}C-NMR spectroscopic data and elemental analysis.

In addition to experimental study in order to find molecular properties. Quantum-chemical calculations of the new pyrazolo[1,5-c]pyrimidin-7(1*H*)-one derivatives (**2a**, **b**) were carried out by using DFT/B3LYP method with basis 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, chemical potential, dipole moment 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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References

1. B. L. Narayana, A. R. R. Rao and P. S. Rao, Synthesis of new 2-substituted pyrido[2,3-d]pyrimidin-4(1H)-ones and their antibacterial activity, *Eur. J. Med. Chem.* **44**, 1369 (2009).
2. S. A. Al-Issa, Synthesis and anticancer activity of some fused pyrimidines and related heterocycles, *Saudi Pharm. J.*, **21**, 305 (2013).
3. S. Raic-Malic, D. Svedruzic, T. Gazivoda, A. Marunovic, A. Hergold-Brundic, A. Nagl, J. Balzarini, E. De Clercq and M. Mintas, Synthesis and antitumor activities of novel pyrimidine derivatives of 2,3-o,o-dibenzyl-6-deoxy-l-ascorbic acid and 4,5-didehydro-5,6- dideoxy-l-ascorbic acid, *J. Med. Chem.*, **43**, 4806 (2000).
4. P. F. Tuby, T. W. Hudyma, M. Brown, J. M. Essery and R. A. Partyka, Preparation and antiinflammatory properties of some 5-(2-anilinophenyl)tetrazoles, *J. Med. Chem.*, **11**, 111 (1968).
5. A. Angelucci, S. Schenone, G. L. Gravina, P. Muzi, C. Festuccia, C. Vicentini, M. Botta and M. Bologna, Pyrazolo[3,4-d]pyrimidines c-Src inhibitors reduce epidermal growth factor-induced migration in prostate cancer cells, *Eur. J. Cancer*, **42**, 2838 (2006)
6. M. Amir, S. Javed and H. Kumar, Pyrimidine as antiinflammatory agent: a review, *Indian J. Pharm. Sci*., **69,** 337 (2007).
7. E. El-Bendary and F. Badria, Synthesis, DNA-binding, and antiviral activity of certain pyrazolo[3,4-d]pyrimidine derivatives, *Arch. Pharm.*, **333**, 99 (2000).
8. T. Novinson, R. K. Robins and T. R. Matthews, Synthesis and antifungal properties of certain 7-alkylaminopyrazolo[1,5-a] pyrimidines, *J. Med. Chem*., **20**, 296 (1977).
9. Z. Önal and B. Altural, Reactions of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione with various carboxylic anhydrides, *Asian J. Chem.*, **18**, 1061 (2006).
10. Z. Önal and A. C. Daylan, Reactions of 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine derivatives with various isothiocyanates, *Asian J. Chem.*, **19**, 2647 (2007).
11. Z. Önal and B. Altural, reactions of N-aminopyrimidine derivatives. with 1.3-dicarbonyl Compounds, *Turk. J. Chem*., **23**, 401 (1999).
12. A. Özalp, Z. Kökbudak, M. Saraçoğlu, F. Kandemirli, I. Ö. İlhan and C. D. Vurdu, Synthesis and Theoretical study of the novel 2-oxopyrimidin-

1(2H)-ylamides derivative, *Chem. Sci. Rev. Lett.*, **4**,719 (2015).
13. H. G. Aslan, S. Akkoç. Z. Kökbudak and L. Aydın, Synthesis. characterization. and antimicrobial and catalytic activity of a new schiff base and its metal(II) complexes, *J. Iran Chem. Soc.*, **14**, 2263 (2017).
14. Z. Önal and İ. Yıldırım, Reactions Of 4-(4-Methylbenzoyl)-5-(4-Methylphenyl)-2.3-Furandione with Semi-Thiosemi-Carbazones, *Heterocycl. Commun.*, **13**, 113 (2007)
15. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman Jr., J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. Pople, Gaussian 03W, Revision D.01, Gaussian Inc., Wallingford, CT, (2004).
16. S. Kaya, C. Kaya, L. Guo, F. Kandemirli, B. Tüzün, İ. Uğurlu, L. H. Madkour and M. Saracoglu, Quantum chemical and molecular dynamics simulation studies on inhibition performances of some thiazole and thiadiazole derivatives against corrosion of iron, *J. Mol. Liq.*, **219**, 497 (2016).
17. E. E. Ebenso, T. Arslan, F. Kandemirli, I. Love, C. Öğretir, M. Saracoglu and S. A. Umoren, Theoretical studies of some sulphonamides as corrosion inhibitors for mild steel in acidic medium, *Int. J. Quantum Chem.*, **110**, 2614 (2010).
18. M. A. Amin, M. A. Ahmed, H. A. Arida, T. Arslan, M. Saracoglu and F. Kandemirli, Monitoring corrosion and corrosion control of iron in HCl by non-ionic surfactants of the TRITON-X series - Part II. Temperature effect, activation energies and thermodynamics of adsorption, *Corros. Sci*., **53**, 540 (2011).
19. M. A. Amin, M. A. Ahmed, H. A. Arida, F. Kandemirli, M. Saracoglu, T. Arslan and M. A. Basaran, Monitoring corrosion and corrosion control of iron in HCl by non-ionic surfactants of the TRITON-X series-Part III. Immersion time effects and theoretical studies, *Corros. Sci.*, **53**, 1895 (2011).
20. S. Zor, M. Saracoglu, F. Kandemirli and T. Arslan, Inhibition effects of amides on the corrosion of copper in 1.0 M HCl: Theoretical and experimental studies, *Corrosion*, **67**, 12, 125003 (2011).
21. F. Kandemirli, M. Saracoglu, G. Bulut, E. Ebenso, T. Arslan and A. Kayan, Synthesis and theoretical study of zinc(II) and nickel(II) complexes of 5-methoxyisatin 3-[N-(4-chlorophenyl)thiosemicarbazone], *ITB J. Science (J. Math. and Fund. Sci.)*, **44A**, 35 (2012).
22. M. A. Amin, O. A. Hazzazi, F. Kandemirli and M. Saracoglu, Inhibition performance and adsorptive behaviour of three amino acids on cold rolled steel in 1.0 M HCl-chemical, electrochemical and morphological studies, *Corrosion*, **68**, 688 (2012).
23. F. Kandemirli, M. Saracoglu, M. A. Amin, M. A. Basaran and C. D. Vurdu, The Quantum chemical calculations of serine, therionine and glutamine, *Int. J. Electrochem. Sci.*, **9**, 3819 (2014).
24. M. A. Amin, N. El-Bagoury, M. Saracoglu and M. Ramadan, Electrochemical and corrosion behavior of cast re-containing inconel 718 alloys in sulphuric acid solutions and the effect of Cl^-, *Int. J. Electrochem. Sci.*, **9**, 5352 (2014).
25. F. Kandemirli, C. D. Vurdu, M. Saracoglu, Y. Akkaya and M. S. Cavus, Some molecular properties and reaction mechanism of synthesized isatin thiosemicarbazone and its zinc(II) and nickel(II) complexes, *Int. Res. J. Pure and Applied Chem.*, **9**, 1, (2015)
26. N. El-Bagoury, M. A. Amin and M. Saracoglu, Effect of aging treatment on the electrochemical and corrosion behavior of nitire shape memory alloy, *Int. J. Electrochem. Sci*., **10**, 5291, (2015).
27. İ. Ö. İlhan, M. Çadır, M. Saracoglu, F. Kandemirli, Z. Kökbudak and S. Akkoç, The reactions and quantum chemical calculations of some pyrazole-3-carboxylic acid chlorides with various hydrazides, *Chem. Sci. Rev. Lett.*, **4**, 838 (2015).
28. M. A. Amin, S. A. Fadlallah, G. S. Alosaimi, F. Kandemirli, M. Saracoglu, S. Szunerits and R. Boukherroub, Cathodic activation of titanium-supported gold nanoparticles: an efficient and stable electrocatalyst for the hydrogen evolution reaction, *Int. J. Hyd. Energy*, **41**, 6326 (2016).
29. S. Kaya, C. Kaya, L. Guo, F. Kandemirli, B. Tüzün, İ. Uğurlu, L. H. Madkour and M. Saracoglu, Quantum chemical and molecular dynamics simulation studies on inhibition performances of some thiazole and thiadiazole derivatives against corrosion of iron, *J. Mol. Liquids*, **219**, 497 (2016).

30. A. Tazouti, M. Galai, R. Touir, M. Ebn Touhami, A. Zarrouk, Y. Ramli, M. Saracoglu, S. Kaya, F. Kandemirli and C. Kaya, Experimental and theoretical studies for mild steel corrosion inhibition in 1 M HCl by three new quinoxalinone derivatives, *J. Mol. Liquids*, **221**, 815 (2016).
31. M. A. Amin, M. Saracoglu, N. El-Bagoury, T. Sharshar, M. M. Ibrahim, J. Wysocka, S. Krakowiak and J. Ryl, Microstructure and corrosion behaviour of carbon steel and ferritic and austenitic stainless steels in NaCl solutions and the effect of p-Nitrophenyl phosphate disodium salt, *Int. J. Electrochem. Sci.*, **11**, 10029 (2016).
32. M. Saracoglu, F. Kandemirli, A. Ozalp and Z. Kokbudak, Synthesis and quantum chemical calculations of 2,4-dioxopentanoic acid derivatives-Part I, *Chem. Sci. Rev. Lett.*, **6**, 1 (2017).
33. M. Saracoglu, F. Kandemirli, A. Ozalp and Z. Kokbudak, Synthesis and quantum chemical calculations of 2,4-dioxopentanoic acid derivatives-part II, *Int. J. Sci. Eng. Inv.*, **6**, 50 (2017).
34. B. Saima, A. Khan, R. Un Nisa, T. Mahmood, K. Ayub, Theoretical insights into thermal cyclophanediene to dihydropyrene electrocyclic reactions; a comparative study of Woodward Hoffmann allowed and forbidden reactions, *J. Mol. Model*., **22**, 81 (2016).
35. M. Saracoglu, M. I. A. Elusta, S. Kaya, C. Kaya, F. Kandemirli, Quantum chemical studies on the corrosion inhibition of $Fe_{78}B_{13}Si_9$ glassy alloy in Na_2SO_4 solution of some thiosemicarbazone derivatives, *Int. J. Electrochem. Sci*., **13**, 8241 (2018).
36. M. Saracoglu, S. G. Kandemirli, A. Başaran, H. Sayiner, F. Kandemirli, Investigation of structure-activity relationship between chemical structure and CCR5 anti-HIV-1 activity in a class of 1-[*N*-(methyl)-*N*-(phenylsulfonyl)amino]-2-(phenyl)-4-[4-(substituted)piperidin-1-yl] butanes derivatives: The electronic-topological approach, *Curr. HIV Res.*, **9**, 300 (2011).
37. M. N. Arshad, A. M. Asiri, K. A. Alamry, T. Mahmood, M. A. Gilani, K. Ayub, A. S. Birinji Synthesis, crystal structure, spectroscopic and density functional theory (DFT) study of N-[3-anthracen-9-yl-1-(4-bromo-phenyl)-allylidene]-Nbenzenesulfonohydrazine, *Spectrochim. Acta A*, **142**, 364 (2015).
38. R. Un Nisa, M. A. Hashmi, S. Sajjad, T. Mahmood, J. Iqbal, K. Ayub, Quantum mechanical investigation on acceleration of electrocyclic reactions through transition metal catalysis, *J. Org. Chem.*, **808**, 78 (2016).
39. R. G. Parr and R. G. Pearson, Absolute hardness: companion parameter to absolute electronegativity, *J. Am. Chem. Soc.*, **105**, 7512 (1983).
40. P. K. Chattaraj, U. Sarkar and D. R. Roy, Electrophilicity index, *Chem. Rev.*, **106**, 2065 (2006).
41. E. E. Ebenso, M. M. Kabanda, T. Arslan, M. Saracoglu, F. Kandemirli, L. C. Murulana, A. K. Singh, S. K. Shukla, B. Hammouti, K. F. Khaled, M. A. Quraishi, I. B. Obot and N.O. Edd, Quantum chemical investigations on quinoline derivatives as effective corrosion inhibitors for mild steel in acidic medium, *Int. J. Electrochem. Sci*.,**7**, 5643 (2012).
42. H. El-Kashef, A. R. Farghaly, A. Al-Hazmi, T. Terme and P. Vanelle, Pyridine-Based Heterocycles. Synthesis of new pyrido [4',3':4,5]thieno[2,3-d]pyrimidines and related heterocycles, *Molecules*, **15,** 2651 (2010).
43. S. Linz, J. Müller, H. Hübner, P. Gmeiner and R. Troschütz, Design. synthesis and dopamine D4 receptor binding activities of new *n*-heteroaromatic 5/6-ring mannich bases, *Bioorg. Med. Chem*., **17**, 4448 (2009).
44. A. Rauk, New York, Orbital interaction theory of organic chemistry. 2rd ed; Wiley & Sons, (2001).
45. L. Santos, L. A. Lima, V. Cechinel-Filho, R. Correa, F. C. Buzzi and R. J. Nunes, Synthesis of new 1-phenyl-3-(4-[(2E)]-3-phenylprop-2-enoyl]phenyl)-thiourea and urea derivatives with anti-nociceptive activity, *Bioorg. Med. Chem.*,**16**, 8526 (2008).
46. R. G. Pearson, The Principle of Maximum Hardness, *Acc. Chem. Res*. **26**, 250 (1993).
47. R. G. Pearson, Absolute electronegativity and hardness correlated with molecular orbital theory, *Proc. Natl. Acad. Sci. USA*, **83**, 8440 (1986).
48. S. I. Gorelsky, AOMix Program, http://www.sg-chem.net/aomix/.
49. S. I. Gorelsky, A. B. P. Lever, Electronic structure and spectra of ruthenium diimine complexes by density functional theory and INDO/S. Comparison of the two methods, *J. Org. Chem.*, **635**, 187 (2001).