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MOLECULAR GEOMETRY AND BIOLOGICAL ACTIVITY OF 2-(4-SUBSTITUTED-PHENYLIMINO)THIAZOLIDIN-4-ONE COMPOUNDS

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ABSTRACT. A series of 2-(4-substituted-phenylimino)thiazolidin-4-one compounds was synthesized *via* heterocyclizing the corresponding *N*-aryl-2-chloroacetamides with ammonium thiocyanate. Their chemical structures were elucidated based on an extensive analysis of their spectroscopic data, including infrared, ^{1}H NMR, ^{13}C NMR, and mass analyses. The possible tautomeric forms of synthesized thiazolidine-4-ones were studied. The tautomerization equilibrium parameters, ΔH, ΔG, and K_{eq} were calculated using the DFT/B3LYP methodology, where it has been indicated that the tautomeric form, phenylimino, is more favourable than the phenylamino form. The antibacterial and antioxidant properties of the synthesized thiazolidin-4-ones were investigated. 2-(Chlorophenyl-imino)thiazolidin-4-one displayed potent antibacterial activity against *E. coli* (88.46%) and *S. aureus* (91.66%), and highest percent of inhibition (81.8%, ABTS assay).

KEY WORDS: *N*-aryl-2-chloroacetamides, Ammonium thiocyanate, 2-(Arylimino)thiazolidin-4-ones, Mulliken's charges, Dipole moment, ABTS assay

INTRODUCTION

Numerous nitrogen and/or sulfur containing heterocyclic compounds have been identified as promising drug candidates. The thiazolidinone ring has been proven as a privileged scaffold in a wide variety of known biologically active compounds. The thiazolidinone ring has a sulfur atom at position 1, a nitrogen atom at position 3, and a carbonyl group at the 2, 4, or 5 positions. The various derivatives are associated with numerous pharmacological properties, such as bactericidal, pesticidal, fungicidal, insecticidal, antiviral (anti-HIV), antidiabetic, anticonvulsant, tuberculostatic, antiinflammatory, anticancer, antithyroid, and immunostimulant properties [1-5]. It is worth noting that substituents in the 2-, 3-, and 5-positions can be changed, but the group attached to the C2-position exerts the greatest influence on structure and properties [6-9]. As a result, a few thiazolidin-4-one derivatives with C2 and N3 substituted positions, as well as the presence of an electron-withdrawing substitution on the aromatic ring at the C2 position, present good inhibition against Gram-positive and Gram-negative bacteria. On the other hand, a retrospective analysis of these compounds revealed that anticancer activity increases when the cycloalkyl moiety located in position C2 is replaced with a hetero(aryl) moiety [1]. Indeed, 2-imino-4-thiazolidinone compounds have attracted great attention due to their diverse biological activities [10]. They display anticancer [11–13], kinase inhibitors [14, 15], antimicrobial [16], and anti-inflammatory [17] activities (Figure 1). A notable congener of this group are the 2-arylaminothiazol-4-ones, which are effective growth inhibitors of HT29 adenocarcinoma cells [18] and lung cancer cells H460 and H460/TaxR [19, 20]. Furthermore, thiazolidin-4-one compounds are efficient integrin avb3 antagonists [21] and inhibitors of CDK1/cyclin B [22]. Herein we report on the synthesis of five 2-(arylimino)thiazolidin-4-one derivatives where the aryl group is either unsubstituted or substituted with electron-donating (methyl and methoxy) or

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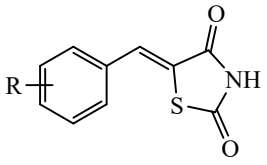
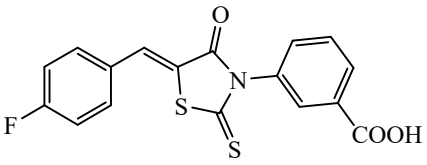
electron-attracting (nitro and chlorine) groups. Moreover, investigating the two possible tautomeric forms (phenylamino and phenylamino forms) in light of their thermodynamic parameters (ΔH and ΔG), and equilibrium constant (K_{eq}). Finally, their antibacterial and antioxidant activities were evaluated.

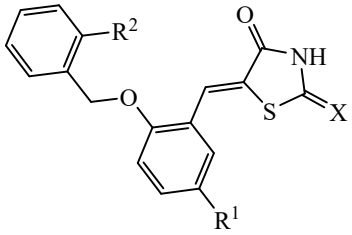


R = 3-CF_3, 4-BuO

Pim-1 protein kinases inhibitors



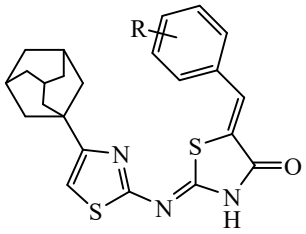
JSP-1 inhibitor



Translation initiation inhibitors

R^1 = Hal, t-Bu, Me, NO_2,; X = S, O; R^2 = H

PRL-3 inhibitor (R^1 = R^2 = Br; X = S)



R = Cl, NO_2, OCH_3, OH

R = 4-OH-3,5-$(OCH_3)_2$

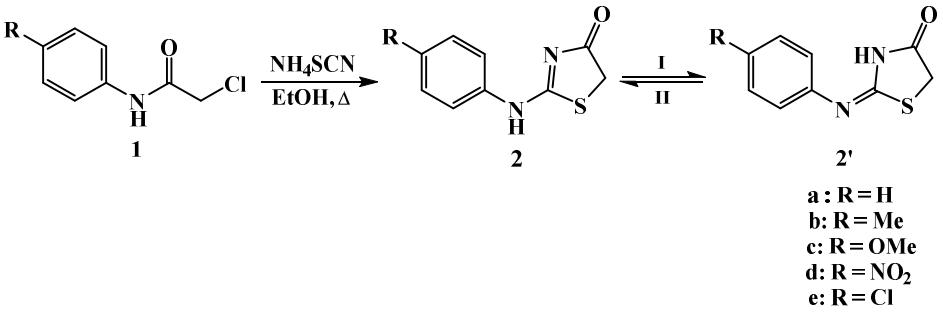
Antifungal and antibacterail agents

Figure 1. Structures of biologically active 4-thiazolidinones.

RESULTS AND DISCUSSION

Synthesis of 2-(arylimino)thiazolidin-4-ones

As a part of our continuous research program on the chemistry of *N*-aryl-2-chloroacetamide compounds [23-25], herein we report on the chemical reactivity of 2-chloroacetamide reagents towards the highly versatile sulfur donner, ammonium thiocyanate. The heterocyclization of *N*-aryl-2-chloroacetamide derivatives **1** upon treatment with ammonium thiocyanate has been achieved by refluxing in ethanol for 4 hours to generate the corresponding 2-(arylimino) thiazolidin-4-ones **2a-e** (Scheme 1). The chemical structures of these thiazolidine-4-ones were elucidated based on their spectral data. The infrared spectra exhibited absorptions bands of the N-H and carbonyl functionalities at 3225-3200 and 1686-1657 cm^{-1}, respectively. The ^{1}H NMR spectra displayed the singlet signal, integrated for two protons, corresponding to the methylene group in the range δ 3.96 to 4.05 ppm. While the proton of imino function (cyclic N-H) was resonated in the range from δ 11.03 to 12.01 ppm. The carbon signal of methylene group was recorded in the ^{13}C NMR spectra ranging from δ 32.68 to 33.37 ppm.



Scheme 1. Synthesis of 2-(arylimino)thiazolidin-4-one compounds **2a-e**.

Energetic and thermodynamic parameters

The synthesized derivatives have two possible tautomeric forms, i.e., phenylamino, **2**, and phenylimino, **2'**, as shown in Scheme 1. To estimate the tautomerization equilibrium and so the predominated form, the reaction thermodynamic parameters (ΔH and ΔG), and equilibrium constant (K_{eq}) for the tautomeric pathways **I** (**2** → **2'**) and **II** (**2'** → **2**) were calculated at P = 1 bar and 298 K and summarized in Table 1. The tautomeric reaction **I** in all derivatives, **2a-e**, exhibited negative enthalpies (ΔH_{298K}) and free energy (ΔG_{298K}) change ranging from -15.34 to -23.80 and -9.78 to -26.53 kcal mol^{-1}, respectively, and thus it is a spontaneous exothermic process. On contrary, the tautomeric reaction **II** displayed positive values for both enthalpies and free energy change which indicate its non-spontaneous endothermic nature. Furthermore, the equilibrium constant (K_{eq}) calculation of both **I** and **II** pathways showed that **I** has high equilibrium constant with positive power, range 5.19×10^{1}-4.45×10^{4}, while II has low values with negative power, range 2.25×10^{-5}-1.93×10^{-2}, and thus it discloses that the tautomer **2'**, phenylimino, is favourable more than the phenylamino form, **2** [26]. In addition, the data showed that the nitro derivative has the dramatically lower equilibrium constant than other derivatives where the chloro displayed the higher value, according to the following order **2d** < **2b** < **2c** < **2a** < **2e**, which may be attributed to that the electron withdrawing effect of the nitro group hindered the transformation toward the phenylimino tautomer whereas the other electron donating groups facilitate tautomerization.

Table 1. Reaction thermodynamic parameters (ΔH and ΔG in kcal mol^{-1}) and equilibrium constant (K_{eq}) for the tautomeric pathways **I** and **II**.

Derivative	Pathway	ΔH_{298K}	ΔG_{298K}	$K_{eq(298K)}$
2a	I	-20.34	-21.35	5.52×10^{3}
	II	20.34	21.35	1.81×10^{-4}
2b	I	-19.31	-19.78	2.93×10^{3}
	II	19.31	19.78	3.41×10^{-4}
2c	I	-20.25	-19.94	3.13×10^{3}
	II	20.25	19.94	3.19×10^{-4}
2d	I	-15.74	-9.78	5.19×10^{1}
	II	15.74	9.78	1.93×10^{-2}
2e	I	-23.8	-26.52	4.45×10^{4}
	II	23.8	26.52	2.25×10^{-5}

Molecular geometry

Figure 2 displayed the DFT optimized structures of the phenylimino tautomers of the compounds **2a-e**. The dihedral angle revealed that the imino nitrogen atom were almost coplanar with the thiazole ring where the N_{am}-Th^2-N_{Th}-Th^4 and N_{am}-Th^2-S-Th^5 ≈ 177.5°. The investigated derivatives were non-planar where the phenyl ring tilted on the thiazole ring, i.e., Ph^2-Ph^1-N_{am}-Th^2 ≈ 56.0-61.3°. The different substituents on the phenyl ring were coplanar with it in compounds **2b-e**. The bond length and angles, comparing to those of analogous compounds X-ray single crystal [27], exhibited significant matching with 0.00-0.09 Å and 0.0-7.7° divergences, RMSD 3.64-3.96×10^{-2} Å and 2.2-2.8°, respectively, which may be arisen from that in the practical, there are interaction between molecules forming the solid crystal lattice, while in theoretical calculations, no intermolecular columbic interactions present as sole molecule in gaseous status was considered [28].

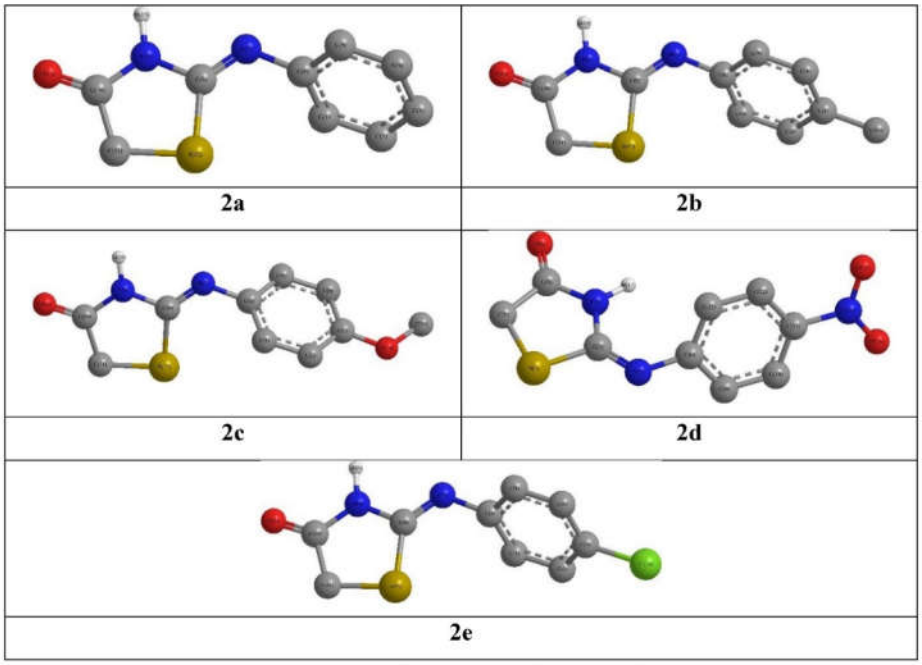


Figure 2. Optimized structures of compounds **2a-e**.

Frontier molecular orbitals (FMO's)

The energies of the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) were computed (Table 2). The HOMO-LUMO gap, $\Delta E = E_H – E_L$, illustrates the molecule's chemical stability and charge transfer [29-30]. The frontier orbitals plot of the investigated compounds (Figure 3) showed that: (i) The HOMO for compounds **2a-e** was consisted mainly from the π-orbital of the 4-substituted phenylimino moiety and heteroatoms lone pair of electrons of the thiazole ring. The LUMO was constructed mainly from the π*-orbital of the whole molecule without contribution of the substituents except in **2d** where the nitro group was strongly involved in formation. (ii) The E_{HOMO} data clears the effect of substitution participation where the derivative **2c** has the lowest value, -5.88 eV, while the highest one is **2d**,

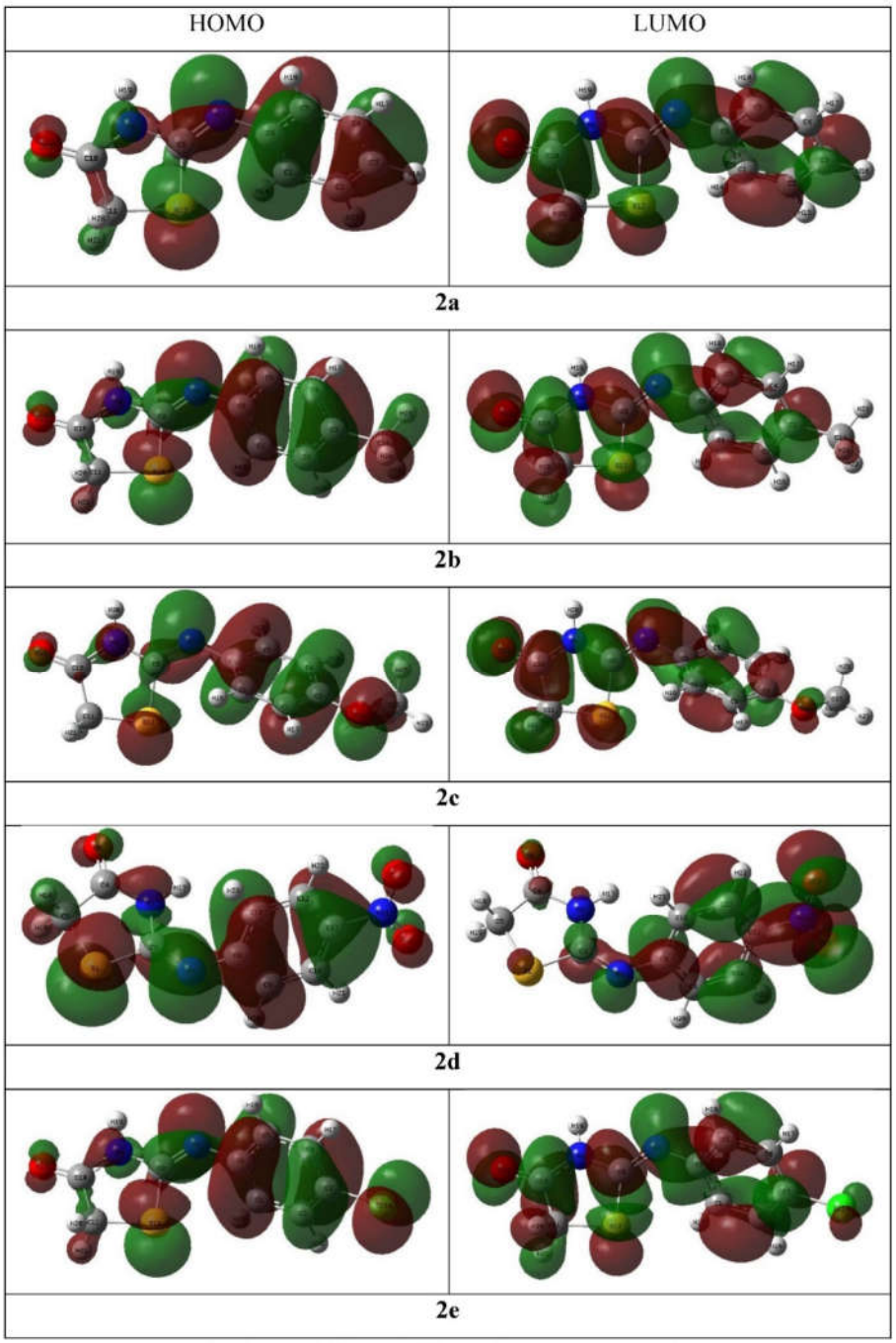


Figure 3. The HOMO and LUMO parts of the investigated compounds.

-7.17 eV. Likewise, the E_{LUMO} data of all derivatives exhibited close values, -1.15 to -2.91, following the same order of the E_{HOMO}, i.e., **2c** < **2b** < **2a** < **2e** < **2d**. (iii) The **2a-e** derivatives exhibited ΔE values ranges from 4.26 eV, for **2d** derivative, to 5.17 eV, for **2a** derivative, where the lowering of HOMO-LUMO energy gap implies within molecule feasible charge transfer, that may be relevant for the molecules' bioactivity [31]. Hence, the studied derivatives may be sorted owing to their ΔE values as **2d** < **2c** < **2b** < **2e** < **2a**.

Table 2. Studied thiazolidine-4-one compounds HOMO-LUMO energies and chemical reactivity descriptors (eV).

Compound	E_H	E_L	ΔE_{H-L}	χ	η	δ	ω
2a	-6.42	-1.26	5.17	3.84	2.58	0.39	2.85
2e	-6.47	-1.35	5.12	3.91	2.56	0.39	2.99
2b	-6.21	-1.20	5.01	3.70	2.51	0.40	2.74
2c	-5.88	-1.15	4.73	3.51	2.36	0.42	2.61
2d	-7.17	-2.91	4.26	5.04	2.13	0.47	5.96

Chemical reactivity descriptors and dipole moment

The chemical reactivity descriptors, such as the electronegativity (χ), that quantify the molecule's attraction ability of electrons, was estimated (Eq. 1) where Lewis's acid stand for high χ values while bases were for lesser values. Global hardness (η), determine the charge transfer resistance, whereas the global softness (δ) defines the capacity of receiving electrons (Eq. 2 and Eq. 3). The electrophilicity (ω) is the lowering in energy owing to the utmost flow of electrons between molecular orbitals (Eq. 4) [29]:

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

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

$$\delta = \frac{1}{\eta} \quad (3)$$

$$\omega = \frac{\chi^2}{2\eta} \quad (4)$$

Hence, compound **2d** has the maximum electronegativity and compound **2c** has the minimum, 5.04 and 3.51 eV, respectively, and so all compounds have Lewis's acids character (Table 2). Soft molecules, low ΔE, have higher reactivity than hard ones since they can easily donate electrons. Therefore, the data demonstrated that derivatives **2a** and **2d** were the hardest and softest, respectively. Also, compounds **2c** and **2d** exhibited the lowest and highest electrophilicity index.

Mulliken atomic charges

The electrophilic or nucleophilic reaction reactivity may affect mostly by the Mulliken atomic charge. The atomic charges of the sulfur and carbon atoms of thiazole ring at the position 1 and 4 in all **2a-e** derivatives, have positive charges, 0.027-0.116 and 0.237-0.259, respectively, while those at 2-, 3- and 5-positions were negatively charged. Furthermore, the azomethine nitrogen's have the positive charges in all derivatives while all oxygen atom of carbonyl groups on thiazole have negative charges following the order **2d** < **2e** > **2a** = **2b** ≈ **2c** (Table 3).

Table 3. The atomic Mulliken's charges of the studied thiazolidine-4-one compounds.

Atom	**2a**	**2b**	**2c**	**2d**	**2e**
S	0.113	0.102	0.084	0.027	0.116
Th^2	-0.205	-0.185	-0.187	-0.187	-0.204
N_{th}	-0.032	-0.030	-0.033	-0.081	-0.031
Th^4	0.251	0.248	0.259	0.237	0.252
Th^5	-0.488	-0.484	-0.490	-0.700	-0.492
O_{th}	-0.314	-0.314	-0.315	-0.291	-0.309
N_{am}	0.016	0.026	0.009	0.267	0.034
Ph^1	-0.584	-0.735	-0.675	-0.822	-0.992
Ph^2	0.108	0.067	0.226	0.095	-0.080
$Ph^{2'}$	0.225	0.212	0.133	0.287	0.231
Ph^3	-0.117	-0.427	-0.213	0.071	-0.310
$Ph^{3'}$	-0.193	-0.125	0.379	-0.479	-0.551
Ph^4	-0.419	0.314	-0.734	-0.005	0.389
Me		-0.601	-0.309		
OMe			-0.156		
NO_2				-0.180	
ONO_2				-0.010	
ONO_2				-0.016	
Cl					0.393

Antibacterial and antioxidant activity

The antibacterial properties of the synthesized 2-(arylimino)thiazolidin-4-one compounds **2a-e** were explored against Gram-negative bacteria (*Escherichia coli)* and Gram-positive bacteria (*Staphylococcus aureus*) according to the previously published methodology [27]. The % activity index for the explored thiazolidine-4-one compounds was calculated by the formula:

$$\%\,\text{Activity Index} = \frac{\text{Zone of inhibition by test compound (diameter)}}{\text{Zone of inhibition by standard (diameter)}} \times 100$$

A survey of the results (Table 4) shows that the synthesized 2-(arylimino)thiazolidin-4-one compounds inhibit the growth of *E. coli* with activity indices ranging from 53.84% to 88.46%. The presence of substituent on the phenyl group promoted the inhibition activity from 53.84% (no substituent on the phenyl group) to maximum activity when chlorine is substituted on the phenyl group (88.46%). Compound **2e**, 2-(chlorophenyl-imino)thiazolidin-4-one, achieved very close activity to that displayed by the reference drug, Ampicillin, which inhibits the growth of the *E. coli* bacterium with an inhibition zone of 26 mm. By exploring the activity of the tested 2-(4-substituted-phenylimino)thiazolidin-4-one compounds **2b**, **2c**, **2d**, and **2e** against the *S. aureus* bacterium, they displayed excellent antibacterial properties with diameter zones (19, 21, and 22 mm) and activity indices ranging from 79.16 to 91.66%. Fortunately, the best antibacterial activity was displayed by the targeting compound 2-(chlorophenyl-imino)thiazolidin-4-one (**2e**) with an inhibition zone of 22 mm and an activity index of 91.66% when compared with Ampicillin, which inhibits the growth of the *S. aureus* bacterium with an inhibition zone of 24 mm.

The constructed 2-(arylimino)thiazolidin-4-one compounds **2a-e** were estimated for their antioxidant activities (Table 5) by using the ABTS Radical Cation Decolorization Assay [28]. The tested 2-(arylimino)thiazolidin-4-ones **2a-e** showed antioxidant activity ranging from inhibition percent 68.8% to 81.8%. The results indicated that the presence of chlorine atom on the phenyl group promoted the antioxidant activity to the highest percent of inhibition = 81.8%, that is close to that observed by the reference antioxidant L-Ascorbic acid (88.2%). The next important

antioxidant agent is 2-(4-methoxyphenyl-imino)thiazolidin-4-one **(2c)**, which showed percent of inhibition = 80.2%.

Table 4. Antibacterial activity (inhibition zone, mm) of the tested 2-(arylimino)thiazolidin-4-ones **2a-e**.

Compound No.	*E. coli*		*S. aureus*	
	Diameter (mm) inhibition zone	Activity index (%)	Diameter (mm) inhibition zone	Activity index (%)
2a	14	53.84	16	66.66
2b	17	65.38	21	87.50
2c	21	80.76	21	87.50
2d	16	61.53	19	79.16
2e	23	88.46	22	91.66
Ampicillin	26	---	24	---

Table 5. Antioxidant activity of the tested 2-(arylimino)thiazolidin-4-ones **2a-e**.

Method	ABTS [Abs(control)-Abs(test)/Abs(control)] × 100	
Compounds	Absorbance of samples	% inhibition
Control of ABTS	0.500	0
Ascorbic-acid	0.059	88.2%
2a	0.156	68.8%
2b	0.123	75.4%
2c	0.099	80.2%
2d	0.137	72.6%
2e	0.091	81.8%

EXPERIMENTAL

Melting points (uncorrected) are measured on Gallenkamp apparatus. The IR spectra were recorded (KBr) on Thermo Scientific Nicolet iS10 FTIR spectrometer. NMR spectra (DMSO-d_6) were measured at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) on JEOL's NMR spectrometer. Quadrupole GC/MS Thermo Scientific Focus/DSQII has been utilized to perform the mass analyses. Perkin-Elmer 2400 analyzer has been utilized to measure the elemental analyses (C, H, and N).

*Synthesis of 2-(arylimino)thiazolidin-4-ones **2a-e***. To a solution of *N*-aryl chloroacetamide derivatives **(1)** (0.002 mol) in ethanol (40 mL), ammonium thiocyanate (0.003 mol, 0.22 g) was added and then the mixture was refluxed for 4 hours. The mixture was cooled to 20°C and the solid that obtained in each case was separated by filtration and dried. The solid was crystallized from ethanol to yield the thiazolidine-4-one products **2a-e**.

*2-(Phenylimino)thiazolidin-4-one (**2a**)*. Brown solid, yield = 68% (0.26 g), m.p. = 154-155 °C; lit. m.p. = 150-152 °C [34]. IR (KBr): 3202 (N-H), 1657 (C=O), 1610 cm^{-1} (C=N). ^{1}H NMR: δ 3.96 (s, 2H), 7.11 (t, *J* = 7.50 Hz, 1H), 7.30-7.34 (m, 2H), 7.58 (d, *J* = 7.50 Hz, 2H), 11.16 ppm (s, 1H, NH-cyclic). ^{13}C NMR: δ 32.87, 122.09 (2C), 126.23, 129.78 (2C), 149.35, 160.20, 173.96 (C=O) ppm. Mass analysis: 192 (M^+, 31.43%). Analysis of $C_9H_8N_2OS$ (192.24): calculated: C, 56.23; H, 4.19; N, 14.57%. Found: C, 56.08; H, 4.26; N, 14.64%.

*2-((4-Methylphenyl)imino)thiazolidin-4-one (**2b**)*. Buff crystals, yield = 74% (0.30 g), m.p. = 185-186°C; lit. m.p. = 180-183°C [34]. IR (KBr): 3203 (N-H), 1675 (C=O), 1635 cm^{-1} (C=N). ^{1}H

NMR: δ 2.26 (s, 3H), 3.97 (s, 2H), 7.17 (d, *J* = 8.00 Hz, 2H), 7.58 (d, *J* = 8.00 Hz, 2H), 11.17 ppm (s, 1H, NH-cyclic). ^{13}C NMR: δ 21.17, 32.81, 120.90 (2C), 130.49 (2C), 134.36, 147.53, 160.19, 173.85 (C=O) ppm. Mass analysis: 206 (M^+, 47.16%). Analysis of $C_{10}H_{10}N_2OS$ (206.26): calculated: C, 58.23; H, 4.89; N, 13.58%. Found: C, 58.12; H, 4.93; N, 13.50%.

2-((Methoxyphenyl)imino)thiazolidin-4-one (***2c***). Yellow needles, yield = 78% (0.34 g), m.p. = 186-187°C; lit. m.p. = 188–191°C [34]. IR (KBr): 3208 (N-H), 1672 (C=O), 1640 cm^{-1} (C=N). ^{1}H NMR: δ 3.73 (s, 3H), 3.97 (s, 2H), 6.99 (d, *J* = 9.00 Hz, 1H), 7.58 (d, *J* = 9.00 Hz, 2H), 11.03 ppm (s, 1H, NH-cyclic). ^{13}C NMR: δ 32.68, 55.87, 114.74 (2C), 122.11 (2C), 158.06, 141.93, 160.34, 173.73 (C=O) ppm. Mass analysis: 222 (M^+, 42.85%). Analysis of $C_{10}H_{10}N_2O_2S$ (222.26): calculated: C, 54.04; H, 4.54; N, 12.60%. Found: C, 54.15; H, 4.60; N, 12.66%.

2-((4-Nitrophenyl)imino)thiazolidin-4-one (***2d***). Buff powder, yield = 82% (0.39 g), m.p. = 245-247°C. IR (KBr): 3225 (N-H), 1686 (C=O), 1633 cm^{-1} (C=N). ^{1}H NMR: δ 4.05 (s, 2H), 7.60 (d, *J* = 9.00 Hz, 2H), 8.32 (d, *J* = 9.00 Hz, 2H), 12.01 ppm (s, 1H, NH-cyclic). ^{13}C NMR: δ 33.37, 123.26 (2C), 125.15 (2C), 145.09, 155.41, 160.58, 174.48 (C=O) ppm. Mass analysis: 237 (M^+, 54.07%). Analysis of $C_9H_7N_3O_3S$ (237.23): calculated: C, 45.57; H, 2.97; N, 17.71%. Found: C, 45.48; H, 2.99; N, 17.82%.

2-((4-Chlorophenyl)imino)thiazolidin-4-one (***2e***). Gray powder, yield = 66% (0.30 g), m.p. = 210-212°C. IR (KBr): 3200 (N-H), 1675 (C=O), 1638 cm^{-1} (C=N). ^{1}H NMR: δ 3.98 (s, 2H), 6.96 (d, *J* = 7.00 Hz, 2H), 7.77 (d, *J* = 8.00 Hz, 2H), 11.66 ppm (s, 1H, NH-cyclic). ^{13}C NMR: δ 32.94, 122.01 (2C), 129.84 (2C), 131.16, 148.52, 160.22, 173.90 (C=O) ppm. Mass analysis: 228 (M^+ +2, 21.59%), 226 (M^+, 67.28%). Analysis of $C_9H_7ClN_2OS$ (226.68): calculated: C, 47.69; H, 3.11; N, 12.36%. Found: C, 47.78; H, 3.04; N, 12.29%.

Computational studies

The Gaussian 09W software [35] was employed for geometrical optimization and frequency calculations using DFT/B3LYP/6-311^{++}G(d,p) methodology [36-38]. All compounds calculated positive frequencies confirmed the stability of the optimized geometries. Thermodynamic parameters of the tautomeric reactions were performed using the kinetic and statistical thermodynamic package (KiSThelP) under atmospheric pressure and at *T* = 298 K [39]. In DMSO, the ^{1}H NMR chemical shifts were computed by the gauge-invariant atomic orbital (GIAO) method [40]. The Gauss View program was used in assignment of NMR spectral data [41]. The Materials Studio package DMol3 module has been utilized in estimating the Fukui indices [42] using gradient-corrected (GGA) and B3LYP functional with a double numeric plus polarization (DNP 3.5) basis set [43].

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