

## Preparation and Structure Studies of Thiazolidine and Bisthiazolidine Derivatives

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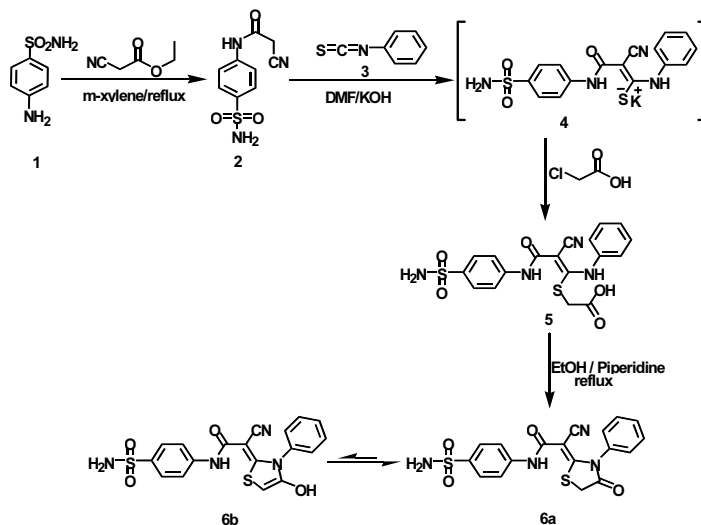
*Abstract.* In this work we propose the synthesis of thiazolidine and bisthiazolidine derivatives, and the structure of these compounds were studied using elemental analysis, IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectroscopy. Tautomeric properties and conformations were investigated by semi-empirical AM1, MNDO and PM3, and *ab initio* calculations to illustrate the conformational analysis. All calculations lead to the same result that the keto-form is energetically favored.

### Introduction

Bisheterocyclic compounds exhibit various biological activities<sup>[1,2]</sup>. Also, heterocycles containing the thiazole moiety are present in many natural products and confirmed as a novel class of potent and selective antitumor agents. In addition, Indisulam (E7070), N-(3-chloro-1*H*-7-indolyl)-1,4-benzenedisulfonamide is a novel antitumor sulfonamide<sup>[3]</sup>. Thus, a series of bisthiazole derivatives possess free SO<sub>2</sub>NH<sub>2</sub> groups were synthesized on the hope of obtaining bisheterocycles with anticipated biological activity and can be used as pharmaceutical. The important tools for the study of biological activity are the use of optimized structures and conformational features and other theoretical calculation to provides description of how molecular interact and form their 3D shapes which in turn determines molecular function<sup>[4]</sup>. Moreover, this approach can show the connecting link between experimentally determined structures and biological function<sup>[5]</sup>.

## Results and Discussion

In the present contribution, we investigated the reaction of cyanoacetanilide derivative (**2**) with isothiocyanates in the presence of potassium hydroxide followed by heterocyclization in situ of the resulting adducts with various  $\alpha$ -halogenated compounds. The required starting material cyanoaceto-4-sulfamoylanilide (**2**) was synthesized in a good yield (92%) through the reaction of sulfanilamide (**1**) with ethyl cyanoacetate in refluxing *m*-xylene (Scheme 1). The non-isolable potassium sulfide salt (**4**) was achieved by the nucleophilic addition of active methylene group in compound (**2**) to phenylisothiocyanate (**3**) in dry dimethylformamide at room temperature in the presence of potassium hydroxide (Scheme 1). The potassium salt (**4**) was exploited to synthesize some new thiazolidine derivatives. Treatment of intermediate (**4**) with chloroacetic acid at room temperature gave (**5**) in high yield. On the other hand, refluxing of (**5**) in ethanolic solution containing a few drops of piperidine as basic catalyst afforded the novel thiazolidinone (**6**), through elimination of ethanol with partial hydrolysis of cyano group (Scheme 1).



Scheme 1

The thiazolidinone (**6**) exists in two tautomeric Keto-enol forms. Molecular calculations of possible tautomeric forms in vacuum using semi-empirical AM1, PM3 and MNDO methods using HyperChem 7.5 software have been investigated. The initial geometries of the molecules were built means of standard parameters and then optimized by Polak-Ribiere

geometrical optimization. The heat of formation and relative stabilities of the two tautomeric forms are (**6a**) and (**6b**) are listed in Table 1.

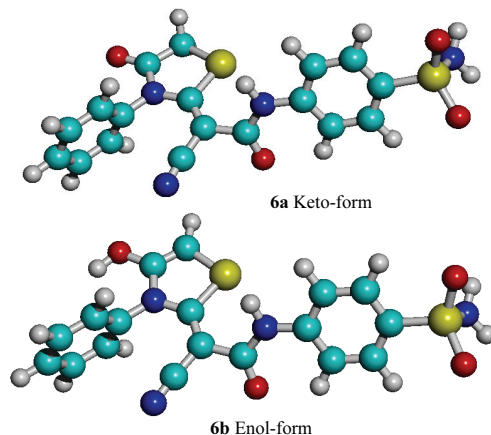
**Table 1.** The comparison of the formation enthalpies ( $\Delta H_f^\circ$ ) and relative stabilities ( $\Delta\Delta H_f^\circ$ , Kcal.mol<sup>-1</sup>) of enol-keto tautomeric forms.

Method	$\Delta H_f^\circ$		$\Delta\Delta H_f^\circ$
	<b>6a(Ketone)</b>	<b>6b(enol)</b>	
MNDO	108.58	118.17	- 9.59
AM1	53.42	66.16	-12.74
PM3	-3.20	7.38	-10.58

$$\Delta\Delta H_f^\circ = \Delta H_f^\circ(\text{enol}) - \Delta H_f^\circ(\text{Keto})$$

All semiempirical calculations lead to the same result that the enol form has more heat of formation than the keto form. The negative signs of the  $\Delta\Delta H_f^\circ$  indicate that the keto form is more stable by all computational methods. Similar results we have previously reported for some molecules which exhibit enol-keto tautomerism<sup>[6]</sup>.

The geometry optimization of keto-enol tautomerization was made by AM1 of two forms are represented in Fig. 1.



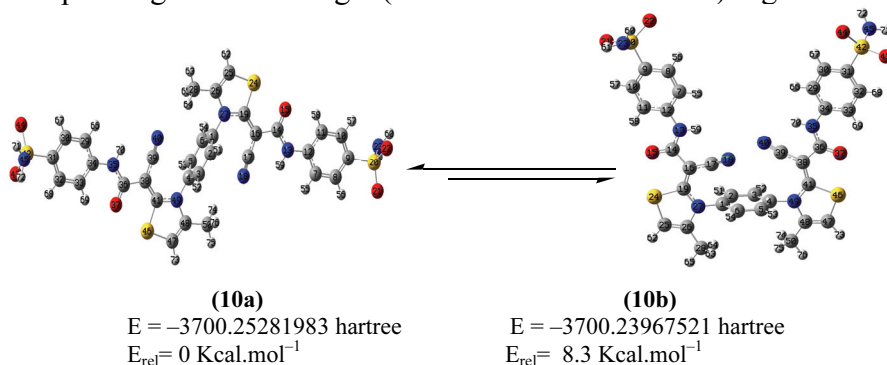
**Fig. 1.** AM1 optimized geometries of keto-form (**6a**) and enol-form (**6b**).

Bisthiazolidine (**9**) and (**10**) were prepared via a four-steps process, starting from cyanoaceto-4-sulfamoylanilide (**2**) was synthesized in good yield (92%) through the reaction of sulfanilamide (**1**) with ethyl cyanoacetate in refluxing *m*-xylene. The reaction of 1,4-phenylenediisothiocyanate (**7**) with cyanoacetanilide in the presence of potassium hydroxide at room temperature gave the non-isolated potassium salt (**8**). The latter was converted into bisthiazolidinone derivative (**9**) upon treatment with ethyl chloroacetate at

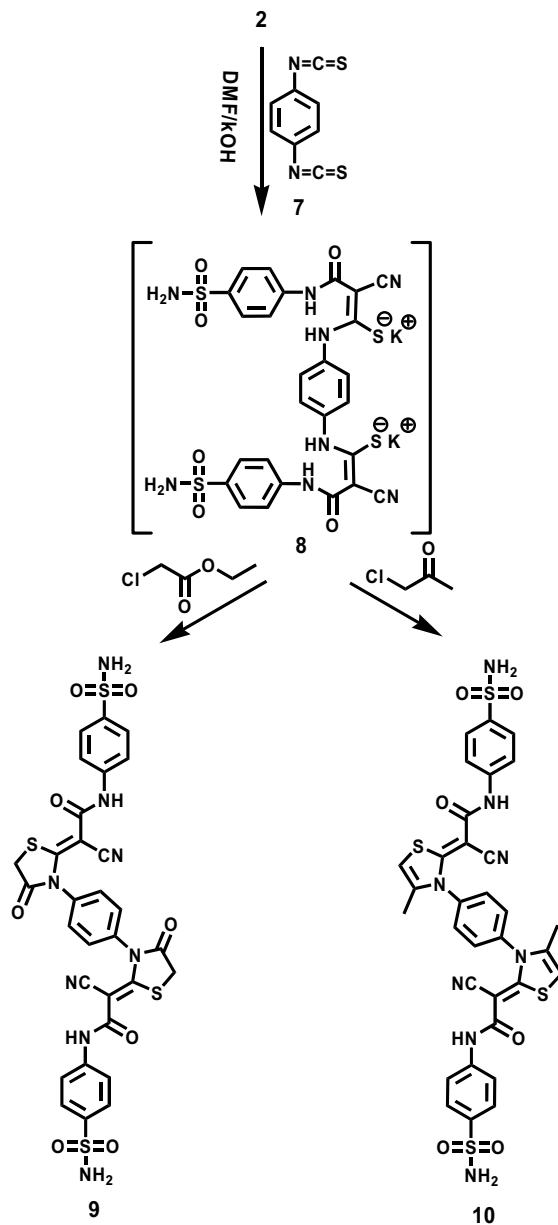
room temperature, through initial alkylation and elimination of water. Also, cyclization of the potassium salt (**8**) with chloroacetone afforded the corresponding bisthiazolidinone derivative (**10**) via initial alkylation and elimination of ethanol (Scheme 1). The mass spectrum of compound (**9**) exhibited a molecular ion peak at  $m/z = 750.1$  (11.2%) corresponding to the molecular formula  $C_{30}H_{22}N_8O_8S_4$  with base peak at  $m/z = 63$ . and mass spectrum of compound (**10**) exhibited a molecular ion peak at  $m/z = 746.1$  (31.0%) corresponding to the molecular formula  $C_{32}H_{26}N_8O_6S_4$ .

The conformational study aimed to establish the relationship between structure properties and biological activity of bisthiazolidine derivative (**9**) and (**10**). The synthesis and determination of the biological activity of these compounds were reported by our group<sup>[7]</sup>. We undertook a semiempirical (AM1) and *ab initio* calculations to illustrate the conformational analysis.

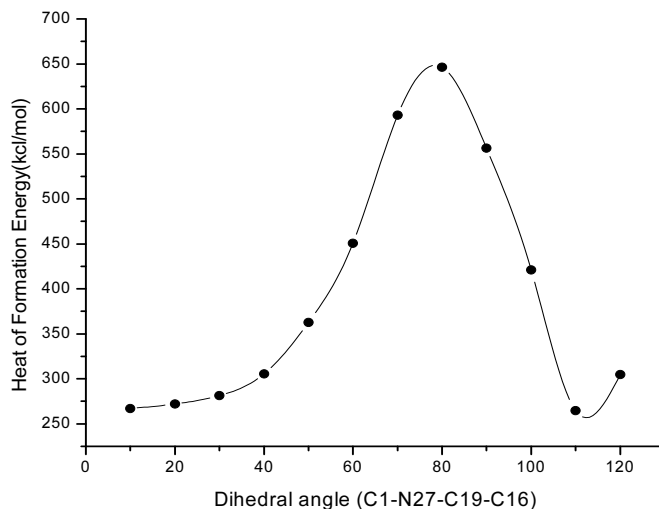
For the conformational profile of, *e.g.* (**10a**) obtained at the semiempirical (AM1) level, the torsion angle corresponding to rotation around the (C1-N27-C19-C16) Fig. 3. The calculations were performed at the semiempirical level (AM1) first and the minima points of the resulting energetic profile were further optimized at the level of *ab initio* (HF/6-31G). The changes in the total energy with the dihedral angle was mentioned of (**10a**) rotamers were calculated by a stepwise variation of the dihedral angle. All the calculation using the GAUSSIAN 98W package<sup>[8]</sup>. As shown the (**10a**) rotamer is the most stable conformer in this profile (C1-N27-C19-C16) = 10°) and other stable conformer (**10b**) corresponding to torsion angle (C1-N27-C19-C16 = 110°) Fig. 3.



**Fig. 2.** Optimized geometries structure of bisthiazolidine derivative (**10a**, **10b**) rotamers obtained at the *ab initio* (HF/6-31G) levels collated energies ( $E$ /hartree) and the relative energy difference at different conformations.



Scheme 2



**Fig. 3.** Conformation profile of (10a) obtained at the semiempirical (AM1) level.

In Fig. 3, the relative energy difference ( $E/\text{Kcal.mol}^{-1}$ ) for (9a) and (10b) rotamers obtained at *ab initio* (HF/6-31G) level. In this figure benzene ring and thiazolidine planes, linked by the C-N bond, are approximately orthogonal, Table 2.

**Table 2.** Dihedral angles of rotamers (9a) and (10b), (Fig. 2).

Dihedral Angles	9a	10b
C6-C1-N27-C19	-89.08	101.0
C2-C1-N27-C19	92.8	-82.2
C1-N27-C19-C16	5.5	-19.2
C1-N27-C26-C28	-5.9	15.9
C1-N27-C26-C25	175.1	-164.4
C1-N27-C19-S24	-174.7	162.3
C19-C16-C17-N18	171.5	-143.7
C19-C16-C14-O15	0.30	1.0
C19-C16-C14-N13	-179.6	-178.7
C3-C4-N49-C41	86.0	101.0
C5-C4-N49-C48	87.96	84.49
C3-C4-N49-C48	-90.8	-92.4
C4-N49-C41-C38	-5.5	-19.2
C4-N49-C48-C50	5.9	15.9
C4-N49-C48-C47	-175.1	-164.4
C4-N49-C41-S46	174.7	162.3
C41-C38-39-N40	-177.7	-143.7
C41-C38-C36-O37	-0.44	1.0
C41-C38-C36-N35	179.6	-178.7

## Experimental

All the computations were on a Intel centrino™ Mobile Technology, personal computer (CPU at 2.1 GH) with windows XP operating system.

<sup>1</sup>H NMR spectra were recorded with Bruker ARX 250 spectrometers. <sup>13</sup>C NMR spectra were recorded at room temperature at 75 MHz. NMR spectra were recorded at room temperature in deuterated dimethylsulphoxide (DMSO). IR spectra of crystalline compounds were recorded at room temperature in dichloromethane and of liquids as thin films using a Perkin-Elmer 298 spectrometer. Standard mass spectra were recorded on a Kratos Concept 1H Magnetic sector Mass Spectrometer with fast atomic bombardment (FAB). Elemental analysis was carried out by CHN analysis. Melting point were determined on a Kofler hot stage and are uncorrected.

### *Preparation of Cyanoaceto-4-Sulfamoylanilide (2)*

A mixture of sulfa-nilamide (**1**) ( 0.01 mole) and ethyl cyanoacetate (0.01 mole) in *m*-xylene (30 ml) was refluxed for 4 h, the solid product which produced on heating was collected and crystallized from dioxane as colorless crystals, m.p. 230°C ( lit. m.p. 228°C)<sup>[9]</sup>.

### *3-Carboxymethylthio-3-Phenylamino-2-(4-Sulfamoylcarbanilide) Acrylonitrile (5)*

To a suspension of finely powdered potassium hydroxide (0.01 mole) in dry dimethylformamide (10 ml) at 0°C the anilide (**2** g, 0.01 mol) and then the isothiocyanate (0.01 mol) were added in portions. The reaction mixture was stirred at room temperature for 3 h and then treated with  $\alpha$ -halogenated compound (0.01 mole) and left at room temperature for 24 h, then it was poured into ice/water and acidified with 0.1 N HCl at pH 3-4. The resulting precipitate was filtered off, dried and the product was crystallized from benzene to give (**5**) (75%) as colourless crystals, m.p. 150-152°C. (Found: MH<sup>+</sup>, 432.0642. C<sub>12</sub>H<sub>14</sub>NO<sub>5</sub> requires MH, 432.0642); IR/  $\nu_{\max}$  (cm<sup>-1</sup>) 3432 (OH), 2190 (C≡N), 1720 (C=O); <sup>1</sup>H NMR,  $\delta_{\text{H}}$  (DMSO-*d*<sub>6</sub>) 3.97 (2H, s, CH<sub>2</sub>S), 6.51-7.92 (11H, m, Ar-H+NH<sub>2</sub>), 8.57, 9.1 and 10.2 (3H, 3s, 2NH and OH; D<sub>2</sub>O exchangeable).

***4-Hydroxy-2-[Cyano-(4-Sulfamoylphenyl)Carbamoyl]Methylene-3-Phenyl-2,3-di-Hydro-1,3-Thiazole (6)***

A solution of the 3-Carboxymethylthio-3-phenylamino-2-(4-sulfamoyl-carbanilide)acrylonitrile (**5**) (0.01 mole) was prepared as described above, in ethanol (30 ml) containing piperidine (0.01 mole) was heated under reflux for 2 h, the solid product which produced on heating was collected and recrystallized from ethanol gave (**6**) as colourless crystals (2g, 83%), mp 230-231°C (from ethanol). C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> requires C, 52.1; H, 3.3; N, 13.6, Found: C, 52.2; H, 3.4; N %; IR,  $\nu_{\max}/\text{cm}^{-1}$  3384, 3278 (NH<sub>2</sub>), 2190 (C≡N), 1718 (C=O; thiazolidinone), 1660 (C=O; amide); <sup>1</sup>H NMR,  $\delta_{\text{H}}$  3.95 (s, 2H, CH<sub>2</sub>S), 7.21 (s, 2H, SO<sub>2</sub>NH<sub>2</sub>; D<sub>2</sub>O exchangeable), 7.67-7.79 (9H, m, Ar-H), 10.49 (1H, s, NH; D<sub>2</sub>O exchangeable), 12.30 (1H, s, OH; D<sub>2</sub>O exchangeable).

***1,4-Bis[2-(Cyano-(4-Sulfamoylphenyl)Carbamoyl]Methylene-5-oxo-2,3-Dihydro-1,3-Thiazole]Benzene (9)***

To a suspension of finely powdered potassium hydroxide (0.01 mole) in dry dimethylformamide (10 ml) at 0°C the anilide (**2**, 0.01 mole), isothiocyanate (0.01 mol) were added in portions. The reaction mixture was stirred at room temperature for 3 h and then treated with ethyl chloroacetate (0.01 mol) and left at room temperature for 24 h, then it was poured into water and acidified with 0.1 N HCl at pH 3-4. The resulting precipitate was filtered off, dried and recrystallized from ethanol. C<sub>30</sub>H<sub>22</sub>N<sub>8</sub>O<sub>8</sub>S<sub>4</sub> requires C, 47.99; H, 2.95; N, 14.92, Found: C, 48.00; H, 2.94 ; N, 14.92%; IR,  $\nu_{\max}/\text{cm}^{-1}$  3330, 3256 (NH<sub>2</sub>), 2192 (C≡N), 1734 (C=O), 1684 (C=O; amide); <sup>1</sup>H NMR,  $\delta_{\text{H}}$  3.95 and 4.2 (4H, 2s, CH<sub>2</sub>S), 7.41-7.92 (16H, m, Ar-H + 4NH<sub>2</sub>), 9.70 and 10.2 (2H, 2s, 2NH; exchangeable); <sup>13</sup>C NMR,  $\delta_{\text{C}}$  32.4 (2 × CH<sub>2</sub>), 69.8 (2 × CCN), 121.4, 121.9, 127.1, 127.5, 131.0 and 135.3 [18 × CH(Ar)], 164, 168 (4 × CO) and 179.2 (2 × C=CCO).

***1,4-Bis[2-(Cyano-(4-Sulfamoylphenyl)Carbamoyl]Methylene-4-Methyl-2,3-Dihydro-1,3-Thiazole]Benzene (10)***

Similarly, (**9**) , compound (**10**) was prepared as described above using finely powdered potassium hydroxide (0.01 mole) in dry



dimethylformamide (10 ml) at 0°C the anilide (**2**, 0.01 mole) and then the isothiocyanate (0.01 mole) were added in portions. The reaction mixture was stirred at room temperature for 3 h and then treated with chloroacetone (0.01 mol) and left at room temperature for 24 h, then it was poured into water and acidified with 0.1 N HCl at pH 3-4. The resulting precipitate was filtered off, dried and recrystallized from ethanol. C<sub>32</sub>H<sub>26</sub>N<sub>8</sub>O<sub>6</sub>S<sub>4</sub> requires C, 51.46; H, 3.51; N, 15.00, Found: C, 51.40; H, 3.42; N, 15.10%; IR,  $\nu_{\max}/\text{cm}^{-1}$  3346, 3108 (NH<sub>2</sub>), 2182 (C≡N), 1640 (C=O; amide); <sup>1</sup>H NMR,  $\delta_{\text{H}}$  1.98 (6H, s 2CH<sub>3</sub>), 7.02 (2H, s, 2H, thiazolidine), 7.38-7.85 (16H, m, Ar-H + 4NH<sub>2</sub>), 9.78 and 10.26 (2H, 2s, 2NH; exchangeable); <sup>13</sup>C NMR,  $\delta_{\text{C}}$  19.2 (2 × CH<sub>3</sub>), 98 (2 × CH), 67.9 (2 × CCN), 135.2 (CCH<sub>3</sub>), 117.4, 121.9, 127.1, 127.5, 131.2 and 135.6 [18 × CH(Ar)], 164.9 and 168.4 (4 × CO) and 171.2 (2 × C=CCO).

#### References

- [1] Mohan, J., Anjanegulu, G.S.R., Sudhirand, S. and Arora, D. R., *J. Indian Chem. Soc.*, **66**: 330 (1989).
- [2] Singh, H., Yadav, L.D.S. and Bhattacharya, B.K., *J. Indian Chem. Soc.*, **56**: 1013 (1979).
- [3] Lancode, G., Pommery, N. and Depreux, P., *J. Enzyme Inhib. Med. Chem.*, **18**: 89 (2003).
- [4] Carloni, P. and Alber, F. (eds), *Quantum Medicinal Chemistry*, Wiley, Weinheim (2003).
- [5] Höltje, H-D, Sippl, W., Rognan, D., Folkers, G. (eds) *Molecular Modelling: Basic Principles and Applications*, 2nd ed. Wiley, Weinheim (2003).
- [6] Ibrahim, A., Al-Sehemi, A.G. and El-sharef, H.F., *Al-Azhar Bull. Sci.*, **16**: 103 (2005).
- [7] Amar, Y.A., Aly, M.M., Mohamed, Y.A., Al-Sehemi, A.G., M.A. Salem and El-Gaby, M. S., *Phosphorus, Sulfur and Silicon*, *In press*.
- [8] Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Zakrzewski, V.G., Montgomery, J.A., Jr., Stratmann, R.E., Burant, J.C., Dapprich, S., Millam, J.M., Daniels, A.D., Kudin, R.N., Strain, M.C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, C.A., Ayala, P.Y., Cui, Q., Morokuma, K., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Cioslowski, J., Ortiz, J.V., Baboul, A.G., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Gonzalez, C., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Andres, J.L., Gonzalez, C., Head-Gordon, M., Replogle, E.S. and Pople, J.A., *Gaussian, Inc., Pittsburgh PA* (1998).
- [9] Trivedi, J. M. and Mehta, C. M., *J. Indian Chem. Soc.*, **LII**, 708 (1975).

## تحضير ودراسة التركيب الجزيئي لمشتقات الثيازوليدين وثنائي ثيازولدين

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أبها - المملكة العربية السعودية

المستخلص. يتناول هذه البحث تحضير مشتقات الثيازوليدين (thiazolidine)، وثنائي الثيازوليدين (bisthiazolidine)، وقد تم توصيف وتحديد التركيب الجزيئي لهذه المركبات باستخدام أجهزة الطيف المختلفة (طيف الأشعة تحت الحمراء - طيف الرنين النووي المغناطيسي، للهيدروجين والكربون) والتحليل العنصري. كذلك تمت دراسة التركيب الإلكتروني، وذلك لمعرفة أفضل الأشكال الهندسية لهذه المركبات في الحالة الغازية، كما درست الخواص الإلكترونية لتوتر (Tautomeric properties) وتحليل الهيئة الفراغية باستخدام حسابات (semi-empirical AM1, MNDO and PM3, and ab initio)، وكل الحسابات أعطت نفس النتائج، بأن الشكل الكتيوني هو الأكثر استقراراً.