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ORIGINAL PAPER

Molecular modeling and cyclization reactions of 2-(4-oxothiazolidine-2-ylidene) acetonitrile

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Abstract

Diazotization of 2-(4-oxothiazolidine-2-ylidene) acetonitrile **1** with aryl diazonium chloride derivatives afforded 4-thiazolidinones **2a, b,** whereas **3a, b** derivatives produced through reaction of arylcarbonohydrazonoyl dicyanide with thioglycolic acid. Cyclization of **2a** with aromatic aldehydes and malononitrile gave the expected substituted thiazolo [3,2-a] pyridines **4a, b.** The reaction of **1** with anthraldehyde (1:1 molar ratio) gave the expected 4,5-dihydro-4-oxothiazole derivatives **5** which condensed with other mole *p*-chlorobenzaldehyde and gave the corresponding bisarylidine derivative **6**. Thiazolo [3,2-a] pyridine enaminonitrile derivative **7** produced through addition of malononitrile to bisarylidine **6**. Also, compound **7** reacted with other mole of malononitrile and furnished thiazolo [3,2-a] pyridine **12**, furthermore, compound **7** refluxed with phenyl hydrazine, thiourea, and formic acid, to form the corresponding thiazolo [3,2-a] pyridines **13**, **15** and **17,** respectively. Also, compound **1** reacted with phNCS in presence of KOH and afforded **19**. The molecular modeling of the synthesized compounds has been drawn and their molecular parameters were calculated. Also, valuable information is obtained from calculation of the molecular parameters including electronegativity, net dipole moment of the compounds, total energy, electronic energy, binding energy, electrophilicity index, HOMO and LUMO energy.

Keywords 4-Thiazolidinones · Thiazolo [3,2-a] pyridines · Thiazolo [3,2-a]1,8-naphthyridines · Molecular modeling

Introduction

Thiazoles nucleus appears in the structure of antibiotics as micrococcin [1] and they are synthetic intermediates and common substructures in numerous biologically active compounds [2–5]. There has been considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities [6–8] and exhibits highly specific activity in vitro against mycobacterium tuberculosis [9–12]. Furthermore, the pyridine scaffold is a wide spread structural motif that can be found in many natural products and in several pharmacologically interesting compounds. Therefore, the synthesis of pyridine derivatives, aiming to develop new drugs, is an active research area. Recently, several researchers became interested to cyanopyridine derivatives [13–21].

The experimental studies have been accompanied by computational studies, especially in recent years [22] due to their important role in understanding of the probably behavior of the compound during reactions and identification of the important information about the compounds under investigations, like total energy, binding energy, electronic energy, dipole moment, bond lengths, HOMO, LUMO [23]. The applicability of the semi-empirical methods PM3 for the calculation of novel synthesized compounds has been evaluated [24]. In a continuous of our research program directed toward synthesis of some medicinally heterocyclic compounds [25–31], we report here synthesis of some new series of thiazolidinones with pyridine moiety.

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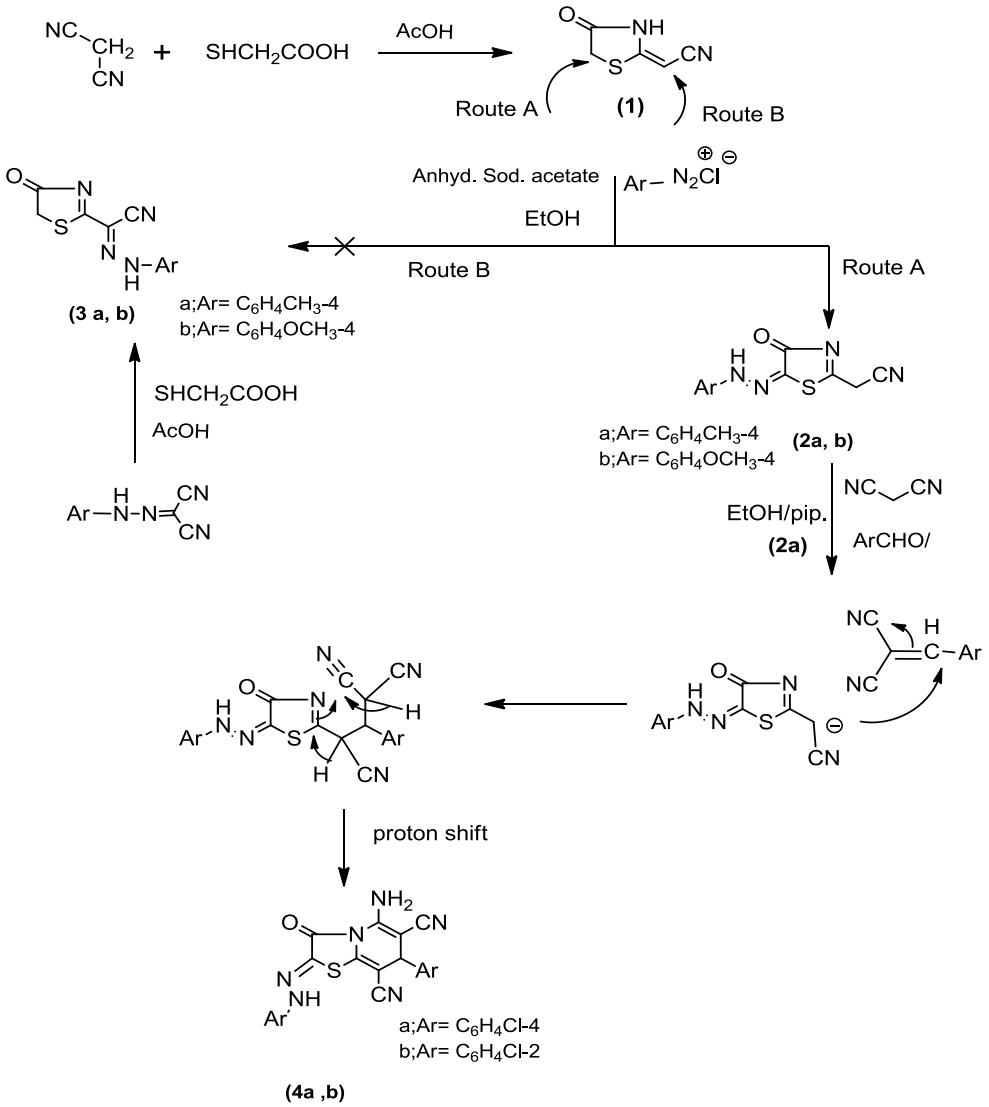
Results and discussion

Chemistry

2-(4-Oxothiazolidine-2-ylidene) acetonitrile **1** [32] used as key starting material for synthesis many biologically and pharmaceutically active heterocycles. Therefore, when (**1**) coupled with either *p*-tolyldiazonium chloride or *p*-methoxy benzene diazonium chloride in the presence of ethanol having anhydrous sodium acetate with stirring in ice bath produced the *N*-aryl-4-oxo-4,5-dihydrothiazole-2-carbohydrazonoyl cyanide. The structure of **2a, b is** confirmed by the help of analytical and spectroscopic data. Thus, IR spectrum of **2a** showed stretching significance absorption bands at 3240, 2214, and 1693 cm^{-1} attributed to imine, nitrile, and carbonyl moieties. Its ^{1}H NMR spectrum (DMSO-d_6) revealed singlet signal at δ 2.25 for methyl protons, singlet signal at 4.20 for methylene, multiple aromatic protons at 7.12–7.87 beside to NH signal at 10.70 ppm, exchangeable with D_2O. Also, ^{1}H NMR spectrum of **2b** (DMSO-d_6) showed characteristic signals at δ 4.03 and 4.20 ppm which referred to (OCH_3) and (CH_2) protons. 4-Oxothiazole derivatives **3a, b** produced through refluxing of aryl carbohydrazonoyl with thioglycolic acid. IR pattern displayed stretching frequencies at 1713 and 1752 cm^{-1} which described 4-thiazolidinone; Scheme 1. One pot reaction of **2a**, malononitrile and aromatic aldehydes in ethanol solution having a few drops of piperidine yielded thiazolo [3,2-a] pyridines **4a, b.** The mechanistically equations which described thiazolo pyridines production are illustrated in Scheme 1. Inferred

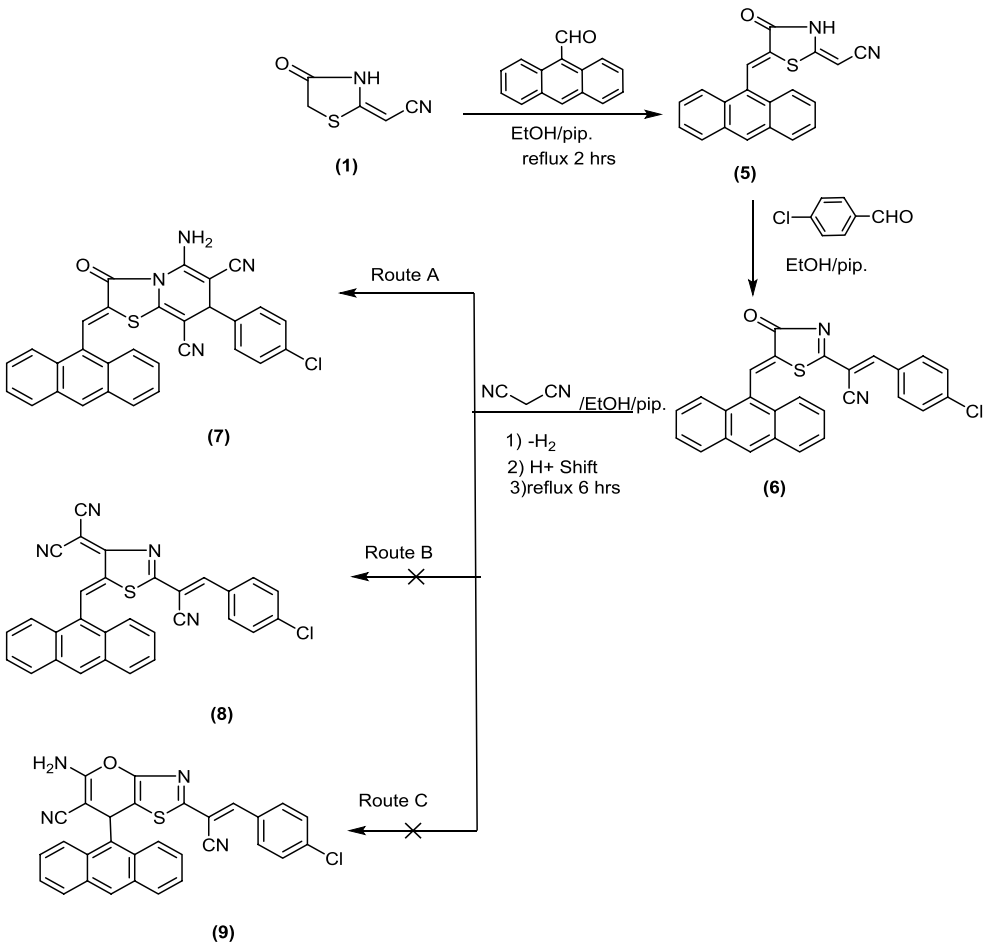


Scheme 1 Synthesis of 4-thiazolidinone derivatives **2a, b, 3a, b** and **4a, b**

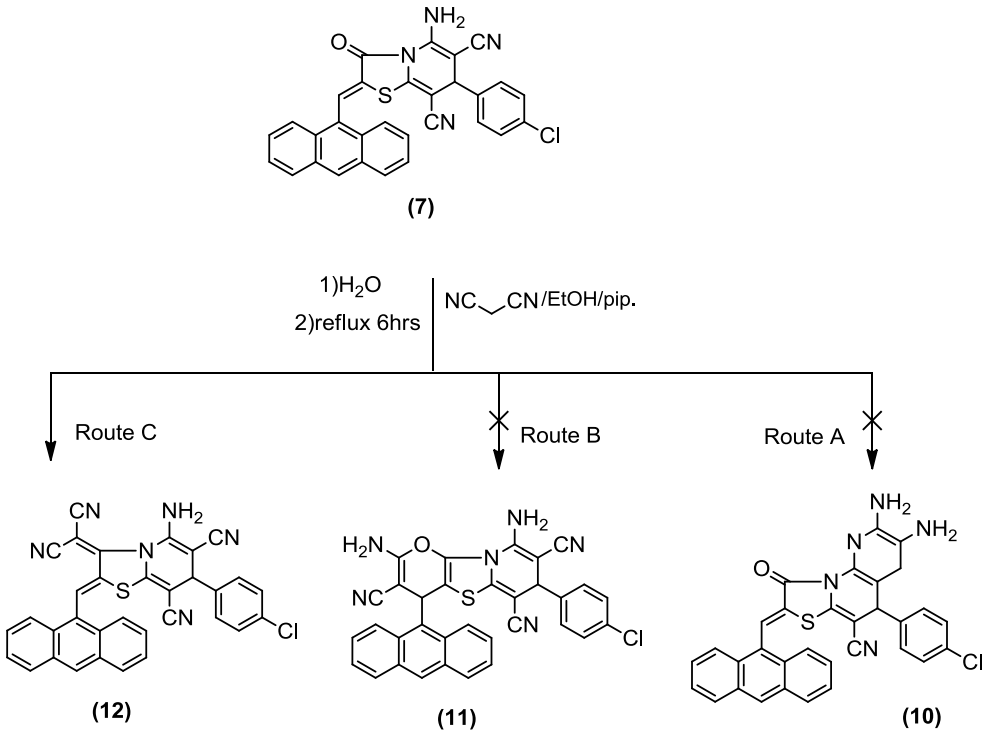
spectrum of **4b** exhibited stretching bands at 3396, 3228 corresponding to (NH_2), 3198 for (NH), (C≡N) stretching frequency at 2204 cm^{-1}, and carbonyl group at 1702 cm^{-1}. Its ^{1}H NMR spectrum (DMSO-d_6) revealed singlet signal for pyridine-4 H at δ 4.00 ppm; Scheme 1.

9-Anthraldehyde condensed with **1** (1:1 molar ratio) in ethanol piperidine and gave the corresponding arylidene derivative **5**, which reacted with *p*-chlorobenzaldehyde and formed the bisarylidine derivative **6**. The obtained structures **5, 6** were confirmed by spectroscopic studies and elemental analysis. The IR spectrum of compound **5** revealed absorption bands in the zone 3183, 2195 and 1707 cm^{-1} corresponding to an imine, cyano and carbonyl, respectively. Its ^{1}H NMR spectrum (DMSO-d_6) showed signals at δ 5.16 for methine-H and 11.49 ppm for NH proton disappeared with D_2O. Also, bisarylidene **6** revealed stretching frequencies at 3056, 2978, 2195 and 1709 cm^{-1} which referred to Ar–H, Aliph-H, cyano and significant carbonyl for thiazolidinone. Its ^{1}H NMR spectrum (DMSO-d_6) revealed two methine signals at 9.01, 9.05 ppm. In view of the growing biological importance of fused cyanopyridones, particularly thiazolo [1,2-a] pyridines [33–35] it was of interest to synthesize some thiazolopyridines containing anthracenyl moiety on the hope of obtaining more active compounds. Thiazolo [3,2-a] pyridine derivative **7** obtained through refluxing of **6** with malononitrile for 6 h (Scheme 2). The analytical and spectral data of **7** were agreement with the proposed structure, and its infrared spectrum assigned stretching bands at 1708 cm^{-1} for carbonyl moiety and ^{1}HNMR spectrum of **7** showed singlet signal at 4.70 ppm for pyridine-4H; Scheme 2.

Refluxing of thiazolo [3,2-a] pyridine **7** with malononitrile in ethanol catalyzed with piperidine gave thiazol [3,2-a] pyridine derivative **12**, instead of thiazolopyridines structure **10**, and **11**. The structure of **12** was assured through spectroscopic and accurate elemental data. Its IR spectrum showed any appearance of stretching carbonyl and this rejected structure **10**, whereas its ^{1}H NMR spectrum revealed lack



Scheme 2 Synthesis of thiazolo [3,2-a] pyridine derivative **7**



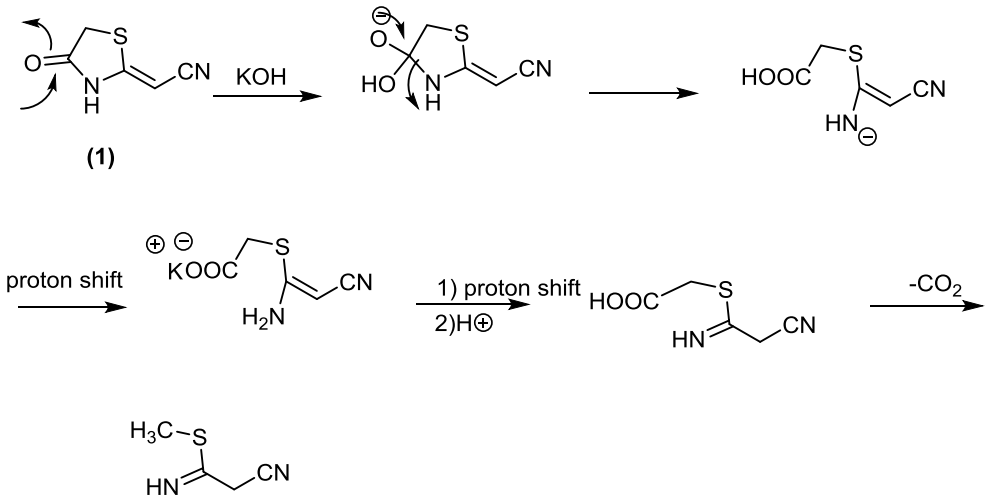
Scheme 3 Synthesis of thiazolo [3,2-a] pyridine derivative **12**

of respectable pyran-4H signal and this excluded pyrano [2,3:4,5] thiazolo [3,2-a] pyridine structure **11** Scheme 3.

Enaminonitrile **7** used to form a novel thiazol [3,2-a] pyridine derivatives through its reaction with different reagents. Phenyl hydrazine condensed with thiazolo [3,2-a] pyridine **7** in absolute ethanol and gave pyrazolo [3′,4′:4,5] thiazolo [3,2-a] pyridine derivative **13** based on perfect spectroscopic data IR spectrum of **13** showed absence of a carbonyl stretching absorbing band and its mass spectrum (**13**; $C_{36}H_{21}ClN_6S$) showed a molecular ion peak at *m*/*z* (604; 44.36%) and a base peak at *m*/*z* 54. Cyclization of **7** with thiourea produced derivative **15**; Scheme 4, thiazolo [3,2-a] pyridine structure **15** was confirmed by correct elemental and spectral data, infrared spectrum of **15** showed presence of broad absorbing band for thiol group. Its ^{1}H NMR spectrum exhibited two singlet signals at δ 4.19 and 9.64 ppm for pyridine-4-H and thiol proton. Furthermore, **7** was allowed to react with formic acid under reflux conditions to produce thiazolo [3,2-a]-3-aza-1,8-naphthyridine **17**. IR spectrum of compound **17** showed an absorbing band for cyano group, its ^{1}HNMR spectrum assigned a singlet signal for methine proton at δ 7.25 ppm.

When PhNCS reacted with 2-(4-Oxothiazolidine-2-ylidene) acetonitrile **1** in the presence of KOH/DMF solution with refluxing for 2 h, it is found that, opening of, 4-thiazolidinone ring was occurring rather than ketene formation **18** and produced methyl 2-cyanoethanimidothioate **19** instead of 4-oxothiazole derivative **18** Scheme 5.

The mechanistic route for methyl 2-cyanoethanimidothioate (**19**) production can be illustrated as follow.



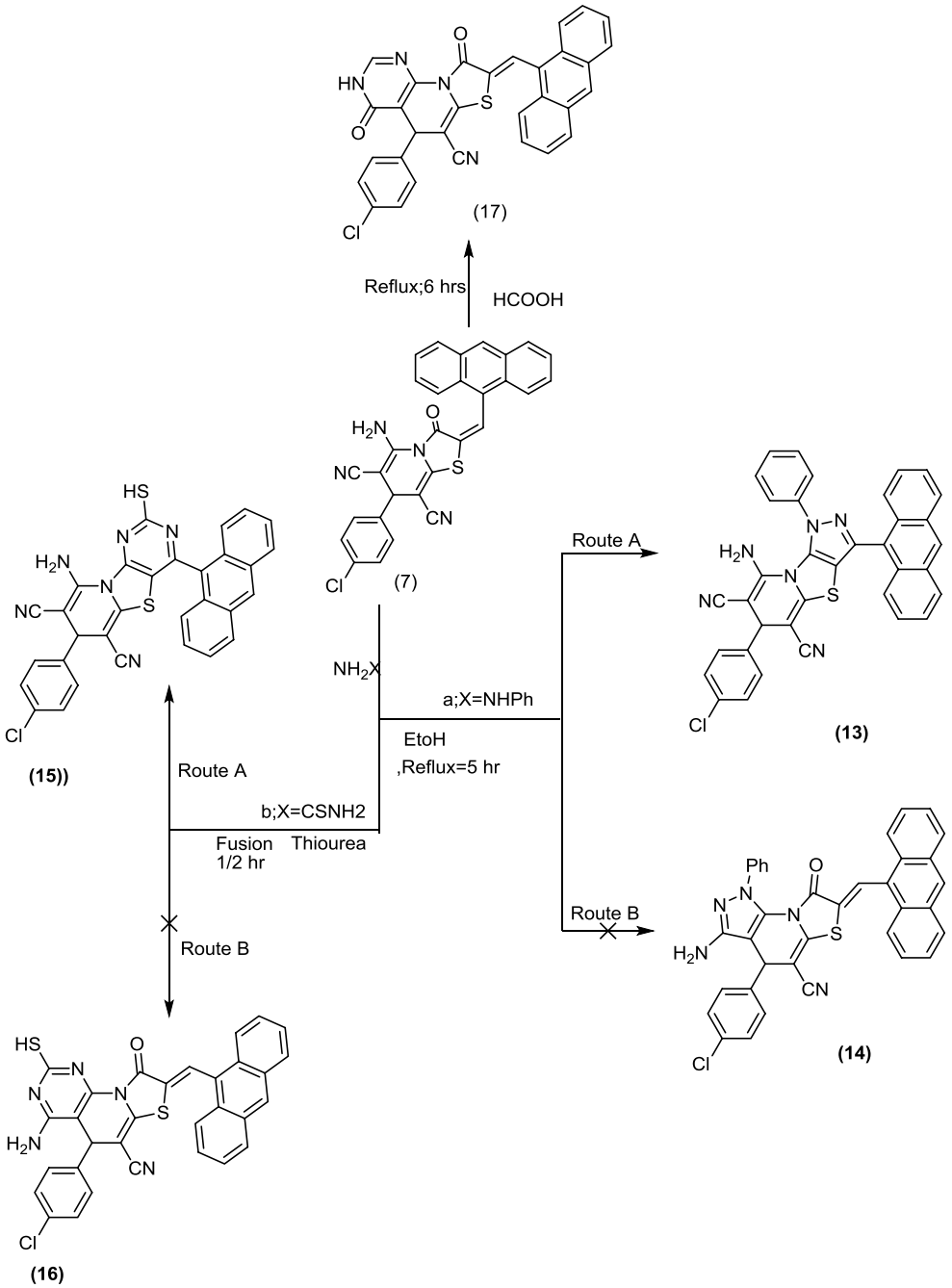
This can attributed to broken of thiazolidine ring by OH nucleophile easier than removal of hydrogen proton from methylene group in position 5.

Methyl 2-cyanoethanimidothioate **19** obtained approved by using adjusted elemental analysis and spectroscopic techniques. IR spectrum of **19** assigned the presence of stretching frequencies at 3431 and 2183 for NH, and cyano bands and absence of thiazolidinone function, also ^{1}H NMR spectrum showed a lack of methine proton and presence of methyl and methylene protons at δ 3.28 and 4.23 ppm, respectively.

Simulation results

The electronic structural orientation and frontier molecular orbital location of synthesized compounds [36] along with the calculated HOMO energy, LUMO energy, HOMO–LUMO energy gap (ΔE), dipole moment and heat of formation (HF) (Tables 1, 2). The electron densities and energies of frontier molecular orbital are important electronic parameters. These were used to determine the most reactive sites in the unsaturated system [37]. In fact, the energy of the HOMO is related directly to the ionization potential and it characterizes the susceptibility of the molecule toward an attack by electrophiles. On the other hand, the LUMO is related with electron affinity and gives an idea of the susceptibility of the molecule toward attack by nucleophiles. The synthesized heterocyclic compounds used in this study according to the HOMO and LUMO data are presented in Table 1. In this, the high negative HOMO value − 9.055 eV was belonging to compound **2a**. Moreover, the compound **3a** has − 9.007 eV HOMO energy and the compound **4a** has − 8.952 eV. The HOMO values of − 8.896, − 8.852 and − 8.923 eV corresponding to the compounds **2b**, **3b** and **4b**, while the other compounds have low negative HOMO energy and compound **17** has the least negative HOMO (− 3.841 eV). Further, discussion about LUMO energy, the compound **7** showed most negative LUMO energy value − 2.719 and − 2.301 eV was the next lead LUMO energy was corresponded to the compound **12**. In case of **4f**, **4g**, **4h**, **4j**, **4l** and **4m** compounds, their LUMO energy was in the order **5** > **13** > **15** > **12** > **4a** > **3b** > **4b** > **2a** > **2b** > **6** > **3a**. The negative values of the HOMO and LUMO (Table 4) indicate the title synthesized compounds are stable molecules [38–40]. Literally, the most essential stability index is ΔE between HOMO and LUMO [41, 42]. The HOMO–LUMO energy separation has been used as an important stability index and an indicator for the chemical reactivity of the molecule. Generally, the high chemical reactivity compounds have small ΔE and low reactivity compounds have higher ΔE [43, 44]. The values of the energy separation between the HOMO and LUMO for the synthesized compounds lie in the range 2.317–7.951 eV. This large HOMO–LUMO gap automatically means high excitation energies for many of the excited states and good stability for the title compounds. The low value of energy gap may be due to the groups that enter into conjugation [27].

The reactivity index measures the energy stabilization when the system acquires an additional electronic charge (ΔN_{max}) from the environment. The electrophilicity index is positive quantity and the direction of the charge transfer is completely determined by the electronic chemical potential (Pi) of the molecule because an electrophile is a chemical species capable of accepting electrons from the environment and its energy must decrease upon accepting electronic

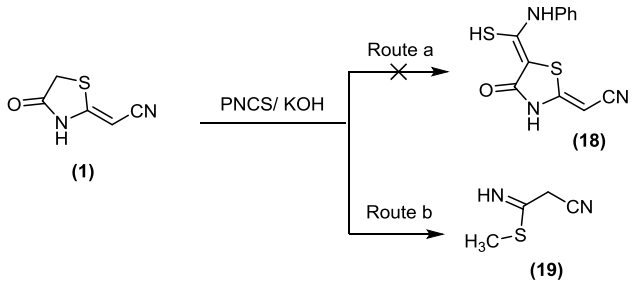


Scheme 4 Synthesis of thiazolo [3,2-a] pyridine derivatives **13, 15** and **17**

charge. Therefore, the electronic chemical potential must be negative, exactly as supported by the values in Table 1.

The molecular stability and reactivity can be measured by important properties like hardness (η) and softness (σ). Soft molecules have small energy gap and more reactive than hard molecules with a large energy gap. This can be attributed to the fact that soft molecules could easily offer electrons to an acceptor. Also, the reactivity of soft molecules increases than hard molecules if electron transfer or rearrangement is necessary for the reaction.

The electrophilicity index (ω) which shows the ability of the molecule to accept electrons follows the trend; **7** (ω = 5.46) > **12** (ω = 4.71) > **5** (ω = 3.79) > **3a** (ω = 3.67) > **15** (ω = 3.65) > **3b** (ω = 3.63) > **2a** (ω = 3.58) > **4b** (ω = 3.57) > **13** (ω = 3.550) > **2b** (ω = 3.530) > **6** (ω = 3.400) > **3a** (ω = 3.180) > **17** (ω = 3.110). Compound (**7**) exhibits the highest value of



Scheme 5 Synthesis of methyl 2-cyanoethanimidothioate

electrophilicity (Table 1) which confirms its highest capacity to accept electrons.

The dipole moment is frequently used to study the intermolecular interactions involving the non-bonded-type dipole–dipole interactions, because, higher the dipole moment lead to stronger intermolecular interactions. The dipole moment of the synthesized compounds was varied from 1.86 to 11.57 Debye (Table 2).

Theoretical calculations have paid a considerable attention to the characterization and inferences of geometrical optimization of the prepared compounds; therefore, we could obtain the optimized structure for the prepared compounds by computing the theoretical physical parameters, such as, bond lengths and bond angles using the HyperChem 7.5 software. The optimized structure for the **2a**, **2b**, **3a** and **3b** with the atomic numbering scheme is shown in Figs. 1,

Table 1 The calculated quantum chemical parameters of the synthesized compounds

Compound	HOMO	LUMO	ΔE	x	η	σ	pi	ω	S	ΔN_{max}
2a	− 9.055	− 1.412	7.643	5.2335	3.8215	0.261677	− 5.2335	3.583609	0.130839	1.369488
3a	− 9.007	− 1.056	7.951	5.0315	3.9755	0.251541	− 5.0315	3.184001	0.12577	1.265627
4a	− 8.952	− 1.507	7.445	5.2295	3.7225	0.268637	− 5.2295	3.673294	0.134318	1.404835
2b	− 8.896	− 1.400	7.496	5.148	3.748	0.266809	− 5.148	3.535473	0.133404	1.373533
3b	− 8.852	− 1.494	7.358	5.173	3.679	0.271813	− 5.173	3.636848	0.135906	1.406089
4b	− 8.923	− 1.433	7.49	5.178	3.745	0.267023	− 5.178	3.579664	0.133511	1.382644
5	− 8.347	− 1.699	6.648	5.023	3.324	0.300842	− 5.023	3.795206	0.150421	1.511131
6	− 8.466	− 1.363	7.103	4.9145	3.5515	0.281571	− 4.9145	3.400297	0.140786	1.383782
7	− 7.494	− 2.719	4.775	5.1065	2.3875	0.418848	− 5.1065	5.461014	0.209424	2.138848
12	− 8.534	− 2.301	6.233	5.4175	3.1165	0.320873	− 5.4175	4.708697	0.160436	1.738328
13	− 8.161	− 1.540	6.621	4.8505	3.3105	0.302069	− 4.8505	3.553444	0.151035	1.465187
15	− 8.642	− 1.538	7.104	5.09	3.552	0.281532	− 5.09	3.646974	0.140766	1.432995
17	− 3.841	− 1.524	2.317	2.6825	1.1585	0.863185	− 2.6825	3.105657	0.431593	2.315494

HOMO and LUMO are given in eV

Table 2 Some energetic properties of synthesized compounds calculated by PM3 method

Compound	Total energy kcal/mol	Binding energy kcal/mol	Electronic energy kcal/mol	Heat of formation kcal/mol	Dipole moment
2a	− 62,297.3	− 3058.4	− 377,951.2	90.18	4.85
3a	− 62,295.6	− 3057.9	− 382,022.3	91.74	2.22
4a	− 106,141.2	− 5212.4	− 871,638.2	161.5	4.79
2b	− 69,057.8	− 3147.6	− 419,311.9	61.62	4.32
3b	− 69,056.2	− 3146.0	− 424,068.6	63.15	1.86
4b	− 106,144.2	− 5210.5	− 884,175.9	163.05	5.89
5	− 77,370.4	− 4278.6	− 584,593.8	116.3	5.84
6	− 104,839.3	− 5618.8	− 856,287.9	157.7	4.91
7	− 121,172.8	− 6383.6	− 1,129,197.4	235.7	11.57
12	− 130,050.2	− 6969.9	1,165,730.3	328.5	5.57
13	− 139,706.1	− 7724.6	1,352,079.2	294.7	5.49
15	− 128,948.7	− 6767.7	1,141,991.4	255.2	6.25
17	− 132,439.7	− 6741.4	1,160,245.4	154.7	4.44

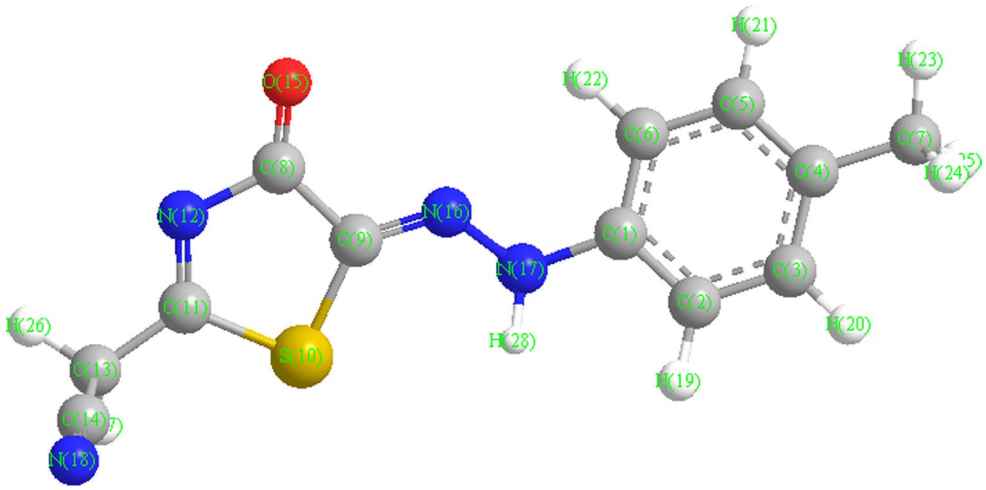


Fig. 1 The molecular structure of compound **2a** along with the atom numbering scheme

2, 3 and 4. The bond angles and bond lengths (Å) obtained from the energy minimum optimized structures of **2a** as a representative example of the synthesized compounds are given in Tables 3 and 4. In most of the cases, the actual bond lengths and bond angles are close to the optimal values, and thus the proposed structure of the compounds is acceptable.

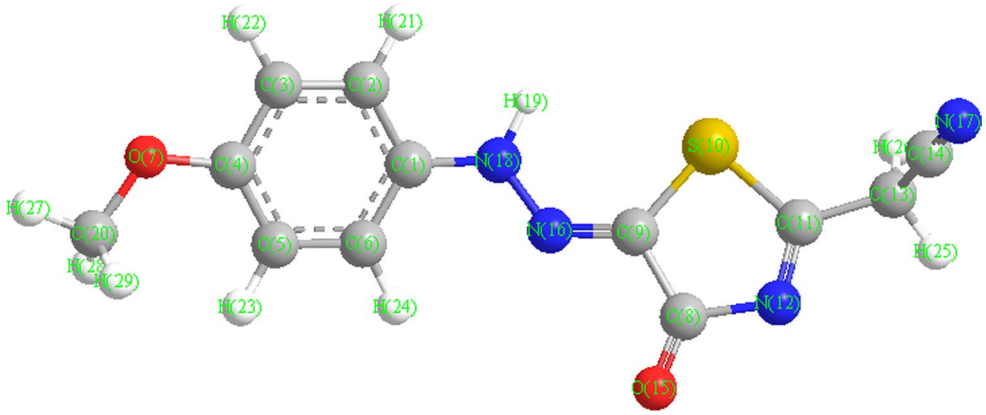


Fig. 2 The molecular structure of compound **2b** along with the atom numbering scheme

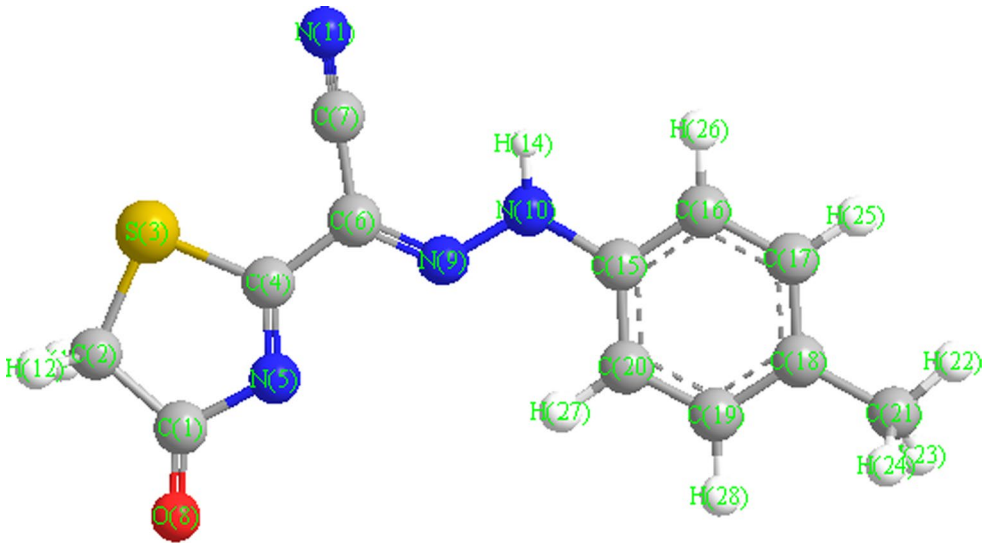


Fig. 3 The molecular structure of compound **3a** along with the atom numbering scheme

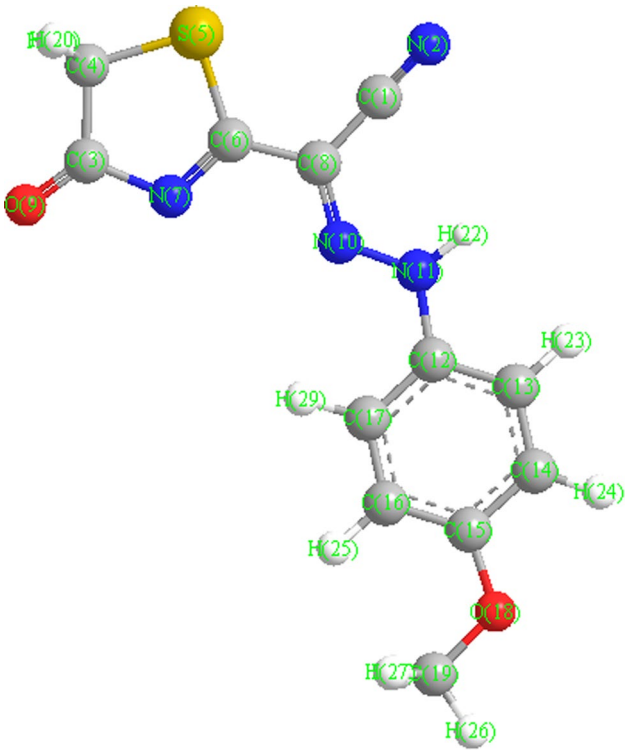


Fig. 4 The molecular structure of compound **3b** along with the atom numbering scheme

Table 3 Selected bond lengths (Å) of **2a** compound

Bond length	Actual bond lengths	Optimal bond lengths
N(17)–H(28)	1.001	1.05
C(14)–N(18)	1.159	1.158
C(13)–H(27)	1.11	1.113
C(13)–H(26)	1.111	1.113
C(13)–C(14)	1.449	1.47
C(11)–C(13)	1.5	1.497
C(11)–N(12)	1.298	1.26
S(10)–C(11)	1.799	1.856
C(8)–O(15)	1.202	1.208
C(8)–N(12)	1.473	1.426
C(8)–C(9)	1.51	1.517
C(7)–H(25)	1.099	1.113
C(7)–H(24)	1.098	1.113
C(7)–H(23)	1.098	1.113
C(6)–H(22)	1.097	1.1
C(5)–H(21)	1.096	1.1
C(5)–C(6)	1.39	1.42
C(4)–C(7)	1.485	1.497
C(4)–C(5)	1.395	1.42
C(3)–H(20)	1.096	1.1
C(3)–C(4)	1.397	1.42
C(2)–H(19)	1.097	1.1
C(1)–N(17)	1.453	1.462
C(1)–C(2)	1.401	1.42

Experimental

Materials and methods

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^1H NMR spectra were recorded on a Varian Gemini spectrometer (δ; ppm) 200 MHz using TMS as internal standard. Mass spectra were recorded on a Jeol-JMS-600 mass spectrometer. ^{13}C NMR spectra were run out at 75 MHz Micro analytical data were obtained from the Micro analytical Research Centre, Faculty of Science, Cairo University. The reactions were monitored by thin layer chromatography (TLC) using TLC sheets with UV fluorescent silica gel Merck 60f254 plates using UV lamp and different solvents as mobile phases.

Chemistry

***Synthesis of 2-(4-oxo-5-(2-(aroyl hydrazono)-4,5-dihydrothiazol-2-yl) acetonitrile* (2a, b)** Aryl diazonium chloride (0.01 mol) in (20 mL) ethanol was stirred for ½ h with **1** (0.01 mol) in ice bath in the presence of anhydrous sodium acetate (0.01 mol), then the stirring will continue in room temperature for 2 h. The solid products formed were collected by filtration and recrystallized from ethanol.

***2-(4-oxo-5-(2-(p-tolyl)hydrazono)-4,5-dihydrothiazol-2-yl) acetonitrile* (2a)** Reddish browns crystals (EtOH); yield 72%; m.p. 245–47 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3240 (NH), 3051(CH-arom.), 2931 (CH-aliph.), 2214(C≡N) and 1693 (C=O thiazolidinone) ^1H NMR (DMSO-d_6): δ/ppm 2.25 (*s*, 3H, CH_3), 4.20 (*s*, 2H, CH_2), 7.12–7.87 (*m*, 4H, Ar–H),10.70(*s*, 1H, NH, canceled with D_2O); Anal. Calcd. for $C_{12}H_{10}N_4OS$ (258.30): C, 55.80; H, 3.90; N, 21.69 found: C, 56.12; H, 3.56, N, 21.72.

***2-(4-oxo-5-(2-(p-methoxyphenyl) hydrazono)-4,5-dihydrothiazol-2-yl) acetonitrile* (2b)** Reddish browns crystals (EtOH); yield 88%; m.p. 210–12 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3181 (NH), 3040(CH-arom.), 2930 (CH-aliph.), 2212(C≡N) and 1697 (C=O thiazolidinone); ^1H NMR (DMSO-d_6):δ/ppm 4.03 (*s*, 3H, OCH_3), 4.20 (*s*, 2H, CH_2), 7.21–7.58 (*m*, 4H, Ar–H), 10.70(*s*, 1H, NH, canceled with D_2O); Anal. Calcd. for $C_{12}H_{10}N_4O_2S$ (274.30): C, 52.54; H, 3.67; N, 20.43 found: C, 52.77; H; 3.92; N, 20.72.

Table 4 Selected bond angles (°) of **2a** compound

Bond length	Actual bond angles	Optimal bond angles
H(28)–N(17)–N(16)	115.364	113
N(16)–N(17)–C(1)	116.89	124
N(18)–C(14)–C(13)	179.508	180
H(27)–C(13)–H(26)	106.798	109.4
H(27)–C(13)–C(14)	109.047	109.41
H(27)–C(13)–C(11)	110.113	109.41
H(26)–C(13)–C(14)	108.798	109.41
H(26)–C(13)–C(11)	111.179	109.41
C(14)–C(13)–C(11)	110.797	110.2
C(11)–N(12)–C(8)	113.598	115
C(13)–C(11)–S(10)	120.697	120
N(16)–C(9)–S(10)	130.69	126
N(16)–C(9)–C(8)	119.237	120
O(15)–C(8)–N(12)	120.642	124.3
O(15)–C(8)–C(9)	129.169	123
H(25)–C(7)–H(24)	107.517	109
H(25)–C(7)–H(23)	107.551	109
H(25)–C(7)–C(4)	110.621	110
H(24)–C(7)–H(23)	107.61	109
H(24)–C(7)–C(4)	111.104	110
H(23)–C(7)–C(4)	112.234	110
H(22)–C(6)–C(5)	119.365	120
H(22)–C(6)–C(1)	121.21	120
H(21)–C(5)–C(6)	119.419	120
H(21)–C(5)–C(4)	119.876	120
C(7)–C(4)–C(5)	120.726	121.4
C(7)–C(4)–C(3)	119.827	121.4
C(5)–C(4)–C(3)	119.446	120
H(20)–C(3)–C(4)	119.618	120
H(20)–C(3)–C(2)	119.863	120
H(19)–C(2)–C(3)	119.203	120
H(19)–C(2)–C(1)	121.184	120
N(17)–C(1)–C(6)	121.242	120
N(17)–C(1)–C(2)	118.346	120
C(6)–C(1)–C(2)	120.292	120

***Synthesis of N′-aryl-4-oxo-4,5-dihydrothiazole-2-carbohydrazonoyl cyanide* (3a, b)** A mixture of arylcarbonohydrazonoyl dicyanide (0.01 mol) and thioglycolic acid was heated 2 h in acetic acid. The solid products formed were collected by filtration and recrystallized from ethanol.

***N′-p-tolyl-4-oxo-4,5-dihydrothiazole-2-carbohydrazonoyl cyanide* (3a)** Dark browns crystals (EtOH); yield 72%; m.p. 180–82 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3235 (NH), 3059(CH-arom.), 2117(C≡N) and 1713 (C=O thiazolidinone); ^{1}H NMR (DM SO-d6): δ/ppm 2.35(*s*, 3H, CH_3), 4.29(*s*, 2H, CH_2), 7.32–7.87(*m*, 5H, Ar–H + NH, canceled with D_2O); Anal. Calcd. for $C_{12}H_{10}N_4OS$ (258.30): C, 55.80; H, 3.90; N, 21.69 found: C, 55.10; H, 3.65; N, 21.85.

***N′-p-methoxy phenyl-4-oxo-4,5-dihydrothiazole-2-carbohydrazonoyl cyanide* (3b)** Dark browns crystals (EtOH); yield 79% m.p. 170–72 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3177 (NH), 3092(CH-arom.), 2119(C≡N) and 1752 (C=O thiazolidinone); ^{1}H NMR (DMSO-d6):δ/ppm 3.82(*s*, 3H, OCH_3),4.25(*s*, 2H, CH_2), 7.21–7.58 (*m*, 5H, Ar–H + NH, canceled with D_2O); Anal. Calcd. for $C_{12}H_{10}N_4O_2S$ (274): C, 52.54; H, 3.67; N, 20.43 found: C, 52.12; H, 3.13; N, 20.10.

***Synthesis of 5-Amino-7-(aryl)-3-oxo-2-(2-(p-tolyl) hydrazono)-3,7-dihydro-2H-thiazolo [3,2-a] pyridine-6,8-dicarbonitrile* (4a, b)** A mixture of (**2a**), aromatic aldehyde and malononitrile (1:1:1 molar ratio) was refluxed for 6 h in absolute ethanolic piperidine solution. The solid products formed were collected by filtration and recrystallized from ethanol.

***5-Amino-7-(p-chlorophenyl)-3-oxo-2-(2-(p-tolyl) hydrazono)-3,7-dihydro-2H-thiazolo [3,2-a] pyridine-6,8-dicarbonitrile* (4a)** Reddish browns crystals (EtOH); yield 62%; m.p. 245–47 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3429, 3312, 3215 (NH_2, NH), 3034(CH-arom.), 2921 (CH-aliph.), 2222(C≡N) and 1701 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6): δ/ppm 2.25 (*s*, 3H, CH_3), 4.10 (*s*, 1H, pyridine-H), 7.13–7.83 (*m*, 11H, Ar–H + NH_2, canceled with D_2O + NH, canceled with D_2O); Anal. Calcd. for $C_{22}H_{15}ClN_6OS$ (446.31): C, 59.12; H, 3.38, N; 18.80 found: C, 59.77; H, 3.96; N, 18.52.

***5-Amino-7-(o-chlorophenyl)-3-oxo-2-(2-(p-tolyl) hydrazono)-3,7-dihydro-2H-thiazolo [3,2-a] pyridine-6,8-dicarbonitrile* (4b)** Reddish browns crystals (EtOH); yield 66%; m.p. 270–72 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3396, 3228, 3189 (NH_2, NH), 3037(CH-arom.), 2921 (CH-aliph.), 2204 (C≡N) and 1702 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6):δ/ppm 2.25 (*s*, 3H, CH_3), 4.00 (*s*, 1H, pyridine-H), 7.14–7.79 (*m*, 10H, Ar–H + NH_2, canceled with D_2O), 8.53 (*s*, 1H, NH, canceled with D_2O); Anal. Calcd. for $C_{22}H_{15}ClN_6OS$ (446.31): C, 59.12; H, 3.38; N, 18.80 found: C, 59.45; H, 3.07; N, 19.32.

***Synthesis of 2-[5-(anthracen-9-ylmethylene)-4-oxothiazolidine-2-ylidene) acetonitrile* (5)** A mixture of anthraldehyde (0.01 mol) was heated under reflux for 2 h with (**1**) (0.01 mol) in absolute ethanol (20 mL) catalyzed piperidine. The solid product formed was collected by filtration and recrystallized from ethanol.

Browns crystals; (EtOH); yield 72%; m.p. 125–27 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3183 (NH), 3055(CH-arom.), 2923 (CH-aliph.), 2195 (C≡N) and 1707 (C=O thiazolidinone); ^{1}H

NMR (DMSO-d_6):δ/ppm 5.16 (*s*, 1H, methine-H), 7.51–8.75 (*m*, 10H, Ar–H + methine-H) and 11.49 (*s*, 1H, NH, canceled with D_2O); ^{13}C NMR 123.40, 124.99, 125.75, 126.66; 127.79, 129.05, 129.18, 129.27, 130.61, 130.74, 131.32, 135.16 and 160.00; Anal. Calcd. for $C_{20}H_{12}N_2OS$ (328.39): C, 73.15; H, 3.68; N, 8.53 found: C, 73.52; H, 3.81; N; 8.85.

***Synthesis of 2-[5-(anthracen-9-ylmethylene)-4-oxo-4,5-dihydrothiazolidin-2-yl)]-3-(p-chlorophenyl) acrylonitrile* (6)** To 4-thiazolidinone derivative **5** (0.01 mol) in absolute ethanol (20 mL) having little amount of piperidine, *p*-chlorobenzaldehyde (0.01 mol) was added and heated for 3 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Reddish brown crystals (EtOH); yield 67%; m.p. 150–52 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3056 (CH-arom.), 2978 (CH-aliph.), 2195(C≡N) and 1709 (C=O thiazolidinone); ^1H NMR (DMSO-d_6):δ/ppm 6.58–8.66 (*m*, 13H, Ar–H), 9.01, 9.05 (2 s, 2H, methine-H); Anal. Calcd. for $C_{27}H_{15}ClN_2OS$ (450.94) C, 71.91; H, 3.35; N, 6.21 found: C, 72.01; H, 3.89; N, 6.19.

***Synthesis of 5-amino-2-(anthracen-9-ylmethylene)-7-(4-chlorophenyl)-3-oxo-3,7-dihydro-2H-thiazolo [3,2-a] pyridine-6,8-dicarbonitrile* (7)** A mixture of 4-thiazolidinone derivative **6** (0.01 mol) and malononitrile (0.01 mol), in absolute ethanol (20 mL) containing little quantity of piperidine, was refluxed for 6 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Brown powder, (EtOH); yield 73%; m.p. 160–62 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3331, 3354 (NH_2), 3051 (CH-arom.), 2200 (C≡N) and 1708 (C=O thiazolidinone); ^1H NMR (DMSO-d6): δ/ppm 4.70 (*s*, 1H, pyridine-H), 6.37–8.80 (*m*, 16H, Ar–H + methine-H + NH_2; Exchangeable with D_2O); MS *m*/*z* (%): 516, (*m*+, 6.89); Anal. Calcd. for $C_{30}H_{17}ClN_4OS$ (517.00) C, 69.69; H, 3.31; N, 10.84 found: C, 70.12; H, 3.64; N; 10.37.

***Synthesis of 6-amino-2-(anthracen-9-ylmethylene)-7-(4-chlorophenyl)-3-(dicyanom- ethylene)-3,7-dihydro-2H-thiazolo [3,2-a] pyridine-5,8-dicarbonitrile* (12)** To a solution of thiazolo [3,2-a] pyridine derivative **7** (0.01 mol) in absolute ethanol (20 mL) catalyzed with piperidine malononitrile (0.01 mol) was added. The reaction mixture was heated for 6 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Yellow powder; (EtOH); yield 59%; m.p. 233–35 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3373, 3216 (NH_2), 3056 (CH-arom.), 2928 (CH-aliph.) and 2196 (C≡N); ^1H NMR (DMSO-d_6), 4.10 (*s*, 1H, pyridine-H), 7.50–8.19 (*m*, 16H, Ar–H +methine-H + NH_2, canceled with D_2O) Anal. Calcd. for $C_{33}H_{17}ClN_6S$ (565.06) C, 70.15; H; 3.03, N, 14.87 found: C, 70.21, H, 2.91; N; 14.92.

***Synthesis of 8-amino-3-(anthracen-9-yl)-6-(4-chlorophenyl)-1-phenyl-1,6-dihydropy- razolo-[3′,4′:4,5] thiazolo [3,2-a] pyridine-5,7-dicarbonitrile* (13)** To a solution of **7**(0.01 mol) in absolute ethanolic solution (20 mL), phenyl hydrazine (0.01 mol) was added. The reaction was heated for 6 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Brown powder, (EtOH); yield 59%; m.p. 190–92 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3432, 3216 (NH_2), 3056 (CH-arom.), 2928 (CH-aliph.) and 2211(C≡N); MS *m*/*z* (%): 604(m^+), 44.36); Anal. Calcd. for $C_{36}H_{21}ClN_6S$ (604.50) C, 71.40; H, 3.50, N, 13.89. Found: C, 71.03, H, 3.71; N; 14.12.

***Synthesis of 9-amino-4-(anthracen-9-yl)-7-(4-chlorophenyl)-2-mercapto-7H-pyrido [2′,1′:2,3] thiazolo [4,5-d] pyrimidine-6,8-dicarbonitrile* (15)** Thiourea (0.01 mol) was fused with **7** (0.01 mol) for ½ h. The reaction mixture was allowed to cool. The solid product formed was collected by filtration and recrystallized from ethanol.

Yellow powder; (EtOH); yield 59%; m.p. 252–54 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3430, 3337 (NH_2), 3056(CH-arom.), 2928(CH-aliph.) and 2209 (C≡N); ^1H NMR (DMSO-d_6), 4.19(*s*, 1H, pyridine-H), 7.20–8.22 (*m*, 15H, Ar–H + NH_2; Canceled with D_2O), 9.64 (*s*, 1H, SH; Exchangeable with D_2O); Anal. Calcd. for $C_{31}H_{17}ClN_6OS_2$ (572.5.09) C, 64.97; H, 2.99, N, 14.66 found: C, 64.21; H, 2.54; N, 15.02.

***Synthesis of 8-(anthracen-9-ylmethylene)-5-(4-chlorophenyl)-4,9-dioxo-4,5,8,9-tetra-hydro-3H-thiazolo [3′,2′:1,6] pyrido [2,3-d] pyrimidine-6-carbonitrile* (17)** A mixture of **7** (0.01 mol) was heated in enough quantity of formic acid for 6 h. The solid product formed was collected by filtration and recrystallized from ethanol. Brown powder; yield 61%; m.p. 225–27 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3181 (NH), 2227 (C≡N) and 1712 (C=O); ^1H NMR (DMSO-d_6), 4.97(*s*, 1H, pyridine-H), 5.20 (*s*, 1H, pyrimidine-H),7.20–8.22 (*m*, 13H, Ar–H), 8.88(*s*, 1H, methine-H), 9.64 (*s*, 1H, NH; exchangeable with D_2O); Anal. Calcd. for $C_{31}H_{17}ClN_4O_2S$ (545.50) C, 68.32; H, 3.14; N, 10.28 found: C, 68.21; H, 2.98; N, 10.52.

***Synthesis of methyl 2-cyanoethanimidothioate* (19)** To a solution of **1** (0.01 mol) in DMF solution (20 mL), PhNCS (0.01 mol) and KOH (0.01 mol) were added. The reaction was heated for 3 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Brown powder; 74%; m.p. 225–27 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3381 (NH), 2216 (C≡N) and ^1H NMR (DMSO-d_6), 3.28(*s*, 3H, CH_3), 3.65 (*s*, 1H, NH), 4.23 (*s*, 2H, CH_2). Anal. Calcd. for $C_5H_6N_2O_2S$ (158.18) C, 37.96; H, 3.82; N, 17.71 found: C, 38.23; H, 3.53; N, 17.21.

Molecular modeling studies

An attempt to gain a better insight on the molecular structure of the synthesized compounds, geometric optimization and conformation analysis has performed using semi-empirical method PM3 as implemented in HyperChem 7.5 [45]. The structures of synthesized reported compounds were optimized with semi-empirical method PM3. A gradient of 0.01 kcal/Å was set as a convergence criterion in all the molecular mechanics and quantum calculations. The lowest energy structure was used for each molecule to calculate physicochemical properties.

Conclusions

We reported herein a novel route for synthesis of some thiazolidinone derivatives having different aroyl hydrazonoyl and aryl moieties. Also, this article include synthesis of different thiazolo [3,2-a] pyridines and thiazolo [3,2-a]-1,8-naphthyridine derivatives. To support the solid-state structure, the molecular modeling optimization and electronic parameters have been calculated using PM3 method.

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