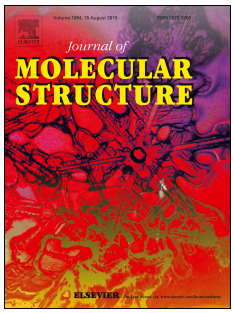
Accepted Manuscript



A novel series of 1, 4-Dihydropyridine (DHP) derivatives bearing thiazolidin-4-one: From synthesis to structure

Tahseen S. Bade, Hossein Pasha Ebrahimi, Tahseen A. Alsalim, Salam J.J. Titinchi, Hanna S. Abbo, Zeinab Bolandnazar, Amirpasha Ebrahimi

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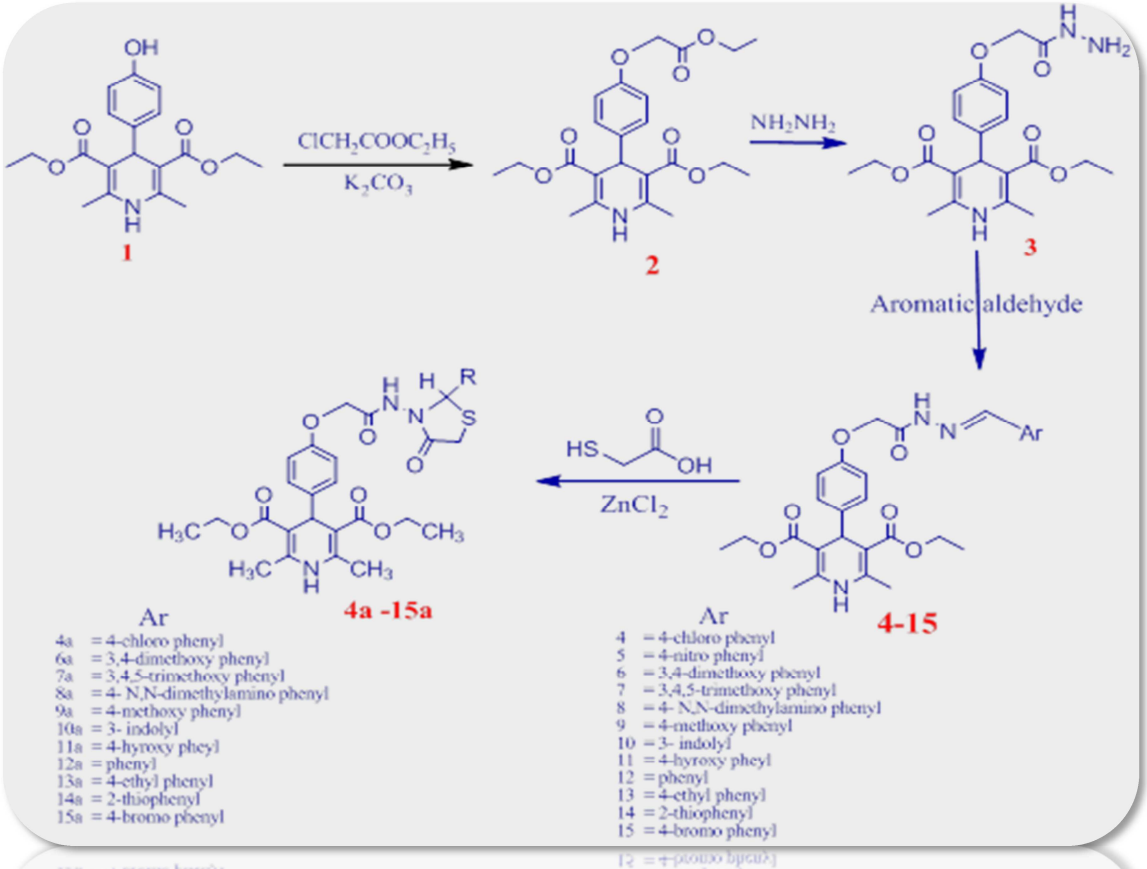
OH
ClCH2COOC2H5
K2CO3
NH2NH2
1
2
3
Aromatic aldehyde
HS
OH
ZnCl2
4-15
4a -15a
Ar
4a = 4-chloro phenyl
6a = 3,4-dimethoxy phenyl
7a = 3,4,5-trimethoxy phenyl
8a = 4- N,N-dimethylamino phenyl
9a = 4-methoxy phenyl
10a = 3- indolyl
11a = 4-hyroxy pheyl
12a = phenyl
13a = 4-ethyl phenyl
14a = 2-thiophenyl
15a = 4-bromo phenyl
Ar
4 = 4-chloro phenyl
5 = 4-nitro phenyl
6 = 3,4-dimethoxy phenyl
7 = 3,4,5-trimethoxy phenyl
8 = 4- N,N-dimethylamino phenyl
9 = 4-methoxy phenyl
10 = 3- indolyl
11 = 4-hyroxy pheyl
12 = phenyl
13 = 4-ethyl phenyl
14 = 2-thiophenyl
15 = 4-bromo phenyl

ACCEPTED MANUSCRIPT

A Novel Series of 1, 4-Dihydropyridine (DHP) Derivatives Bearing Thiazolidin-4-one: From Synthesis to Structure

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Keywords: 1, 4-dihydropyridine, DHP, Thiozolidin-4-one, Hantzsch dihydropyridine synthesis, Calcium channel blockers (CCBs), Microwave.

Abstract

A novel series of 1, 4-Dihydropyridine (DHP) thiazolidin-4-one compounds derived from dihydropyridine hydrazones Schiff bases with thioglycolic acid were synthesized through an efficient Hantzsch reaction and experimentally characterized by spectral methods using IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic methods. Herein, DHPs were synthesized by an improved Hantzsch procedure in the excellent yields by three different conditions including reflux condensation, fusion, and the microwave irradiation. An additional comparison of applied methodology routes was used to confirm the advantages including short reaction time, good yields, and operational simplicity. Furthermore, the structural and electronic properties of the studied molecules were theoretically investigated by performing density functional theory (DFT) to access reliable results to the experimental values. The molecular geometry, HOMO, and LUMO of the studied compounds were calculated. The theoretical ^{13}C chemical shift results were also calculated using the gauge independent atomic orbital (GIAO) approach and their respective linear correlations were obtained.

ACCEPTED MANUSCRIPT

1. Introduction

1,4-Dihydropyridine derivatives (DHPs) are widely used clinically as L-type calcium channel blockers (CCBs) in the treatment of hypertension and cardiovascular diseases[1,2]. Figure 1 represents some CCBs which prevent calcium from entering cardiac muscle cells and blood vessels, resulting in bradycardia and vasodilation, respectively. In the past, DHPs were generally synthesized by the classical Hantzsch reaction[3–9], which involves the condensation of two equivalents of a β-keto ester with one equivalent of an aldehyde and a nitrogen donor such as ammonia or ammonium acetate[10,11]. A literature survey shows that a number of improved methods have been recently reported to modify Hantzsch procedures either by using the β-diketones instead of the β-keto esters or by replacing ammonia by an aromatic amine in continuous flow condition[12–14]. However, some of these methods suffer from long reaction times, low yields, and use of large quantities of volatile organic solvents, therefore, development of an efficient and versatile method is still required.

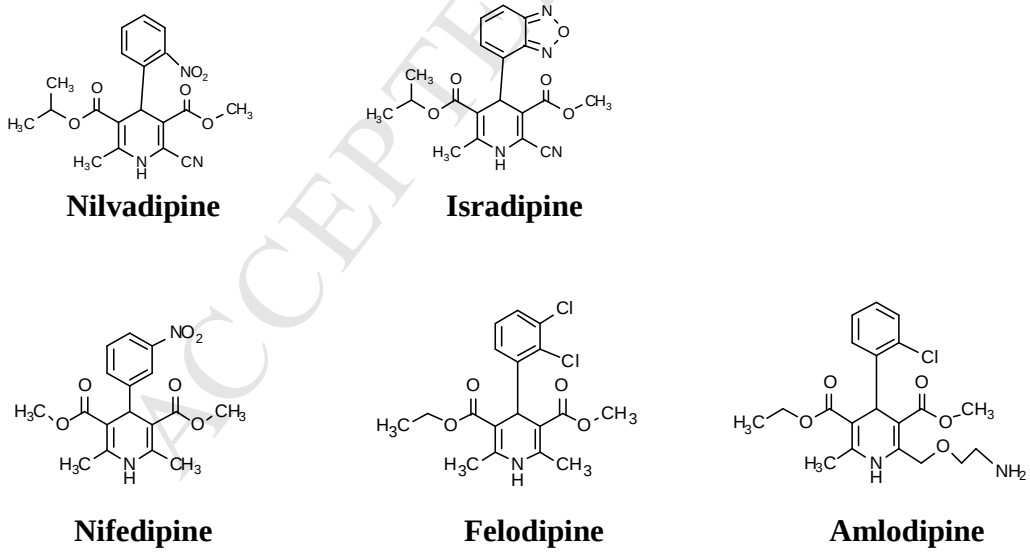


Figure 1. Structures of the most known 1,4-DHP calcium channel blockers

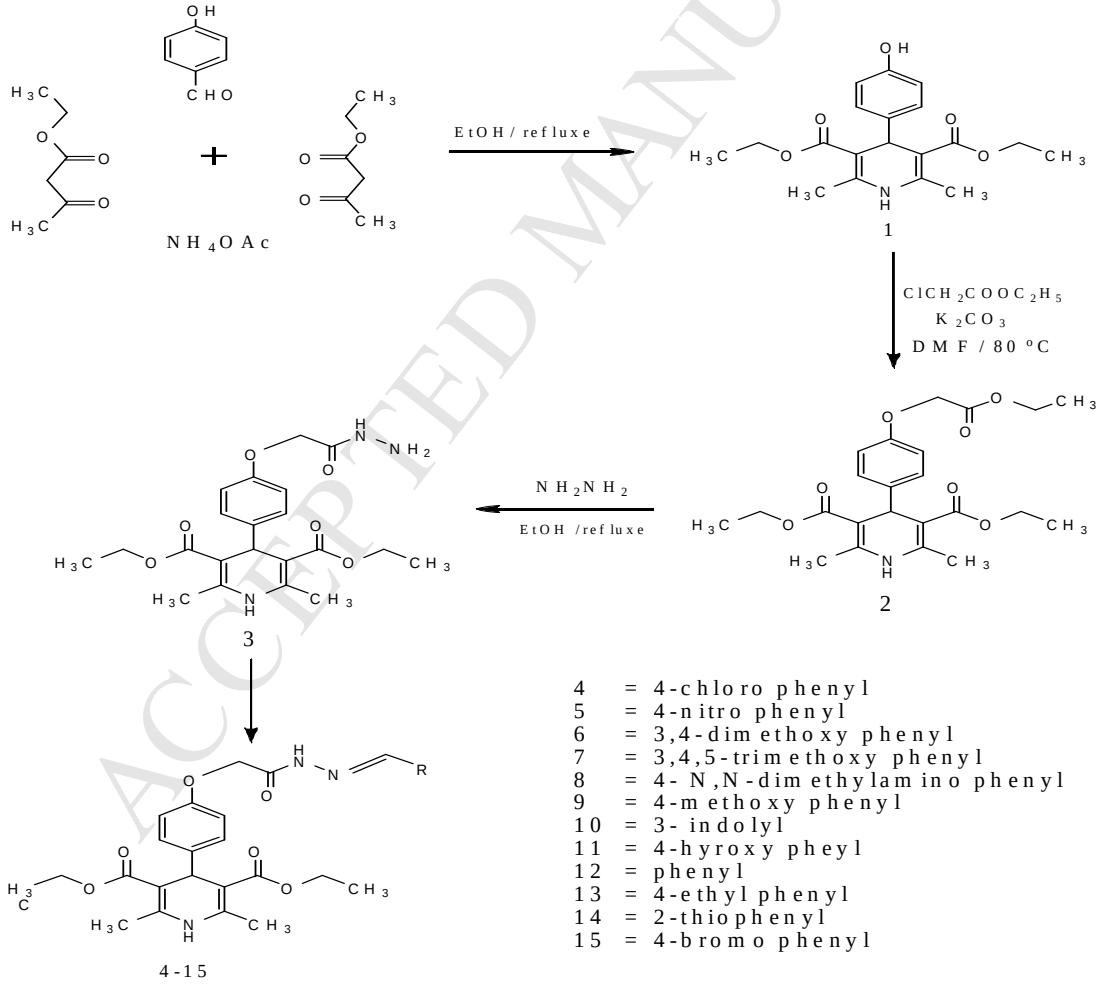
In addition, the occurrence of the nitrogen and sulfur containing heterocyclic ring systems including thiazolidine as well as related cyclic systems in numerous biologically active molecules has been importantly recognized with regards to the spectrum of activity in several remarkable pharmacological drugs including antibiotics, antifungals, antiallergics, antiphlogistics and antitumor substances[15-26]. In addition, the thiazolidine ring system represents a very important structural unit in drug discovery[27].

As a part of our endeavor toward the synthesis of new heterocyclic bioactive agents as probes for biomolecules in medicinal, biophysical and bioanalytical chemistry to enhance many physiological activities[28-36], herein, we synthesized and characterized a new series of 1, 4-Dihydropyridine derivatives bearing thiazolidin-4-one by three different conditions including Hantzsch condensation, fusion and microwave irradiation methods. The synthesized compounds were characterized on the basis of spectroscopic methods including IR, ^{1}H and ^{13}C NMR, as well as mass spectroscopy. To additionally verify the proposed assignments, quantum chemical calculations were performed. Therefore, the structural and electronic properties of the studied compounds were theoretically investigated and the results were discussed. In the present study, we have also extended the probing into the application of Density Functional Theory (DFT) methods. The DFT methods are more advantageous owing to their accuracy and low computational cost. These properties make DFT more practical and feasible for the computations of different molecules. Therefore, these synthesized compounds were theoretically investigated by B3LYP, as the more popular DFT methods. Thus, a comparison was made between the theoretically calculated ^{13}C chemical shift constants and the experimentally measured ^{13}C chemical shifts. GIAO (Gauge Including Atomic Orbital) as the most widely used approach for

calculating NMR shielding tensors were applied[37–42]. The Gaussian 09 package was employed to perform optimization of structures and all the calculations[43].

2. Results and discussion

All the intermediate and the target compounds (DHPs thiazolidine-4-one derivatives) were synthesized according to the methods summarized in scheme 1 and 2. As outlined in Scheme 1 and 2, the reaction included several steps which the dihydropyridine **1** was synthesized in a general Hantzsch procedure by the condensation of two equivalents of ethyl acetoacetate with one equivalent of p-hydroxybenzaldehyde and ammonium solution under ethanol medium.



Scheme 1. Preparation procedure of DHPs hydrazone (Schiff bases) with general structure

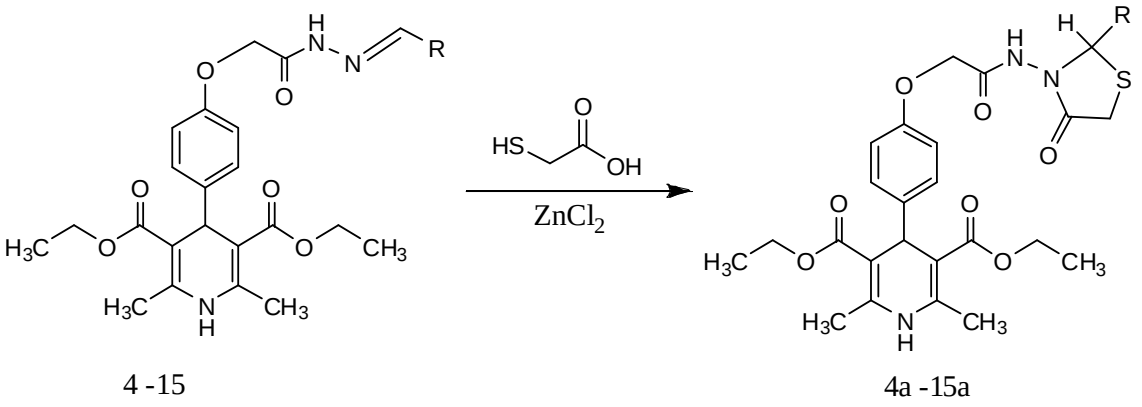
The solid product was converted to ester **2** by using ethyl chloroacetate in DMF medium. The only hydroxyl group of DHP ring undergoes alkylation during this step. A nucleophilic substitution reaction converted ester **2** to its hydrazide **3** by refluxing it with hydrazine monohydrate in ethanol. DHP Schiff bases (hydrazone) **4-15** were synthesized by the condensation of an aromatic aldehyde with prepared hydrazide using different methods reflux, fusion and MW irradiation. The yield and reaction time of different methods for newly synthesized compounds are collected in Table 1.

Table 1. The yield and reaction time of prepared DHPs Hydrazone in different methods

Compound	Reflux		MW irradiation		Fusion	
	Time (hr)	Yield %	Time (min)	Yield %	Time (min)	Yield %
4	4	76	13	87	15	85
5	4	81	13	92	15	91
6	4	78	13	86	15	85
7	4	80	13	83	15	87
8	4	72	13	80	15	83
9	4	81	9	92	10	91
10	6	63	15	79	15	81
11	6	61	15	87	15	85
12	4	78	9	84	10	89
13	4	75	9	87	10	90
14	6	77	9	85	10	87
15	4	76	13	87	15	91

As is clear from Table 1, the maximum time of fusion and MW methods measured about 15 min while reflux takes 4-6 hrs. DHP Schiff bases (hydrazone) **4-15** were converted to the corresponding DHPs thiadiazolin-4-one **4a-15a** by the condensation reaction of the obtained Schiff bases with thioglycolic acid and hydrazone under reflux. The synthetic route of compounds is outlined in Scheme 2. As can be concluded from Table 1, microwave irradiation has major advantages over the classical approach (Method A) since shorter reaction time (from hours to mins) are required and significantly improved yields are observed. For instance,

compound **11** was synthesized in 61% yield, after 6 hours in ethanol at the reflux method. In contrast, the microwave assisted reaction, on neutral alumina, affords an 87% yield in just 15 minutes.



4 -15 4a -15a

4a = 4-chloro phenyl
6a = 3,4-dimethoxy phenyl
7a = 3,4,5-trimethoxy phenyl
8a = 4- N,N-dimethylamino phenyl
9a = 4-methoxy phenyl
10a = 3- indolyl
11a = 4-hyroxy pheyl
12a = phenyl
13a = 4-ethyl phenyl
14a = 2-thiophenyl
15a = 4-bromo phenyl

Scheme 2. Preparation of DHPs Thiazolidin-4-one

2.1 Spectral characterization

In this section, spectral studies including the observed spectroscopic results for the title compounds are discussed. Newly synthesized target compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR as well as mass spectral techniques. All the synthesized compounds gave satisfactory analyses for the proposed structures, which were confirmed on the basis of their spectral data. A complete set of spectral data of the complexes is given in Supplementary data.

IR spectra analysis

The IR spectra of the prepared compounds exhibit characteristic bands of the expected functional groups. The spectral data of compounds **1-3** are in a good agreement with the literature[44]. As shown in Figure 2, the presence of bands 1740 and 3340 cm^{-1} due to carbonyl stretching and NH_2 stretching respectively indicates the condensation of ester **2** and hydrazine in 1:1 mol ratio.

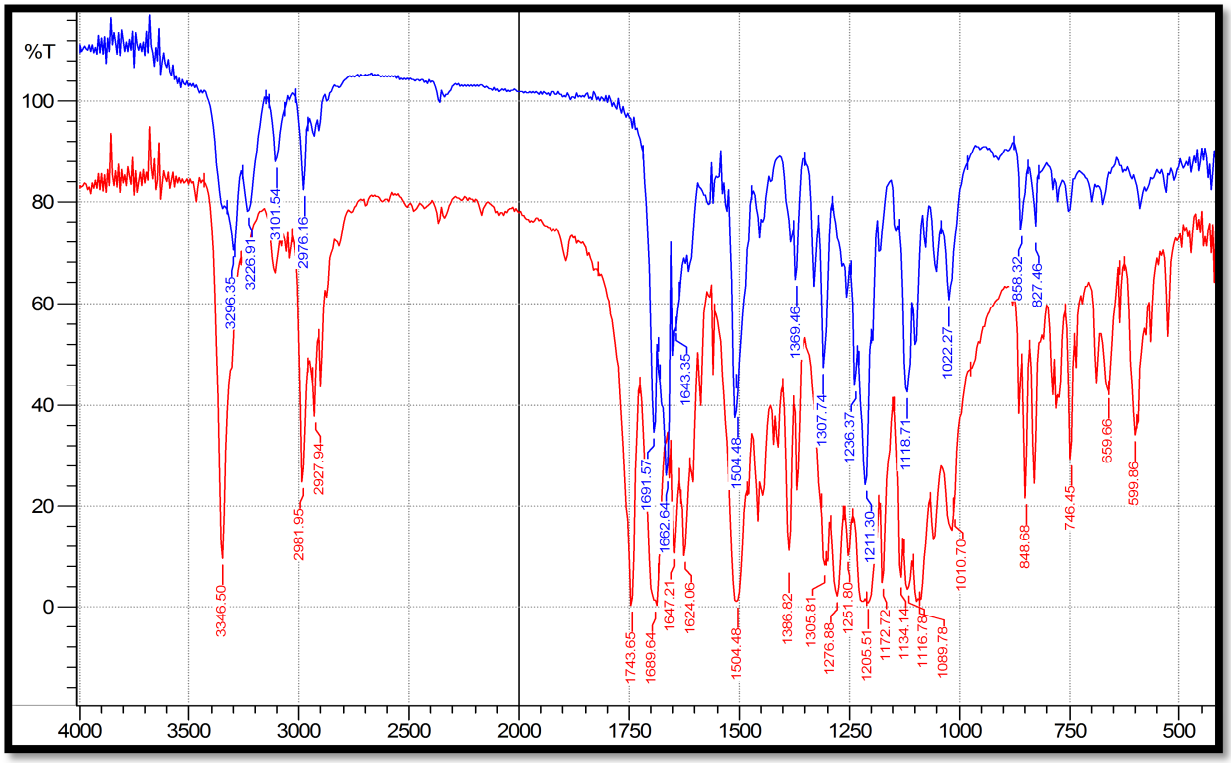


Figure 2. IR spectra of compounds **2** and **3**.

The IR spectrum of DHPs hydrazone derivatives **4-15** shows a strong bond at 1612-1604 cm^{-1} that attributed to the stretching vibration of azomethine as the main characteristic band which obviously confirms the formation of Schiff base.

^{1}H and ^{13}C NMR spectra analysis

The ^{1}H NMR spectral data of all compounds at ambient temperature in DMSO-d_6 confirms the proposed structural elucidation. The spectra of all compounds show the azomethine proton

(CH=N) as singlet signal at δ ~ 7.91–8.37 ppm. The ^{1}H NMR spectra of Schiff bases display the NH proton (-CO-NH=N-) as singlet signal at δ ~ 11.86–11.27 ppm.

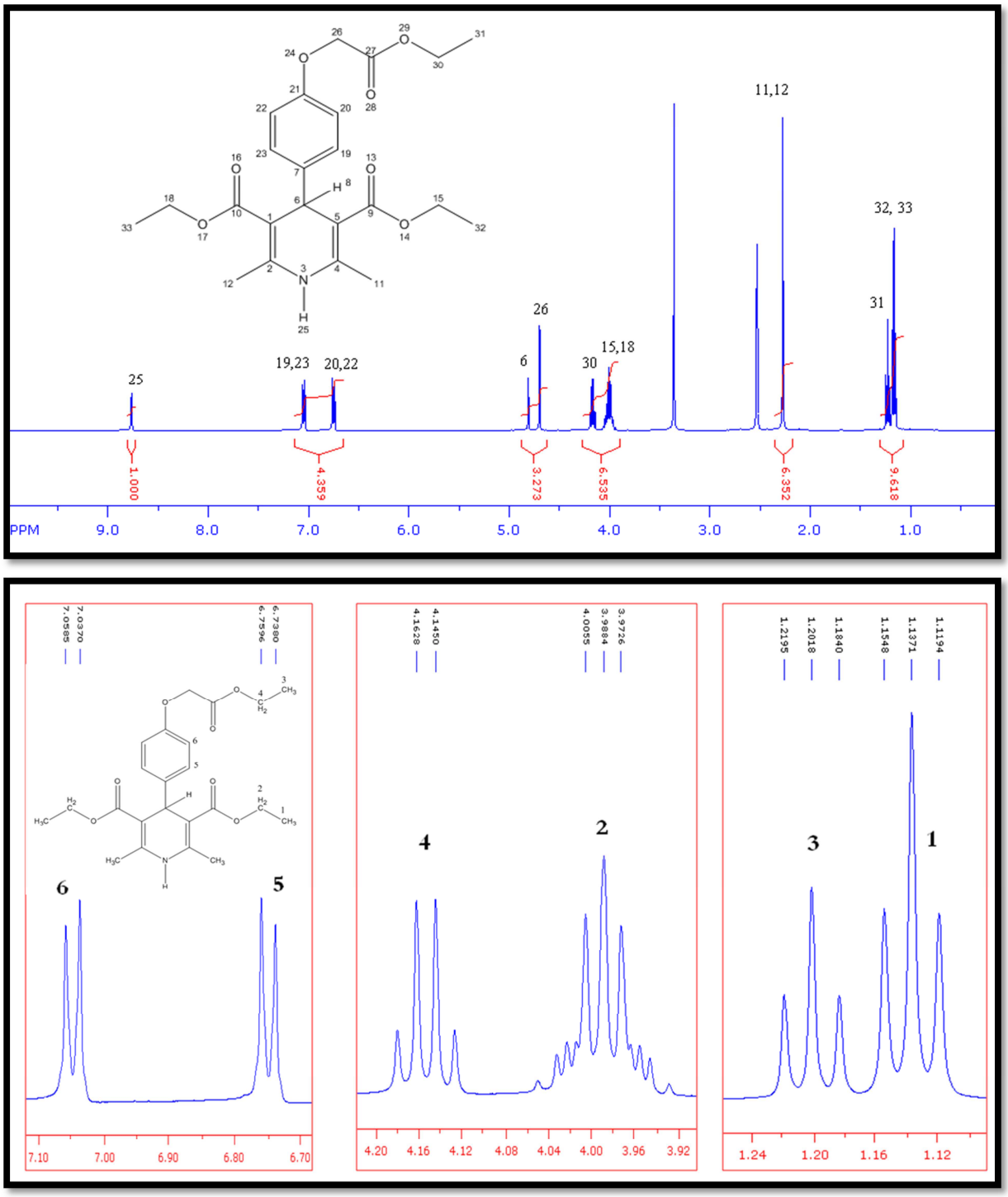


Figure 3. ^{1}H NMR spectra of compound **2**

The spectra of DHPs 4-thiazolidinone compounds **4a-15a** show the heterocyclic proton -CH (-SCHN-) appear at a region between 5.16 and 6.65 ppm as a two signal. They also display a signal at δ ~ 3.51–4.60 ppm which is attributed to the methylene group (-CH_2-S). The disappearance of proton signals attributed to NH_2 in the ^{1}H NMR spectra of DHPs **4-15** supports the condensation of aromatic aldehydes with prepared hydrazides. As it can be observed in Figures 3 and 4, all protons of cyclic, aromatic ring and methyl groups are observed in their expected region for compounds **2** and **12a**, respectively.

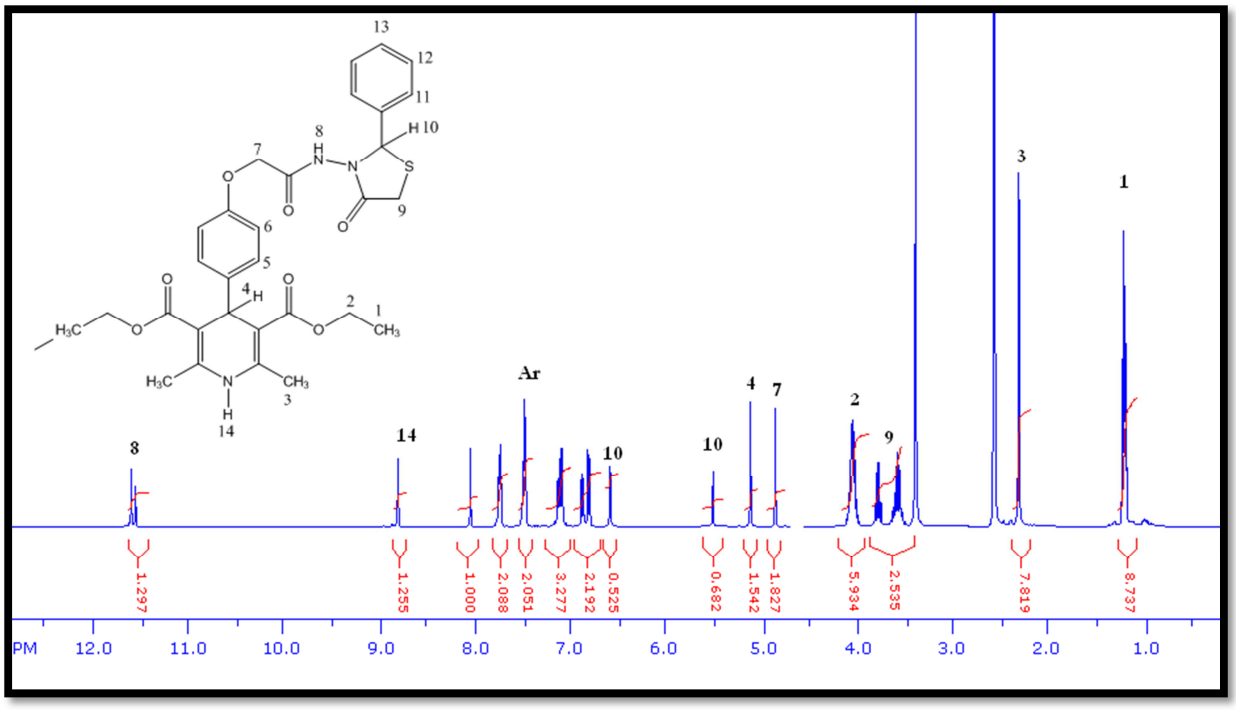


Figure 4. ^{1}H NMR spectra of compound **12a**

Also, the ^{13}C NMR spectra of compounds were recorded in DMSO-d_6. All spectra exhibited signals from azomethine carbon at δ ~ 170 ppm as the highest chemical shift in our synthesized Schiff bases. The carbons of the thiazolidine-4-one system appear between δ ~ 59.1-59.4 ppm and 28.0-28.8 ppm which are attributed to the carbon of S<u>C</u>HN and -<u>C</u>H_2-S, respectively. All

assignments for other carbon were found as expected. In addition, ^{13}C DEPT NMR and ^{15}N NMR of compounds **9a** and **10a** are presented in Figures 5 and 6, respectively.

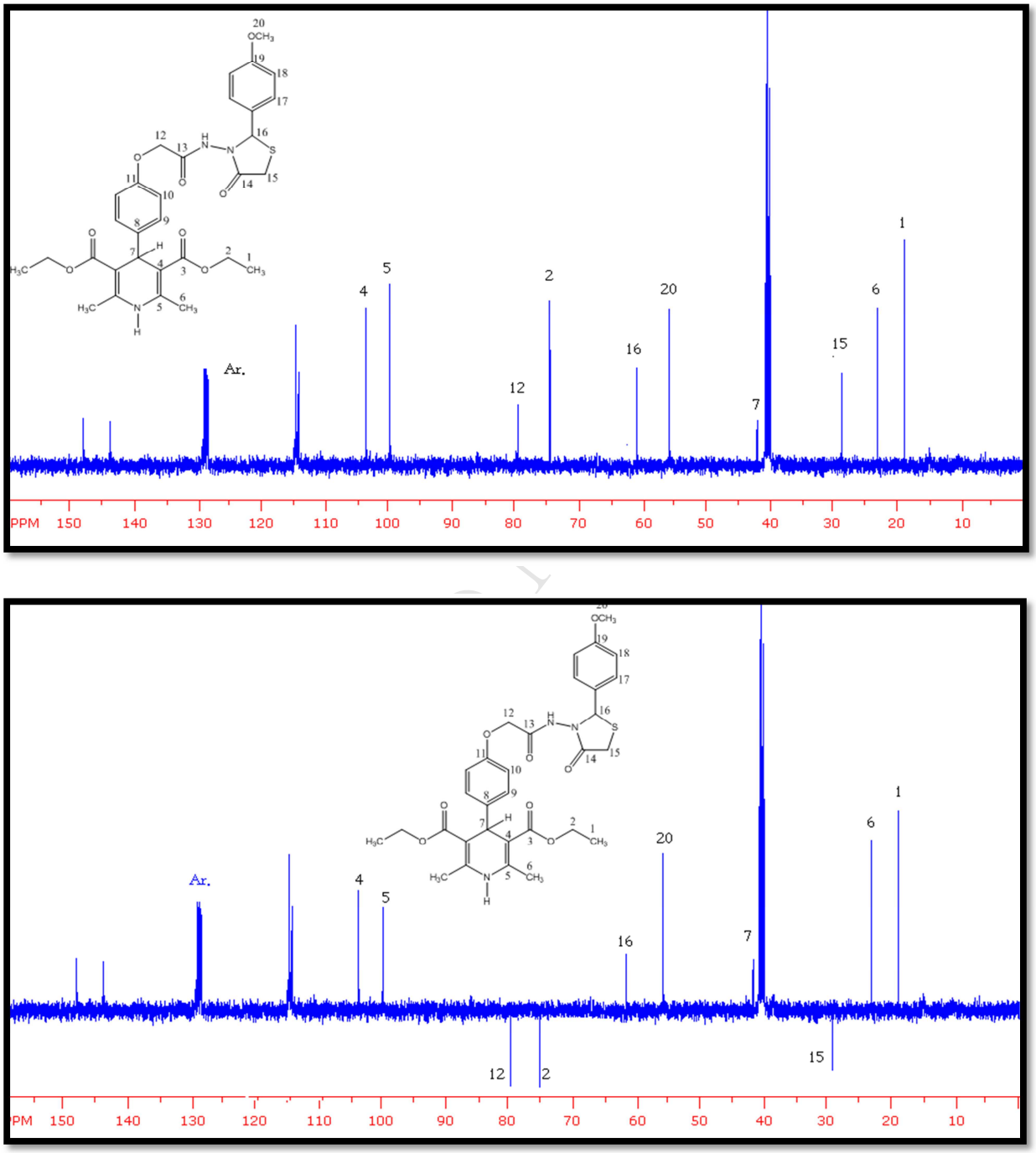


Figure 5. ^{13}C NMR and DEPT spectrum of compound **9a**

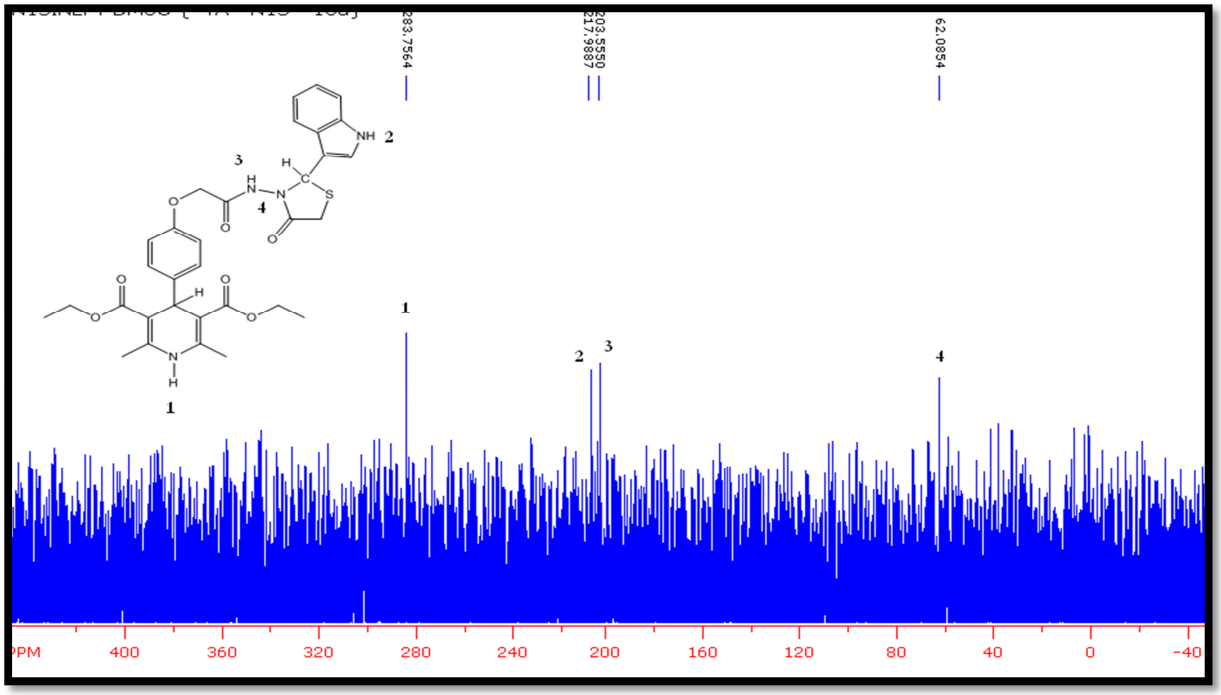


Figure 6. ^{15}N NMR spectrum of compound **10a**

These spectra also support the proposed structure for compounds.

Mass spectra analysis

Mass spectrometry as a powerful structural characterization technique in coordination chemistry has been successfully used to confirm the molecular ion peaks of all compounds. The peaks intensity gives an idea about the stability of fragments, especially with the base peak. The electron impact spectrum of the studied compounds is characterized by high relative intensity molecular ion peaks. The mass spectrum of compound **7a** is presented in Fig. 7 as a case study.

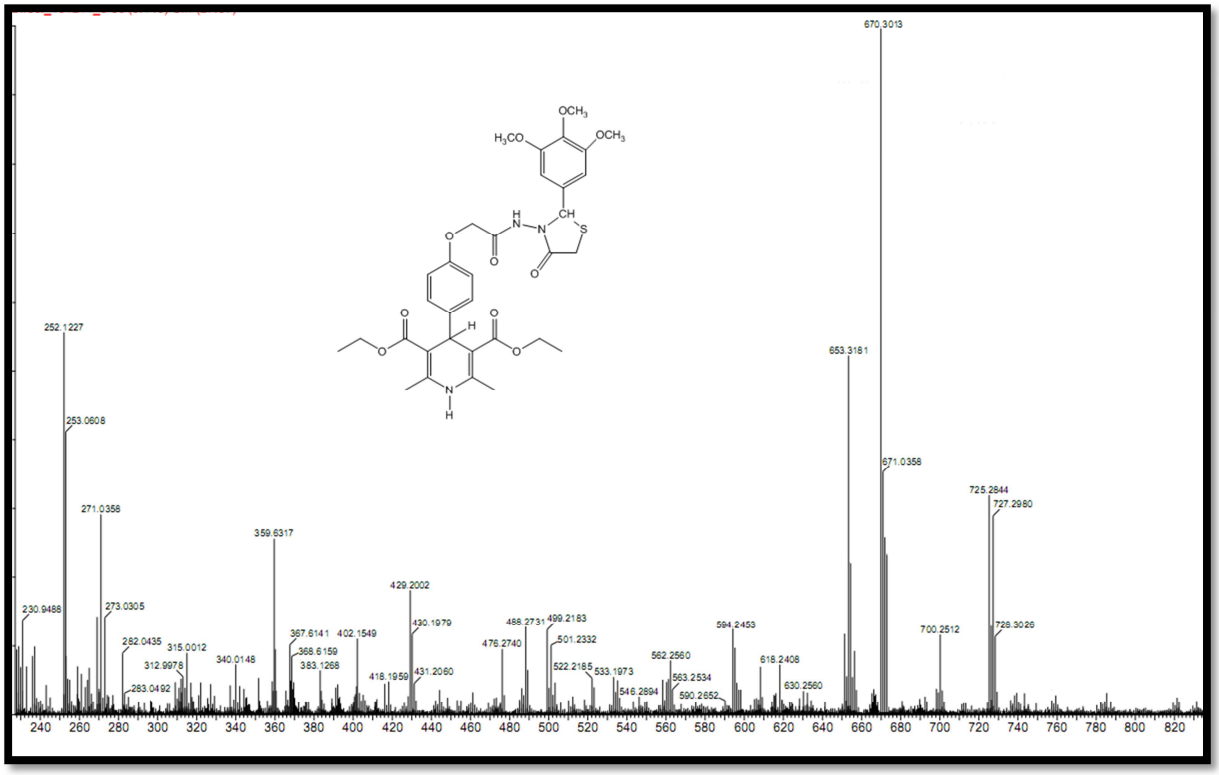


Figure 7. Mass spectrum of compound **7a**

In addition, as can be concluded from Table 2, the ESI reveals the observed [M+H] is in good agreement with calculated [M+H].

Table 2. ESI mass spectra data for DHPs thiazolidin-4-one derivatives

Compound	Structure	Calc. [M+H]	Found. [M+H]
4a	$C_{30}H_{32}ClN_3O_7S$	615.1096	615.2225
6a	$C_{32}H_{37}N_3O_9S$	640.6682	640.1580
7a	$C_{33}H_{39}N_3O_{10}S$	670.7428	670.3013
8a	$C_{32}H_{38}N_4O_7S$	623.7327	623.0603
9a	$C_{31}H_{35}N_3O_8S$	610.6909	610.2073
10a	$C_{32}H_{34}N_4O_7S$	619.7009	6192239
11a	$C_{30}H_{33}N_3O_8S$	596.6643	596.2102
12a	$C_{30}H_{33}N_3O_7S$	580.6649	580.2907
13a	$C_{32}H_{37}N_3O_7S$	608.7180	608.2568
14a	$C_{28}H_{31}N_3O_7S_2$	586.6936	586.2485
15a	$C_{30}H_{32}BrN_3O_7S$	659.5569	659.0400

2.2 Computational study

In present work, a non-local DFT method, B3LYP, was used to perform theoretical calculations on the studied compounds. The geometry of all compounds was fully optimized at the B3LYP level of theory along with standard 6-311+G(d,p) basis set which has amply been proven to give very good ground-state geometries. Also, no constraints were imposed on the structure during the geometry optimizations. The vibrational frequency analyses, calculated at the same level of theory, indicate that the optimized structures are at the stationary points corresponding to local minima without any imaginary frequency. The electronic properties were calculated using B3LYP/6-311+G(d,p) based on the optimized structures. The Gaussian 09 package was employed to perform optimization of structures and all the calculations. The results are discussed for compound **12** and the corresponding thiazolidin-4-one derivative, compound **12a** as cases study. The geometry optimization yields nonplanar structures.

2.2.1 Electronic properties

The frontier molecular orbitals, as the most important orbitals in a molecule, play a significant role in the electronic properties and determine the way the compound interacts with other species and provide useful information about the biological mechanism[45]. The HOMO (the highest occupied molecular orbital) represents the ability to donate an electron and LUMO (the lowest-lying unoccupied molecular orbitals) as an electron acceptor represents the ability to receive an electron. The frontier orbital gap, the energy gap between HOMO and LUMO represents the stability of structures and helps to characterize some significant issues including the kinetic stability as well as chemical reactivity of the compound. In order to evaluate the energetic behavior of the title compounds, we carried out calculations for compounds **12** and **12a**. Taking

the DFT result, the shapes of frontier molecular orbitals for these compounds have been demonstrated in Fig. 8.

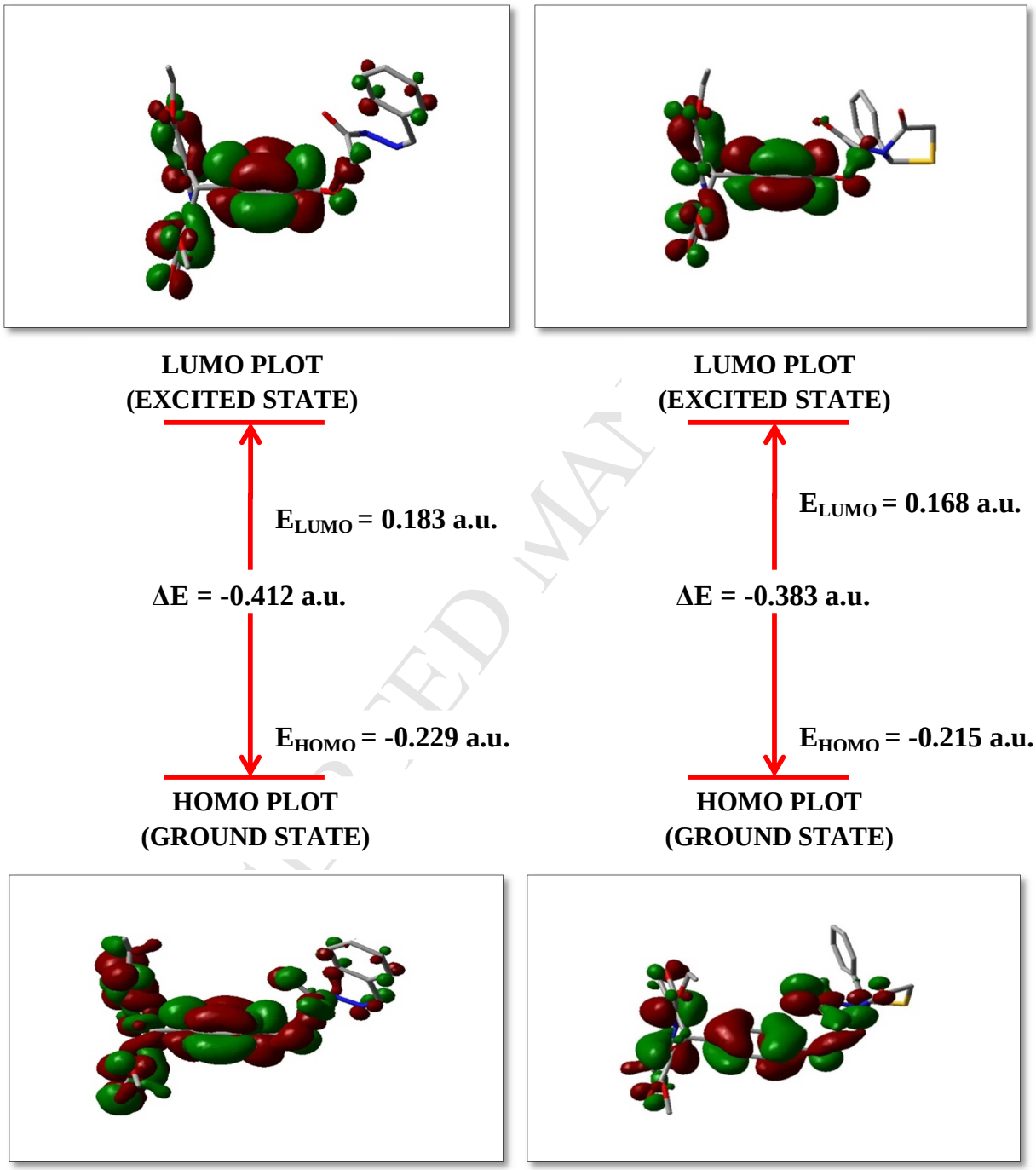


Figure 8. The atomic orbital compositions of the frontier molecular orbital of **12** and **12a**

It is seen that the HOMO of two compounds is mostly located on the benzene ring, azomethine group and partly related to acetate group. It is seen that for compound **12**, while the HOMO is localized on whole the pyridine ring, almost the benzene ring, and a part of azomethine group, the LUMO is localized mainly on the pyridine ring, almost the azomethine group. Also, for compound **12a** the benzene ring and thiazolidin-4-one has no contribution to the orbitals. High instability of this compound **12a** is due to the thiazolidin-4-one specific structural and electronic features. This small energy gap confirms high chemical reactivity as well as high polarizability.

2.2.2 NMR analysis

In order to a comparison between the experimental and theoretical NMR data, which may be helpful in making correct assignments and understanding the relationship between chemical shift and molecular structure, ^{13}C NMR chemical shifts calculation for further clarification of synthesized compounds are reported. To clarify the relation between theoretical and experimental values of NMR chemical shift constants, the experimental data are plotted vs. computed values. The ^{13}C NMR chemical shifts of all carbons were calculated on the optimized structures of compounds using B3LYP method employing 6-31+G(d,p) basis set for all atoms.

In order to compute the ^{13}C NMR chemical shifts, each couple of carbon atoms on equivalent locations of the compound was considered as equivalent and their average of chemical shifts were calculated.

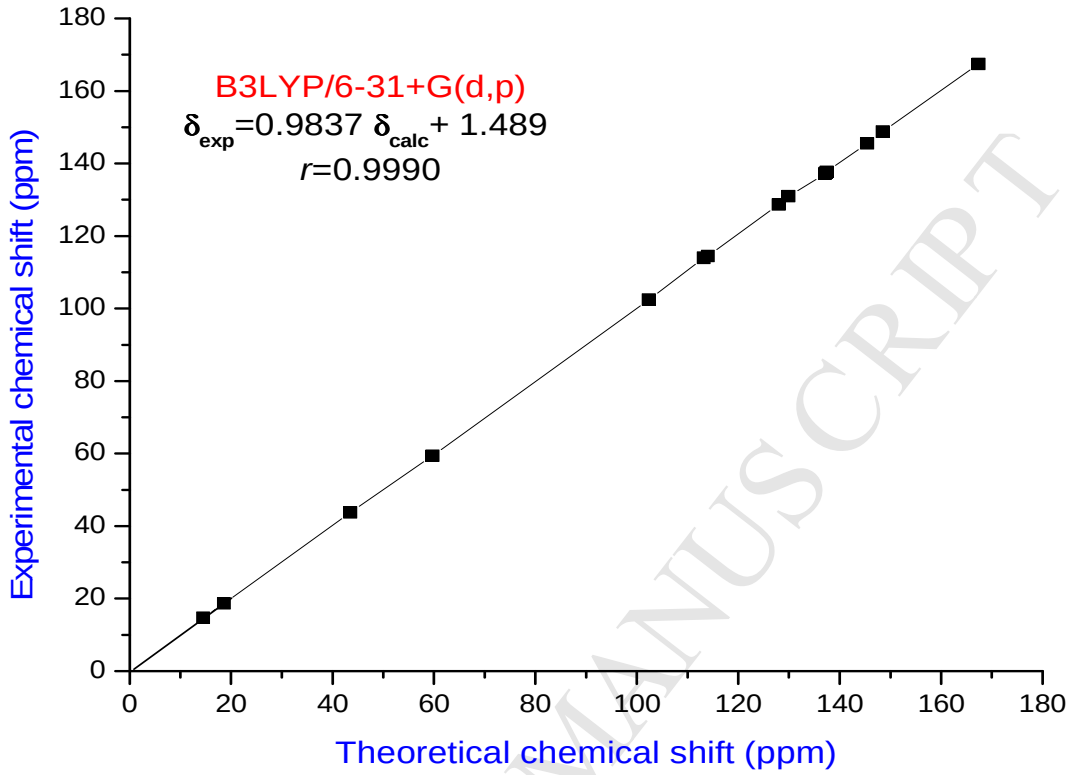


Figure 9. Experimental values vs. theoretical ^{13}C NMR chemical shifts of compound **10**

The statistical parameters of computed ^{13}C NMR chemical shifts along with experimental data for compound **10** are given in Fig. 9. As can be seen, the results are in reasonable agreement with experimental values.

3. Conclusion

Calcium channel blockers (CCBs) were developed in the 1970s and are now widely used. CCBs are drugs that block the entry of calcium into cardiac muscle and arteries. Among pharmacologically important heterocyclic compounds, 1,4-Dihydropyridine derivatives (DHPs) have long been used as CCBs in pharmacology. The biological activity of these compounds is

enhanced on undergoing bearing containing heterocyclic rings, particularly, the agents within the thiazolidine system have been of great scientific exploitation and interest as these are accompanied by almost all the biological profiles and pharmacological activities. In summary, a new series of 1, 4-Dihydropyridine derivatives bearing thiazolidin-4-one has been synthesized by three different conditions including Hantzsch condensation, fusion and microwave irradiation methods and characterized by structural, analytical and detailed spectroscopic methods. All newly synthesized compounds were structurally characterized by different spectroscopic methods including IR, ^{1}H and ^{13}C NMR, as well as mass analysis which they were used to identify the products. To additionally verify the proposed assignment, quantum chemical calculations were performed. Therefore, the structural and electronic properties of the studied compounds were theoretically investigated and the results were discussed.

4. Experimental protocols

4.1 Materials, instrumentation and spectral measurements

All starting materials were purchased from Merck, Sigma, Scharlau, Aldrich, J. S. Baker and used as received. 4-(dimethylamino) benzaldehyde, 4-methoxybenzaldehyde, benzaldehyde, 4-ethylbenzaldehyde, 4-hydoxybenzaldehyde, 4-nitrobenzaldehyde, 3, 4-dimethoxybenzaldehyde, 4-bromobenzaldehyde, 3, 4, 5-trimethoxybenzaldehyde were supplied from Aldrich. Hydrazine, ethylacetoacetate, thiophene -2-carbaldehyde, 2-mercaptoacetic acid, indol-3-carbaldehyde, 2-chloroethylacetate, 4-chlorobenzaldehyde were obtained from Merck. All solvents employed in synthesis were of extra-pure grade and used as received without further purification. Thin-layer chromatography (TLC) was carried out by using aluminum sheet coated with silica gel $60F_{254}$ (Merck), iodine and ultraviolet (UV) light was used for visualized TLC plates.

IR spectra were recorded by using Shimadzu FTIR-Affinity spectrophotometer in the region 4000–400 cm^{-1} in KBr pellet. The spectra were collected with a resolution of 2 cm^{-1} with 15 scans. The mass spectra were scanned by the EI technique at 70 eV with an Agilent Technologies 5975C spectrometer. The experimental values of ^{1}H and ^{13}C NMR spectra for the studied compounds were scanned on a Bruker Avance 400 MHz spectrometer with a field gradient operating at 400.122 MHz for proton observation and 100.61 MHz for carbon observation. TMS as the internal standard was used as referenced to 0.0 ppm and DMSO-d_6 was used as the solvent. The experiments were run in unlock mode, with sufficient a number of scans to achieve S/N ratios 200:1 (ca.). NMR spectra were obtained at a probe temperature of about 298 K. Melting points were recorded on a Fisher-Johns melting point apparatus.

4.2 Preparation methods

Two series of compounds were derived from DHPs. The first series of DHPs Schiff bases were synthesized from DHPs hydrazide with different aromatic aldehydes (Scheme 1). In the second series, the DHPs thiazolidinone were derived by hetero cyclization of the DHPs Schiff bases by using the cyclization agent (mercapto acetic acid) as an efficient route to synthesize substituted DHPs thiazolidin-4-one derivatives (Scheme 2).

1,1'-(4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)dipropan-1-one **(1)** was prepared by mixing (10.0 g, 81.8 mmol) of *p*-hydroxy benzaldehyde and (16.0 g, 123 mmol) of ethyl acetoacetate with (16.5 g, 123 mmol) of ammonium acetate in 100.0 mL of ethanol. The solution was refluxed for 16 h and poured on to crush ice. Then, it was filtered, washed with water and dried at room temperature. Recrystallization from ethanol/DMF afforded the purified crystals.

(Yield, 60%); mp 239-241°C; IR (KBr, cm^{-1}) 3348, 3101, 2985, 1661, 1612, 1591, 1510, 1489, 1369, 1226, 1130, 1022; ^{1}H NMR (DMSO-d6, δ/ppm) 1.13 (t, 6H, *J*=8, $CH_2C\underline{H}_3$), 2.23 (s, 6H, $C\underline{H}_3$), 3.98 (q, 4H, *J*=8, $OC\underline{H}_2CH_3$), 4.74 (s, 1H, C<u>H</u>), 6.57 (d, 2H, *J*=8, Ar-<u>H</u>), 6.92 (d, 2H, *J*=8, Ar-H), 8.70 (s, 1H, N<u>H</u>), and 9.08 (s, 1H, O<u>H</u>); ^{13}C NMR (DMSO-d6, δ/ppm), 167.5, 155.8, 145.2, 139.3, 128.7, 114.8, 102.7, 59.3, 38.2, 18.6, 14.6.

ethyl 2-(4-(2,6-dimethyl-3,5-dipropionyl-1,4-dihydropyridin-4-yl) phenoxy)acetate **(2)** was prepared by the addition of compound **1** (8.0 g, 23 mmol) to chloroethyl acetate (4.2 g, 34 mmol) and K_2CO_3 (4.6 g, 34 mmol) in 125 mL of DMF. The resulting mixture was stirred at 80 ^{o}C for 20 h. The reaction mixture was cooled down to room temperature and poured onto ice-water. The precipitate was filtered, washed with cold ethanol, and then dried in air.

(Yield 74%); mp 239-241^{o}C; IR (KBr, cm^{-1}) 3249, 3228, 3101, 2976, 1691, 1662, 1612, 1570, 1508, 1305, 1211, 1118, 1022; ^{1}H NMR (DMSO-d6, δ/ppm) 8.77 (S, 1H, N<u>H</u>), 7.04 (d, 2H, *J* = 8.6, Ar-<u>H</u>), 6.7 (d , 2H, *J* = 8.6, Ar-<u>H</u>), 4.79 (S, 1H, C<u>H</u>), 4.68 (S, 2H, $OC\underline{H}_2CO$), 4.15 (q, 2H, *J* = 8, $OC\underline{H}_2CH_3$), 3.98 (q, 4H, *J* = 4, $OC\underline{H}_2CH_3$), 2.24 (S, 6H, CH_3), 1.20 (t, 6H, *J*=8, CH_3), 1.13 (t, 6H, *J* = 8, $OCH_2C\underline{H}_3$); ^{13}C NMR (DMSO-d6, δ/ppm): 169.3, 167.4, 156.2, 145.6, 141.6, 128.7, 114.2, 102.4, 65.0, 61.0, 59.4, 38.2, 18.6, 14.6.

2-(4-(2,6-dimethyl-3,5-dipropionyl-1,4-dihydropyridin-4-yl) phenoxy)acetohydrazide **(3)**: An ethanolic solution (75 mL) of compound **2** (6.5 g, 15 mmol) was added to hydrazine monohydrate (2.4 g, 75 mmol). Then, the solution was heated under reflux for 4 h. The reaction mixture was cooled down to room temperature and poured on to crush ice. Recrystallization from ethanol/DMF afforded the purified white precipitate.

(Yield 81%); mp 191-192 ^{o}C; IR (KBr, cm^{-1}) 3346, 3254, 3102, 2981, 1743, 1689, 1624, 1504, 1366, 1305, 1276, 1205, 1089; ^{1}H NMR (DMSO-d6, δ/ppm): 9.20 (S, 1H, NH-NH$_2$), 8.77 (S, 1H, NH), 7.04 (d, 2H, *J* = 8.2, Ar-H), 6.75 (d, 2H, *J* = 8, Ar-H), 4.79 (S, 1H, CH), 4.40 (S, 2H, OCH$_2$CO), 4.30 (S, 2H, NHNH$_2$), 3.98 (q, 4H, *J*=4, OCH$_2$CH$_3$), 2.24 (S, 6H, CH$_3$), 1.13 (t, 6H, *J*=4, OCH$_2$CH$_3$); ^{13}C NMR (DMSO-d6, δ/ppm): 167.4, 167.2, 156.5, 145.6, 141.6, 128.7, 114.3, 102.5, 66.7, 59.4, 38.2, 18.68, 14.6.

4.3 General procedure for the synthesis of DHP- hydrazone (Schiff bases) (4-15)

Method A (Reflux Condensation method)

An ethanolic solution (25 mL) of Hydrazone **3** (0.5 g, 1.2 mmol) was mixed with (1.2 mmol) of aldehyde. The solution was acidified by adding 2 drops of glacial acetic acid and refluxed for 8 h. Then, the reaction mixture was concentrated by evaporation, and the precipitate of Schiff base complexes was collected by filtration, washed with hot water, ethanol and finally with a small portion of diethyl ether to extract all organic impurities solvent.

Method B (Fusion)

Compound (**3**) (1 mmol) was mixed with appropriate aldehydes (1 mmol). Then, the mixture was inserted into a pyrex beaker which was placed in an oil bath heat to fusion for the specified time Table 1). The progress of the reaction was monitored by TLC on completion the resulting mixture. The reaction mixture was extracted with ethyl acetate. The ethereal layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The Extracts were dried over anhydrous sodium sulfate, evaporated and recrystallized with a suitable solvent.

Method C (Microwave irradiation):

A simple and fast synthesis of DHPs hydrazone Schiff bases was performed by the microwave-assisted reaction, on neutral alumina. A mixture of compound **3** (1 mmol, 0.417 g) and

appropriate aldehydes (1 mmol) was inserted into a 200-ml pyrex beaker filled with neutral alumina and subjected to microwave irradiation for the specified time at its full power of 900 watts (Table 1). The completion of the reaction was monitored by TLC. The mixture was then cooled to room temperature and extracted with ethyl acetate. The concentration of the combined extracts under reduced pressure and recrystallization of the residue (EtOH) provided the title compounds (Table 2).

The physical properties and spectral data of prepared DHPs hydrazone are given below.

(E)-diethyl 4-(4-(2-(2-(4-chlorobenzylidene)hydrazinyl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4 dihydropyridine-3,5-dicarboxylate (**4**): recrystallized from DMF/EtOH; mp 246-248^{o}C; IR (KBr, cm^{-1}) 3298, 3234, 3099, 2980, 2900, 1691, 1660, 1612, 1506, 1490, 1215. ^{1}H NMR (DMSO-d6, δ/ppm): 11.62 (S, 1H, CONH), 8.77 (S, 1H, NH), 8.31 (S, 1H, CH=N), 7.7-6.8 (m, 8H, Ar-H), 5.06 (S, 1H, CH) , 4.8 (S, 2H, OCH_2CO), 3.9 (m, 4H, OCH_2CH_3), 2.5 (S, 6H, CH_3), 1.1 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 169.7, 167.5, 156.8, 156.4, 147.0, 145.5, 142.8, 141.7, 141.1, 138.6, 129.3, 129.0, 114.4, 114.2, 102.5, 66.9, 59.4, 43.1, 18.6, 14.6.

(E)-diethyl 4-(4-(2-(2-(4-nitrobenzylidene)hydrazinyl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5**): recrystallized from DMF/EtOH; mp 244-245^{o}C; IR (KBr, cm^{-1}) 3298, 3234, 3099, 2980, 2900, 1691, 1660, 1612, 1506, 1490, 1215. ^{1}H NMR (DMSO-d6, δ/ppm): 11.86 (S, 1H, CONH), 8.7 (S, 1H, NH), 8.3 (S, 1H, CH=N), 8.1- 6.76 (m, 8H, Ar-H), 5.11 (S, 1H, CH), 4.80 (S, 2H, OCH_2CO), 3.98 (m, 4H, OCH_2CH3), 2.24 (S, 6H, CH_3), 1.14 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 167.4, 165.4, 148.2, 145.5, 141.8, 130.0, 128.8, 128.4, 114.2, 102.5, 66.8, 59.4, 43.6, 18.6, 14.6.

(E)-diethyl 4-(4-(2-(2-(3,4-dimethoxybenzylidene)hydrazinyl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**6**): recrystallized from DMF/EtOH; mp 214-215 ^{o}C; IR (KBr, cm^{-1}) 3346, 3186, 3086, 2945, 2843, 1710, 1689, 1678, 1593, 1489, 1290. ^{1}H NMR (DMSO-d6, δ/ppm): 11.52 (S, 1H, CONH), 8.82 (S, 1H, NH), 8.37 (S, 1H, CH=N), 7.36- 6.89 (m, 7H, Ar-H), 5.12 (S,1H, CH), 4.85 (S, 2H, OCH_2CO), 4.63 (m, 4H, OCH_2CH_3), 3.85 (S, 3H, OCH_3), 3.83(S, 3H, OCH_3), 2.3(S, 6H, CH_3), 1.16 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 168.5, 167.1, 149.3, 128.4, 114.5, 111.8, 102.8, 59.3, 55.8, 50.1, 42.8, 18.6, 14.6.

(E)-diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(2-(3,4,5-trimethoxybenzylidene) hydrazinyl) ethoxy) phenyl) - 1,4-dihydropyridine-3,5-dicarboxylate (**7**): recrystallized from DMF/EtOH; mp 212-214^{o}C; IR (KBr, cm^{-1}) 3298, 3234, 3099, 2980, 1689, 1678,1647, 1506, 1492,1215; ^{1}H NMR (DMSO-d6, δ/ppm): 11.59 (S, 1H, CONH), 8.76 (S, 1H, NH), 7.91 (S, 1H, CH=N), 7.0-6.7 (m, 6H, Ar-H), 5.07 (S, 1H, CH), 4.8 (S, 2H, OCH_2CO),3.82 (m, 4H, OCH_2CH_3), 3.8(S, 6H, OCH_3) , 3,69(S, 3H, OCH_3), 2.24(S, 6H, CH_3), 1.16 (t, 6H, OCH_2CH_3);^{13}C NMR (DMSO-d6, δ/ppm): 169.7, 167.4, 164.8, 156.9,153.6, 130.0, 128.8, 128.6, 114.5, 114.2, 104.6, 102.9, 60.6, 59.4, 56.3, 18.6, 14.5.

(E)-diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(2-(4-dimethylaminobenzylidene) hydrazinyl) ethoxy) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8**): recrystallized from DMF/EtOH; mp 217-218 ^{o}C; IR (KBr, cm^{-1}) 3290, 3232, 3099, 2980, 1676, 1660, 1604,1504, 1442, 1220; ^{1}H NMR (DMSO-d6, δ/ppm): 11.27 (S, 1H, CONH), 8.76 (S, 1H, NH), 7.86 (S, 1H, CH=N), 7.5-6.7 (m, 8H, Ar-H), 5.01 (S, 1H, CH), 4.8 (S, 2H, OCH_2CO), 4.0 (m, 4H, OCH_2CH_3), 2.96 (S, 6H, N-CH_3), 2.24 (S, 6H, CH_3), 1.16 (S, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 169.0, 167.4, 156.6,152.0, 151.8, 145.50, 144.9, 128.9, 128.7, 128.6, 121.9, 114.3, 112.4, 102.6, 59.3, 18.7, 14.6.

(E)-diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(2-(4-methoxybenzylidene) hydrazinyl) ethoxy) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**9**): recrystalized from DMF/EtOH; mp 222-224^{o}C; IR (KBr, cm^{-1}) 3315, 3095, 2926, 1678,1643,1608,1504, 1444, 1215. ^{1}H NMR (DMSO-d6, δ/ppm): 11.43(S, 1H, CONH), 8.76(S, 1H, NH), 8.3(S, 1H, CH=N),7.9-6.7(m, 8H, Ar-H), 5.0(S, 1H, CH), 4.8(S, 2H, OCH_2CO),4.0(m, 4H, OCH_2CH_3), 3.98(S, 3H, OCH_3), 2.24(S, 6H, CH_3),1.16(S, 6H, OCH_2CH_3).^{13}C NMR (DMSO-d6, δ/ppm): 169.3, 167.5, 156.8, 145.5, 141.1, 129.1, 128.60, 127.8, 114.2, 102.4, 64.9,59.4, 55.7, 43.9,18.6, 14.6.

(E)-diethyl 4-(4-(2-(2-((1H-indol-3-yl)methylene)hydrazinyl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**10**). recrystallized from MeOH; mp 230-232 ^{o}C; IR (KBr, cm^{-1}) 3334, 3223, 3095, 2978, 1689, 1656, 1604, 1506, 1444, 1213; ^{1}H NMR (DMSO-d6, δ/ppm): 11.56 (S, 1H, CONH), 11.25 (S, 1H, NH-indol), 8.76 (S, 1H, NH), 8.32 (S, 1H, CH=N), 7.9-6.7 (m, 8H, Ar-H), 5.09 (S, 1H, CH), 4.8 (S, 2H, OCH_2CO), 3.97 (m, 4H, OCH_2CH_3), 2.24(S, 6H, CH_3), 1.15 (S, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 168.8, 167.4, 145.5, 137.7, 137.4, 137.1, 131.0,128.7, 114.5,114.0, 102.4, 59.4, 43.7, 18.6, 14.6.

(E)-diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(2-(4-hydroxybenzylidene) hydrazinyl) ethoxy) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**11**): recrystallized from MeOH; mp 237-239 ^{o}C; IR (KBr, cm^{-1}) 3334,3223, 3095, 2978, 1689, 1658, 1604,1506, 1444, 1213; ^{1}H NMR (DMSO-d6, δ/ppm): 11.4 (S, 1H, CONH), 9.6 (S, 1H, OH), 8.8 (S, 1H, NH), 7.9 (S, 1H, CH=N), 7.58-6.77 (m,8H, Ar-H), 5.07 (S, 1H, CH), 4.85 (S, 2H, OCH_2CO), 4.06 (m, 4H, OCH_2CH_3), 1.2(t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 169.1, 167.4, 148.6, 145.5, 144.5, 141.6, 129.4, 129.0, 128.77, 128.6, 116.3, 114.5, 114.2, 102.5, 56.0, 59.4, 118.7, 14.6.

(E)-diethyl 4-(4-(2-(2-benzylidenehydrazinyl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**12**): recrystallized from DMF/EtOH; mp 234-236 ^{o}C; IR (KBr, cm^{-1}) 3277, 3234, 3097, 2926, 1687, 1658, 1604, 1504, 1419, 1228; ^{1}H NMR (DMSO-d6, δ/ppm): 11.61 (S, 1H, CONH), 8.8 (S, 1H, NH), 8.0 (S, 1H, CH=N), 7.75-6.80 (m, 9H, Ar-H), 5.12 (S, 1H, CH), 4.86 (S, 2H, OCH$_2$CO), 4.06 (m, 4H, OCH$_2$CH$_3$), 2.3 (S, 6H, CH$_3$), 1.2 (t, 6H, OCH$_2$CH$_3$). ^{13}C NMR (DMSO-d6, δ/ppm): 169.6, 167.4, 164.8, 156.8, 156.4, 148.3, 145.5, 144.1, 141.2, 134.6, 134.4, 130.3, 130.4, 129.2, 128.8, 128.6, 127.5, 127.3, 102.4, 66.9, 65.08, 59.44, 18.6, 14.6.

(E)-diethyl 4-(4-(2-(2-(4-ethylbenzylidene)hydrazinyl)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**13**): recrystallized from MeOH; mp 231-232 ^{o}C; IR (KBr, cm^{-1}) 3286, 3238, 3099, 2972, 1676, 1660, 1504, 1232; ^{1}H NMR (DMSO-d6, δ/ppm): 11.56 (S, 1H, CONH), 8.82 (S, 1H, NH), 8.03 (S, 1H, CH=N), 7.67-6.80 (m, 8H, Ar-H), 5.1 (S, 1H, CH), 4.86 (S, 2H, OCH$_2$CO), 4.05 (m, 4H, OCH$_2$CH$_3$), 2.7 (m,2H, CH$_2$CH$_3$), 2.3 (S, 6H, CH$_3$), 1.2 (t, 6H, OCH$_2$CH$_3$), 1.19 (t, 3H, CH$_2$CH$_3$); ^{13}C NMR (DMSO-d6, 100 MHz, δ/ppm): 176.6, 146.5, 144.4, 132.0, 128.7, 128.7, 127.6, 127.4, 114.2, 102.5, 59.4, 28.5, 18.6, 14.7.

(E)-diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(2-(thiophen-3-ylmethylene)hydrazinyl)ethoxy) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**14**): recrystallized from DMF/ EteOH; mp 262-263 ^{o}C; IR (KBr, cm^{-1}) 3388, 3284, 3228, 3099, 2974, 1666, 1608, 1583, 1508, 1444, 1228; ^{1}H NMR (DMSO-d6, δ/ppm): 11.51 (S, 1H, CONH), 8.77 (S, 1H, NH), 8.1 (S, 1H, CH=N), 7.66-6.65 (m, 7H, Ar-H), 4.96(S,1H, CH), 4.8 (S, 2H, OCH$_2$CO), 4.0 (m,4H, OCH$_2$CH$_3$), 2.24(S, 6H, CH$_3$), 1.52 (t, 6H, OCH$_2$CH$_3$); ^{13}C NMR (DMSO-d6, δ/ppm): 167.4, 164.6, 145.7, 143.5, 139.3, 132.3, 129.5, 128.7, 128.6, 128.4, 114.4, 114.1, 102.5, 59.6, 18.6, 14.8.

(E)-diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(2-(4-bromobenzylidene) hydrazinyl) ethoxy) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**15**): recrystallized from DMF/ EteOH; mp 235-237 ^{o}C; IR (KBr, cm^{-1}) 3311, 3275, 3097, 2981, 1676, 1647, 1604, 1506, 1489, 1226; ^{1}H NMR (DMSO-d6, δ/ppm): 11.63 (S, 1H, CONH), 8.77 (S, 1H, NH), 7.97 (S, 1H, CH=N), 7.64-6.33 (m, 8H, Ar-H), 5.06 (S, 1H, CH), 4.8(S, 2H, OCH_2CO), 4.0(m, 4H, OCH_2CH_3), 2.24 (S, 6H, CH_3), 1.14 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm): 173.8, 165.2, 158.5, 151.8, 142.9, 135.4, 132.7, 131,2, 126.4, 114.7, 102.3, 68.7, 62.9, 42.8, 18.2, 16.6.

4.4 General procedure for the synthesis of DHP- Thiazolidin-4-one (4a-15a)

To the clear solution of dihydropyridine hydrazones of 4-15 (0.001 mol) in 20ml DMF, thioglycolic acid (0.001mol, 0.184 g) was added and zinc chloride (0.001 mmol) , the reaction mixtures was heated at 80–85 °C for 16 using an oil bath, After the completion of the reaction (TLC) monitoring using Hexane: EtOAc, 7:3, v/v. The mixture was poured in crash ice 150ml, the mixture neutralized with a saturated solution of sodium carbonate. After stirring for few minutes organic layer was separated and washed twice time with distilled water, recrystalized from suitable solvents.

diethyl 4-(4-(2-(2-(4-chlorophenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**): recrystallized from ethanol, Yield 53%,; mp 230-232 ^{o}C; IR (KBr, cm^{-1}) 3300, 3234, 3099, 2981, 1672. 1645, 1506, 1490, 1226; ^{1}H NMR (DMSO-d6, δ/ppm) 11.62 (S, 1H, CONH), 8.76 (S, 1H, NH), 7.72-6.74 (m, 8H, Ar-H), 5.9/5.45 (S, 1H, N-CH-S), 5.06 (S, 1H, CH), 4.8 (S, 2H, OCH_2CO), 3.99 (m, 4H, OCH_2CH_3), 3.88 (m, 1H, SCH_2), 3.65 (d, 1H, SCH_2), 2.24 (S, 6H, CH_3), 1.16 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm), 169.7, 167.4, 166.5, 147.0, 145.5, 130.5, 129.3, 129.2, 129.0, 128.8, 128.6, 114.5,

114.2, 102.4, 79.6, 74.9, 59.4, 43.2, 29.1, 28.7, 14.6; HRMS (ESI), $C_{30}H_{32}ClN_3O_7S$, calculated [M+H] 615.1096, observed [M+H] 615.2225.

diethyl 4-(4-(2-(2-(3,4-dimethoxyphenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**6a**): recrystallized from $CHCl_3$, (Yield 54%); mp 228-229 ^oC; IR (KBr, cm^{-1}) 3346, 3186, 3086, 2945, 2843, 1710, 1689, 1678, 1593, 1489, 1290; ^1H NMR (DMSO-d6, δ/ppm), 11.52/11.44 (d,1H, CONH), 8.84(S, 1H, NH), 7.21-6.91 (m,7H, Ar-H), 5.52 (S,1H, N-CH-S), 5.16 (S, 1H, CH), 4.80 (S, OCH_2CO), 3.65 (d, 1H, S-CH_2), 3.74(d, 1H, S-CH_2), 4.43 (m, 4H, OCH_2CH_3), 4.04 (S, 3H, OCH_3), 3.86 (S,3H, OCH_3), 2.3(S, 6H, CH_3), 1.19 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm), 168.7, 167.3, 165.0, 145.6, 139.4, 129.4, 128.8, 128.4, 114.5, 102.6, 79.8, 74.3, 67.7, 59.3, 50.2, 44.3, 28.7, 14.5; HRMS (ESI), $C_{32}H_{37}N_3O_9S$, calculated [M+H] 640.6682, observed [M+H] 640.1580.

diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(4-oxo-2-(3,4,5-trimethoxyphenyl)thiazolidin-3-ylamino)ethoxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**7a**): recrystallized from $CHCl_3$, (Yield 47%); mp 215-217 ^oC; IR (KBr, cm^{-1}) 3339, 3172, 3083, 2947, 2883, 1711, 1681, 1675, 1590, 1487, 1290; ^1H NMR (DMSO-d6, δ/ppm), 11.59/11.49 (S, 1H, CONH), 8.76 (S, 1H,NH), 7.0-6.73 (m, 6H, Ar-H), 6.54/ 5.65 (S, 1H, N-CH-S), 5.07 (S, 1H , CH), 4.84 (S, 2H, OCH_2CO), 4.80 (S, 2H, S-CH_2), 3.88 (m, 4H, OCH_2CH_3), 3.8 (S, 6H, OCH_3), 3.69 (S, 3H, OCH_3), 3.66 (m, 1H, S-CH_2), 3.51 (m, 1H, S-CH_2), 2.24 (S, 6H, CH_3), 1.14 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm), 167.7, 166.4, 165.0, 146.7, 139.4, 129.4, 127.9, 127.4, 114.6, 102.7, 8.9, 75.6, 67.8, 59.3, 50.3, 44.3, 28.8, 14.5; HRMS (ESI), $C_{33}H_{39}N_3O_{10}S$, calculated [M+H] 670.7428, observed [M+H] 670.3013.

diethyl 4-(4-(2-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**8a**): recrystallized from $CHCl_3$, (Yield

42%); mp 207-208 ^{o}C; IR (KBr, cm^{-1}) 3277, 3086, 3017, 2984, 2931, 1684, 1668, 1648, 1506, 1447, 1213; ^{1}H NMR (DMSO-d6, δ/ppm), 11.27/11.19 (S, 1H, CONH), 8.76 (S, 1H, NH), 8.0-6.8 (m, 8H, Ar-H), 6.41/5.65 (S, 1H, N-CH-S), 4.79(S, 1H, CH), 4.5 (S, 2H, OCH_2CO), 3.98 (m, 4H, OCH_2CH_3), 3.78 (d, 1H, S-CH_2), 3.76 (d, 1H, S-CH_2), 3.1(S, 6H, N-CH_3), 2.24(S, 6H, CH_3), 1.16 (t, 6H, OCH_2CH_3, J =7 MHz);^{13}C NMR (DMSO-d6, δ/ppm), 170.9, 167.4, 164.4, 145.6, 129.4, 129.0, 128.2, 114.3, 102.4, 79.78, 74.8, 59.1, 43.7, 28.0, 18.7, 14.6; HRMS (ESI), $C_{32}H_{38}N_4O_7S$, calculated [M+H] 623.7327, observed [M+H] 623.0603.

diethyl 4-(4-(2-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**9a**): recrystallized from $CHCl_3$, (Yield 49%); mp 190-192 ^{o}C; IR (KBr, cm^{-1}) 3300, 3087, 3029, 2981, 2929, 1691, 1668, 1660, 1508, 1438, 1207; ^{1}H NMR (DMSO-d6, δ/ppm), 11.43/11.38 (d, 1H, CONH), 8.76 (S, 1H,NH), 7.03-6.7 (m, 8H, Ar-H), 6.5/5.6 (S, 1H, N-CH-S), 5.03 (S, 1H, CH), 4.8 (S, 2H, OCH_2CO), 4.0 (m, 4H, OCH_2CH_3), 3.8(S, 3H, OCH_3), 3.63(d, 1H, S-CH_2), 3.52(d, 1H, S-CH_2), 2.24(S, 6H, CH_3), 1.14(t,6H, OCH_2CH_3). ^{13}C NMR (DMSO-d6, δ/ppm), 169.3, 167.5, 156.8, 145.5, 141.1, 129.4, 128.8, 128.6, 127.7, 114.6, 102.4, 64.9, 59.4, 55.7, 43.9, 28.6, 14.6; HRMS (ESI), $C_{31}H_{35}N_3O_8S$, calculated [M+H] 610.6909, observed [M+H] 610.2073.

diethyl 4-(4-(2-(2-(1H-indol-3-yl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**10a**): recrystallized from ethanol, (Yield 45%,); mp 221-222 ^{o}C; IR (KBr, cm^{-1}) 3267, 3086, 3027, 2980, 2931, 1689, 1678, 1658, 1506, 1442, 1215; ^{1}H NMR (DMSO-d6, δ/ppm), 11.61 (S, 1H, CONH), 11.25 (S, 1H, NH-indol), 8.76 (S, 1H, NH), 7.81-6.75 (m, 9H, Ar-H), 6.56/5.21 (S, 1H, N-CH-S), 5.06 (S, 1H, CH), 4.80 (S, 2H, OCH_2CO), 4.02 (m, 4H, OCH_2CH_3), 3.80 (d, 1H, S-CH_2), 3.72 (d, 1H, S-CH_2), 2.24 (S, 6H,

CH_3), 1.14 (t, 6H, OCH_2CH_3); HRMS (ESI), $C_{32}H_{34}N_4O_7S$, calculated [M+H] 619.7009, observed [M+H] 619.2239.

diethyl 4-(4-(2-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**11a**): recrystallized from acetone. (Yield 40%); mp 166-168 ^oC; IR (KBr, cm^{-1}) 3284, 3219, 3095, 2980, 2929, 1685, 1654, 1647, 1508, 1444, 1203; ^1H NMR (DMSO-d6, δ/ppm), 11.35/11.30 (S, 1H, CONH), 9.89 (S, 1H, OH), 8.76 (S, 1H, NH), 7.89-6.73(m, 8H, Ar-H), 6.53/5.70 (S, 1H, N-CH-S), 5.01 (S, 1H, CH), 4.80(S, 2H, OCH_2CO), 4.0(m, 4H, OCH_2CH_3), 3.77 (d, 1H, S-CH_2, J= 21.72 MHz), 3.54 (d, 1H, SCH_2, J= 22.8 MHz), 2.24 (S, 6H, CH_3), 1.14 (t, 6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm), 169.4, 167.0, 164.7, 145.1, 129.6, 129.0, 128.4, 116.1, 114.5, 102.2, 79.6, 74.3, 59.4, 43.5, 28.7, 14.6. HRMS (ESI), $C_{30}H_{33}N_3O_8S$, calculated [M+H] 596.6643, observed [M+H] 596.2102.

diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(4-oxo-2-phenylthiazolidin-3-ylamino) ethoxy) phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**12a**): recrystallized from $CHCl_3$, (Yield 55%); mp 213-215 ^oC; IR (KBr, cm^{-1}) 3319, 3261, 3097, 2983, 1721, 1648, 1514, 1485, 1225; ^1H NMR (DMSO-d6, δ/ppm), 11.57/11.62 (S, 1H, CONH), 8.82 (S, 1H, CH), 8.06-6.80 (m, 9H, Ar-H), 6.56/5.51 (S, 1H, N-CH-S), 5.12 (s, 1H, CH), 4.85 (S, 2H,OCH_2CO), 4.06 (m, 4H, OCH_2CH_3), 3.89 (m, 1H, S-CH_2,), 3.72(m, 1H, S-CH_2), 2.3 (s, 6H, CH_3), 1.12 (t,6H, OCH_2CH_3); ^{13}C NMR (DMSO-d6, δ/ppm), 169.5, 167.4, 164.9, 148.3, 145.4, 144.1, 129.4, 129.2, 128.6, 127.4, 114.2, 102.4, 79.3, 74.1, 65.0, 59.4, 43.5, 28.6, 18.7, 14.6; HRMS (ESI), $C_{30}H_{33}N_3O_7S$, calculated [M+H] 580.6649, observed [M+H] 580.2907.

diethyl 4-(4-(2-(2-(4-ethylphenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**13a**): recrystallized from acetone, (Yield 57%);

mp 209-211 ^{o}C; IR (KBr, cm^{-1}) 3292, 3099, 2972, 1678, 1654, 1643, 1500, 1222; ^{1}H NMR (DMSO-d6, δ/ppm), 11.56/11.50 (S, 1H, CONH), 8.81 (S, 1H, NH), 7.67-6.82 (m, 8H, Ar-H), 6,65/5.61 (S, 1H, N-CH-S), 5.10 (S, 1H, CH), 4.86 (S, 2H, OCH$_2$CO), 4.05 (m, 4H, OCH$_2$CH$_3$), 3.82 (d,1H, S-CH$_2$ J= 13.52 MHz), 3.74(d, 1H, S-CH$_2$, J= 12.36 MHz),), 2.73 (m, 3H, CH$_2$CH$_3$), 2.3 (S, 6H, CH$_3$), 1.2 (m, 3H, CH$_2$CH$_3$), 1.19 (m, 6H, OCH$_2$CH$_3$); ^{13}C NMR (DMSO-d6, δ/ppm), 170.7, 167.6, 165.9, 148.3, 144.2, 128.7, 128.7, 128.7, 128.6, 128.6, 127.6, 127.4, 127.4, 114.4, 114.2, 79.5, 66.5, 59.4, 43.3, 28.54, 18.69, 15.8, 15.7, 14.6; HRMS (ESI), $C_{32}H_{37}N_3O_7S$, calculated [M+H] 608.718 , observed [M+H] 608.2568.

diethyl 2,6-dimethyl-4-(4-(2-oxo-2-(4-oxo-2-(thiophen-3-yl)thiazolidin-3-ylamino) ethoxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**14a**): recrystallized from ethanol, (Yield 52%); mp 108-110 ^{o}C; IR (KBr, cm^{-1}) 3311, 3095, 2978, 1686, 1678, 1647, 1506, 1442, 1213; ^{1}H NMR (DMSO-d6, δ/ppm), 11.54/11.47 (S, 1H, CONH), 8.76 (S,1H, NH), 7.66-6.80 (m, 7H, Ar-H), 6.85/5.63 (S, 1H, N-CH-S), 4.96 (S, 1H, CH), 4.80 (S, 2H, OCH$_2$CO), 3.99(m, 4H, OCH$_2$CH$_3$), 3.61(m, 1H, S-CH$_2$), 3.53(m,1H, S-CH$_2$) 2.24 (S, 6H, CH$_3$), 1.13 (t, 6H, OCH$_2$CH$_3$); ^{13}C NMR (DMSO-d6, δ/ppm), 169.2, 167.1, 166.1, 145.6, 129.4, 128.8, 128.2, 114.5, 113.8, 102.8, 87.4, 74.2, 68.8, 67.0, 59.3, 43.0, 28.4, 18.6, 14.6; HRMS (ESI), $C_{28}H_{31}N_3O_7S_2$, calculated [M+H] 586.6936, observed [M+H] 586.2485.

diethyl 4-(4-(2-(2-(4-bromophenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**15a**): recrystallized from ethanol, (Yield 55%); mp 219-220^{o}C; IR (KBr, cm^{-1}) 3313, 3277, 3097, 2980, 1718, 1653, 1504, 1489, 1228; ^{1}H NMR (DMSO-d6, δ/ppm), 11.62/11.59 (S, 1H, CONH), 8.76 (S, 1H, NH), 7.64-6.74 (m, 8H, Ar-H), 6.74/5.67 (S, 1H, N-CH-S), 5.06 (S, 1H, CH), 4.8 (S, 2H, OCH$_2$CO), 3.99(m, 4H, OCH$_2$CH$_3$), 3,62 (m, 1H, S-CH$_2$), 3.59(m, 1H, S-CH$_2$), 2.24 (S, 6H, CH$_3$), 1.14 (t, 6H, OCH$_2$CH$_3$); ^{13}C NMR

(DMSO-d6, δ/ppm), 170.7, 167.6, 164.2, 145.5, 142.9, 133.8, 132.2, 129.4, 129.2, 128.6, 114.2, 79.2, 74.0, 66.1, 59.1, 43.9, 28.0, 18.7, 14.6; HRMS (ESI), $C_{30}H_{32}BrN_3O_7S$, calculated [M+H] 659.5569, observed [M+H] 659.0400.

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ACCEPTED MANUSCRIPT

- A novel series of 1, 4-Dihydropyridine (DHP) thiazolidin-4-one compounds derived from dihydropyridine hydrazones Schiff bases with thioglycolic acid were synthesized through an efficient Hantzsch reaction.

- Compounds were experimentally characterized using IR, ^{1}H and ^{13}C NMR as well as mass spectroscopy.

- The spectral and structural properties as well as electronic analysis of compounds were presented.

- The theoretical calculations were performed using B3LYP as the more popular DFT method.

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