Erzincan Üniversitesi
Fen Bilimleri Enstitüsü Dergisi
2021, 14(1), 93-116
ISSN: 1307-9085, e-ISSN: 2149-4584
Araştırma Makalesi

Erzincan University
Journal of Science and Technology
2021, 14(1), 93-116
DOI: 10.18185/erzifbed.856269
Research Article

Quantum Chemical Investigation of a Series of 5-substituted 2,4-thiazolidinedione Derivatives as Antineurodegenerative Agents

Nazmiye Sabancı[1*]

[1]Siirt University, Science and Arts Faculty, Department of Chemistry, Siirt, Turkey

Geliş / Received: 08/01/2021, Kabul / Accepted: 11/02/2021

Abstract

A series of 5-substituted 2,4-thiazolidinedione derivatives which exhibit different pharmacological properties such as anti-hyperglycemic, anticancer, antioxidant and anti-neurodegenerative has been quantum chemically investigated to clarify elucidated electronic and geometrical features. B3LYP functional with three different basis sets including 6-31G, 6-31G(d) and 6-31G(d,p) was made use of to optimize the three-dimensional structures of the compounds. Mulliken charges, dipole moments, energies of the HOMO and LUMO were also calculated with the same methods. The calculated geometrical parameters were compared with the experimental data to analyze the results of the different basis set. According to the quantum chemical calculation results obtained, the theoretical bond lengths and angles show good compatibility with the experimental data. Based on the HOMO and LUMO energy gap analysis, compound 24 was found to be the most reactive one in the 5-substituted 2,4-thiazolidinedione derivatives under study.

Keywords: Alzheimer's disease, antineurodegenerative, density functional theory, thiazolidinedione.

Antinörodejeneratif 5-sübstitüe 2,4-tiyazolidindion Türevlerinin Kuantum Kimyasal İncelemesi

Öz

Antihiperglisemik, antikanser, antioksidan ve antinörodejeneratif gibi farklı farmakolojik özellikler gösteren 5-sübstitüe 2,4-tiazolidindion türevleri, elektronik ve geometrik özelliklerini aydınlatmak amacıyla kuantum kimyasal olarak incelenmiştir. Bileşiklerin üç boyutlu yapıları B3LYP fonksiyoneli ile üç farklı temel set (6-31G, 6-31G(d) ve 6-31G(d,p)) kullanılarak optimize edilmiştir. Mulliken yükleri, dipol momentleri, HOMO ve LUMO enerjileri de aynı yöntem ile hesaplanmıştır. Hesaplanan geometrik parametreler, farklı temel setler için deneysel sonuçlar ile karşılaştırılmıştır. Elde edilen kuantum kimyasal hesaplama sonuçlarına göre, teorik bağ uzunlukları ve açıları deneysel verilerle uyum içerisindedir. HOMO ve LUMO enerji değerleri farkı analiz edildiğinde, ele alınan 5-sübstitüe 2,4-tiazolidindion türevleri içerisinde 24 numaralı bileşiğin en reaktif bileşik olduğu belirlenmiştir.

Anahtar Kelimeler: Alzheirmer, antinörodejeneratif, yoğunluk fonksiyonel teorisi, tiyazolidindion.

1. Introduction

Alzheimer's disease (AD) is a permanent neurodegenerative brain disorder that leads to devastation of memory, mental functions and cognitive ability, and inability to perform daily life skills (Masters et al., 2015; Gonzales et al., 2019). AD is an age-dependent illness and the frequency of the AD increases by ageing, which is inevitable. The number of people having AD or other dementias increased by the year (Alzheimer's Association, 2019). ADI (Alzheimer's Disease International), reports that the estimated number of people with dementia including AD is around 50 million in the world. By 2050, this number is expected to reach 152 million (Balsinha et al., 2019).

Although the number of AD-relevant researches has risen, there are still no potent drug or treatment to prevent or decelerate the advance of the AD (Gonzales et al., 2019; Qui and Fratiglioni, 2018). The therapeutic procedures and available drugs with side effects are only able to relieve some symptoms of the disease (Masters et al., 2015; Gonzales et al., 2019; Ulep et al., 2018; Yiannopoulou and Papageorgiou, 2013). Today, immediately development of novel effective AD drugs which can stop, slow or modify the disease is curial for AD therapy. Due to the difficulty in the development of drugs for AD, only five drugs are available for AD treatment including tacrine, donepezil (Holmes, 2004), rivastigmine (Desai and Grossberg, 2001) and galantamine (10) as cholinesterase inhibitors, and memantine as D-aspartate receptor antagonist (Lao et al., 2019; Hyde et al., 2013; Cummings et al., 2014).

AD has a multifactorial and complex nature, arising from genetic, environmental and other endogenous factors, and the action mechanism of this neurodegenerative disease, which cannot be described by a single theory, is still unclear (Liu et al., 2019). Conventional drug molecules have been developed to interact with a sole target protein with high selectivity to handicap undesirable off-target results. Single-molecular target drugs generally adopt acetylcholinesterase inhibition for the treatment of AD and do not offer an entire remedy (Gonzales et al., 2019; Hughes et al., 2016). Additionally, most of the forthcoming treatments under clinical trials are based on one target one ligand paradigm (Kumar et al., 2018). Because of the limited efficiency of existing therapeutic agents, research interest tends to focus on multi target-directed ligands (MTDLs) instead of a single target. MTDLs are expected to be impact different targets simultaneously to accomplish the regulation of several characteristics of the disease pathology altogether. However, one of the most challenging points of MTDLs is to retain the optimum balance of potencies towards each of the relevant targets with the minimum unwanted effects (Prati et al., 2016; Ramsay et al., 2018). Even so, novel MTDLs that are well designed at the hypothetical, biomolecular and chemical level would help the clarification of disease mechanism and guide us to develop more potent therapeutic agents. By avoiding over explored strategies, focusing on new or different hypothesis would be useful for the moderation of the neuronal damage.

In this context, computational techniques such as QSAR, molecular docking, pharmacophore identification, calculation of binding energies and other sophisticated quantum chemical methods have a crucial role in the discovery of new lead compounds.

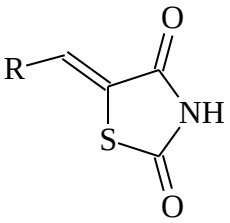
Thiazolidinedione (TZD) is a five-membered heterocyclic ring system including Sulphur at 1 position, carbonyl groups at 2 and 4 positions, nitrogen at 3 position. Binding of different substituents at different positions of TZD imparts it a wide variety of pharmacological behaviours (Naim et al., 2017) such as antioxidant (Reddy et al., 1998), antiviral (Bahare et al., 2015), anti-hyperglycemic (Day, 1999), anticancer (Patil et al., 2010) efficiency. Because TZDs can control different biological targets selectively, they are still focused on research interests. Besides many pharmacological features, TZDs are also found to be declined the neurodegeneration for AD (Perez and Quintanilla, 2015).

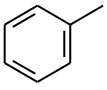
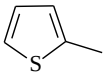
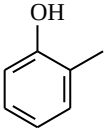
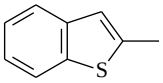
The main objective of the current study is to reveal the electronic and geometric dynamics of 2,4-thiazolidinedione derivatives which direct chemical attitudes and interactions during the biochemical reactions. Although different 2,4-thiazolidinedione derivatives were theoretically investigated by other researchers (Enchev, 1994; Tahmassebi, 2003; Safi, 2016; Fatma et al., 2018; Rančić, 2019), quantum chemical calculations and other molecular modelling studies for 5-substituted 2,4-thiazolidinedione derivatives, including different aromatic and heterocyclic substituents, have not been documented yet according to the literature survey. In this study, thirty-five 2,4-thiazolidinedione derivatives, which was reported that simultaneously inhibiting glycogen synthase kinase 3β (GSK-3β) and tau aggregation process (Gandini et al., 2018), were investigated with quantum chemical calculations in order to clarify electronic and geometrical features. The structures of the compounds are listed in Table 1.

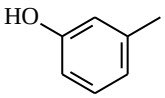
2. Computational Details

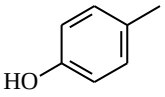
In the current study, geometries of the compounds given in Table 1 were optimized by the Gaussian 09 program (M.J. Frisch et al., 2009) using Density Functional Theory (DFT) method at the B3LYP (Lee et al., 1988; Becke, 1993a and b) functional with three different basis sets (6-31G, 6-31(d), 6-31G(d,p)) in the gas phase. The true minima of the optimized structures were confirmed by the positive vibrational frequency values. Mulliken charges are calculated to characterize the electronic charge distribution in the compounds.

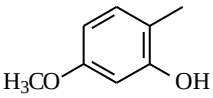
Table 1. Chemical structures and substituents of 2,4-thiazolidinedione derivatives studied

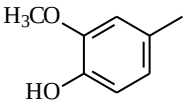


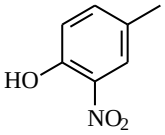
Comp. No	R	Comp. No	R
1		**19**	
2		**20**	

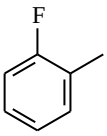
3 

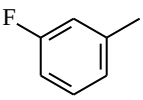
4 

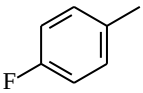
5 

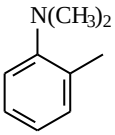
6 

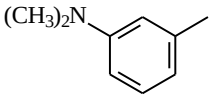
7 

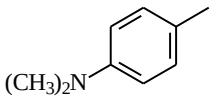
8 

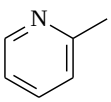
9 

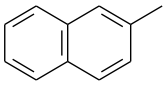
10 

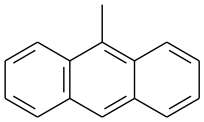
11 

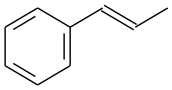
12 

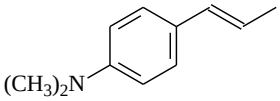
13 

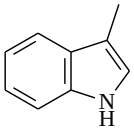
14 

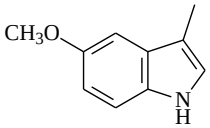
21 

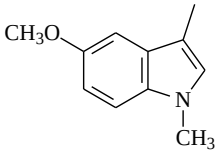
22 

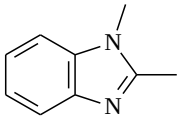
23 

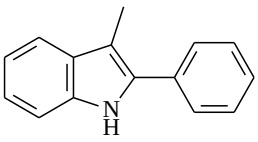
24 

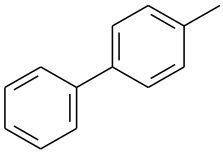
25 

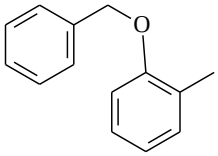
26 

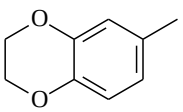
27 

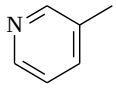
28 

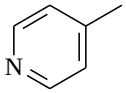
29 

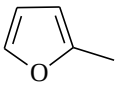
30 

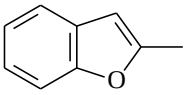
31 

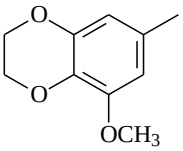
32 

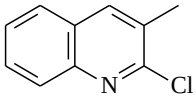
15 

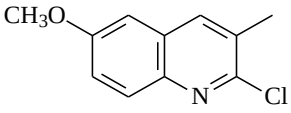
16 

17 

18 

33 

34 

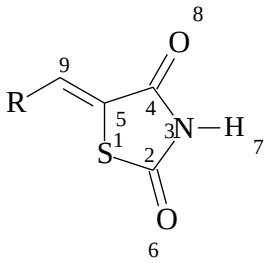
35 

3. Results and Discussion

Since AD has a lack of effective treatment, it is important to search for new lead compounds for further studies. One of the research focus is MTDLs. As a promising MTDL, various studies showed that utilization of TZDs in the AD therapy is important and gives favorable results. The capability of constructing interaction with different target proteins results from their electronic, geometric and hydrogen bond donor/acceptor characteristics. In the current study, we analyzed the thirty-five 2,4-thiazolidinedione derivatives with DFT/B3LYP method for better illumination of their electronic and geometric structure and interaction way over the frontier orbitals.

The geometrical parameters including bond length and angles of the optimized structures in the gas phase are given in tables for three different basis sets (B3LYP/6-31G, 6-31G(d), 6-31G(d,p)). Experimental values for unsubstituted 2,4-thiazolidinedione were taken from the literature (Form et al., 1975) in order to make a comparison. For 2,4-thiazolidinedione derivatives, selected bond lengths optimized by B3LYP/6-31G method and their experimental values (Form et al., 1975) are given in Table 2 along with atom numbering of the main skeleton. In this table, we can see that calculated bond length values by B3LYP/6-31G agree well with the experimental values in general. The apparent difference between the experimental and theoretical values maybe because of the structural difference between the substituted and unsubstituted TZD. The calculated C4-C5 bond length of compounds are between 1.464-1.547Å. The experimental bond length of C4-C5 bond length (1.547 Å) is longer than the calculated values of those. This situation arises from the double bond between the C9 and C5 atoms in the substituted TZD data set which leads to conjugation (between C9-C5, C5-C4 and C4-O8 bonds) in the compound through the delocalization of the π-electrons to the entire system. So, the calculated C4-C5 bonds in the data set have a value between the single (1.54 Å) and double bond (1.34 Å) values. The most significant variance from the experimental data is for the bond between C2 and S1 atoms. It has an average deviation value of 0.12. Additionally, N3-H7, C4-O8 and C2-N3 bonds are in good agreement with experimental values.

Table 2. Selected experimental and calculated bond lengths (in Å) of 2,4-thiazolidinedione derivatives obtained at B3LYP/6-31G level of theory



Bonds	S1-C5	S1-C2	C2-N3	N3-C4	C4-C5	C2-O6	N3-H7	C4-O8
Experimental	1.845	1.751	1.372	1.373	1.547	1.209	0.900	1.219
1	1.839	1.876	1.383	1.401	1.479	1.224	1.012	1.243
2	1.842	1.875	1.382	1.404	1.478	1.225	1.012	1.244
3	1.839	1.875	1.384	1.400	1.480	1.224	1.012	1.243
4	1.840	1.876	1.382	1.402	1.476	1.225	1.012	1.244
5	1.843	1.874	1.381	1.405	1.475	1.226	1.012	1.244
6	1.839	1.875	1.383	1.402	1.477	1.225	1.012	1.244
7	1.835	1.879	1.384	1.399	1.482	1.223	1.012	1.242
8	1.839	1.878	1.382	1.402	1.481	1.224	1.012	1.242
9	1.837	1.878	1.383	1.400	1.482	1.223	1.012	1.242
10	1.838	1.878	1.383	1.401	1.480	1.224	1.012	1.243
11	1.845	1.874	1.383	1.403	1.475	1.225	1.012	1.244
12	1.840	1.878	1.382	1.402	1.481	1.224	1.012	1.242
13	1.843	1.874	1.381	1.406	1.470	1.226	1.012	1.246
14	1.839	1.878	1.382	1.402	1.483	1.223	1.012	1.240
15	1.837	1.879	1.383	1.400	1.482	1.223	1.012	1.242
16	1.835	1.879	1.384	1.399	1.484	1.223	1.012	1.241
17	1.834	1.876	1.386	1.399	1.476	1.225	1.012	1.244
18	1.833	1.876	1.387	1.399	1.477	1.225	1.012	1.244
19	1.836	1.879	1.383	1.401	1.474	1.224	1.012	1.244
20	1.836	1.878	1.383	1.401	1.476	1.224	1.012	1.244
21	1.840	1.875	1.383	1.402	1.478	1.224	1.012	1.243
22	1.841	1.875	1.387	1.399	1.482	1.225	1.012	1.243
23	1.840	1.878	1.384	1.404	1.470	1.225	1.012	1.244
24	1.843	1.876	1.382	1.407	1.464	1.226	1.012	1.246
25	1.840	1.878	1.381	1.407	1.467	1.225	1.012	1.245
26	1.840	1.878	1.380	1.408	1.466	1.226	1.012	1.245
27	1.841	1.877	1.380	1.408	1.465	1.226	1.012	1.246
28	1.827	1.880	1.390	1.395	1.480	1.226	1.012	1.244
29	1.839	1.873	1.384	1.402	1.474	1.226	1.012	1.245
30	1.839	1.876	1.383	1.402	1.478	1.224	1.012	1.243
31	1.843	1.874	1.381	1.404	1.477	1.225	1.012	1.243
32	1.840	1.875	1.382	1.402	1.476	1.225	1.012	1.244
33	1.838	1.875	1.383	1.402	1.478	1.224	1.012	1.243
34	1.837	1.881	1.381	1.402	1.483	1.223	1.012	1.240
35	1.834	1.876	1.388	1.396	1.487	1.223	1.012	1.241

Analogously, selected bond lengths optimized by B3LYP/6-31G(d) and B3LYP/6-31G(d,p) methods associated with their experimental values (Form et al., 1975) are given in Table 3 and Table 4, respectively. Carefully examination of these tables shows that optimization by the 6-31G(d) and 6-31G(d,p) methods give more harmonious results compared to the 6-31G method. In Table 3, the most remarkable deviation from the experimental value was seen in S1-C5 bond (0.068) and S1-C2 bond (0.065). The deviation for S1-C5 bond was increased while S1-C2 bond length deviation was decreased by the method 6-31G(d). There is no significant change for C2-N3 bond length by changing the basis set. However, we obtained more compatible results for N3-C4, C2-O6 and C4-O8 bond length by 6-31G(d) compared to the 6-31G method. Especially, the difference between experimental and theoretical values for C2-O6 (average 0.04) and C4-O8 (average 0.02) bonds was decreased. Although a larger basis set gives a better result for the C4-C5 bond, it is still shorter than the experimental value due to the conjugated double bond as is the case with Table 2.

Table 3. Calculated bond lengths (in Å) of 2,4-thiazolidinedione derivatives obtained at B3LYP/6-31G(d) level of theory

Bonds	S1-C5	S1-C2	C2-N3	N3-C4	C4-C5	C2-O6	N3-H7	C4-O8
Experimental	1.845	1.751	1.372	1.373	1.547	1.209	0.900	1.219
1	1.777	1.816	1.383	1.396	1.492	1.205	1.013	1.216
2	1.779	1.816	1.382	1.398	1.491	1.205	1.013	1.216
3	1.776	1.816	1.383	1.395	1.493	1.205	1.013	1.216
4	1.778	1.816	1.382	1.397	1.488	1.205	1.013	1.217
5	1.780	1.815	1.381	1.399	1.487	1.206	1.013	1.217
6	1.778	1.815	1.383	1.397	1.489	1.205	1.013	1.217
7	1.773	1.819	1.384	1.394	1.494	1.204	1.013	1.216
8	1.776	1.817	1.382	1.396	1.493	1.204	1.013	1.215
9	1.775	1.817	1.383	1.395	1.494	1.204	1.013	1.215
10	1.776	1.817	1.382	1.396	1.492	1.204	1.013	1.216
11	1.781	1.814	1.383	1.397	1.489	1.206	1.013	1.217
12	1.778	1.814	1.383	1.396	1.491	1.205	1.013	1.217
13	1.780	1.814	1.381	1.400	1.483	1.206	1.013	1.218
14	1.776	1.818	1.382	1.396	1.496	1.204	1.014	1.214
15	1.775	1.819	1.383	1.395	1.494	1.204	1.014	1.215
16	1.773	1.819	1.383	1.394	1.497	1.203	1.014	1.214
17	1.774	1.814	1.385	1.395	1.487	1.206	1.013	1.217
18	1.772	1.815	1.386	1.394	1.489	1.205	1.013	1.217
19	1.775	1.818	1.383	1.397	1.486	1.205	1.013	1.217
20	1.775	1.818	1.383	1.396	1.489	1.205	1.013	1.217
21	1.778	1.816	1.383	1.396	1.492	1.205	1.013	1.216
22	1.778	1.813	1.387	1.393	1.494	1.205	1.013	1.216
23	1.777	1.817	1.384	1.398	1.484	1.205	1.013	1.217
24	1.780	1.815	1.383	1.401	1.478	1.206	1.013	1.219

25	1.777	1.817	1.381	1.401	1.480	1.206	1.013	1.218
26	1.778	1.817	1.380	1.402	1.479	1.206	1.013	1.218
27	1.779	1.817	1.380	1.402	1.478	1.206	1.013	1.218
28	1.765	1.817	1.390	1.390	1.492	1.206	1.013	1.217
29	1.777	1.812	1.384	1.397	1.487	1.207	1.013	1.218
30	1.777	1.816	1.382	1.396	1.491	1.205	1.013	1.216
31	1.780	1.815	1.382	1.398	1.490	1.206	1.013	1.216
32	1.778	1.815	1.382	1.397	1.489	1.205	1.013	1.217
33	1.777	1.815	1.382	1.396	1.490	1.205	1.013	1.217
34	1.776	1.819	1.382	1.395	1.495	1.204	1.014	1.214
35	1.773	1.813	1.387	1.391	1.500	1.204	1.013	1.215

Table 4 presents the results of the bond lengths obtained by B3LYP/6-31G(d,p). As previously mentioned for Table 3, the significant difference between the X-ray data and optimized bond lengths was observed for S1-C5 (0.068) and S1-C2 (0.065) bonds. We can say that optimized values for C2-N3 and N3-C4 bonds converged slightly to experimental ones. But it is not remarkable. Also, there is not a change for the calculated C2-O6 and C4-O8 bonds between the results of 6-31G(d) and 6-31G(d,p) basis sets. The calculated values (1.478 Å -1.500 Å) of C4-C5 bond in the substituted TZD derivatives is shorter than the experimental one (1.547), because of the conjugated system. Consequently, among the three basis sets, 6-31G(d) and 6-31G(d,p) exhibit better results for this data set. Although 6-31G(d,p) is a larger basis set, 6-31G(d) also gives good enough results without loss of precision and time.

For the substituted 2,4-thiazolidinedione derivatives, the selected bond angles optimized by three different basis sets (6-31G, 6-31G(d) and 6-31G(d,p) with B3LYP functional and their experimental response (30) are given in Table 5-7, respectively. The atom numbering of the main skeleton is given in Table 2 before. In these tables, even the calculated bond angles by three basis sets are compatible with the experimental values, the difference between the experimental and calculated values is more clear for angles. All three basis sets give similar results for bond angles as seen in Table 5-7. Three basis sets differentiate after the decimal point for bond angles. In each of Table 5-7, the deviation from the experimental angles is not more than 5.2˚. The best fit was seen for the O8-C4-N3 and S1-C2-O6 angles with all three basis sets. By 6-31G basis set, the deviations from the experimental values of these angles are less than 0.9 for each compound. This deviation for 6-31G(d) and 6-31G(d,p) basis set ranges between 0-1.9˚. S1-C2-N3, N3-C4-C5, N3-C2-O6, C5-C4-O8 and C2-N3-C4 angles show deviation about 2-4˚ in comparison to experimental values. Using larger basis sets (6-31G(d) and 6-31G(d,p)), it is seen that the difference is more considerable based on the structural difference. Since the C5 is the position where the substituents are attached, it is seen that the deviation in the angles containing C5, like N3-C4-C5, C5-C4-O8 and C2-S1-C5, is greater. This situation emphasizes that substituents attached to the main skeleton influence the three-dimensional geometry and related parameters.

Table 4. Calculated bond lengths (in Å) of 2,4-thiazolidinedione derivatives obtained at B3LYP/6-31G(d,p) level of theory

Bonds	S1-C5	S1-C2	C2-N3	N3-C4	C4-C5	C2-O6	N3-H7	C4-O8
Experimental	1.845	1.751	1.372	1.373	1.547	1.209	0.900	1.219
1	1.776	1.816	1.382	1.395	1.492	1.205	1.012	1.216
2	1.778	1.816	1.381	1.397	1.491	1.205	1.012	1.216
3	1.776	1.816	1.383	1.395	1.493	1.205	1.012	1.216
4	1.778	1.816	1.382	1.397	1.488	1.205	1.012	1.217
5	1.780	1.815	1.380	1.399	1.487	1.206	1.012	1.217
6	1.777	1.816	1.382	1.396	1.489	1.205	1.012	1.217
7	1.773	1.819	1.383	1.394	1.494	1.204	1.012	1.216
8	1.776	1.818	1.382	1.396	1.493	1.204	1.012	1.215
9	1.775	1.818	1.382	1.395	1.494	1.204	1.012	1.215
10	1.776	1.817	1.382	1.395	1.492	1.204	1.012	1.216
11	1.781	1.814	1.383	1.396	1.489	1.206	1.012	1.217
12	1.778	1.815	1.383	1.396	1.491	1.205	1.012	1.217
13	1.780	1.814	1.381	1.399	1.483	1.206	1.012	1.218
14	1.776	1.818	1.382	1.396	1.496	1.204	1.012	1.214
15	1.775	1.819	1.382	1.395	1.494	1.204	1.012	1.215
16	1.773	1.819	1.383	1.393	1.497	1.203	1.012	1.215
17	1.774	1.814	1.385	1.394	1.487	1.206	1.012	1.217
18	1.772	1.815	1.386	1.393	1.489	1.205	1.012	1.217
19	1.775	1.818	1.382	1.396	1.487	1.205	1.012	1.217
20	1.775	1.818	1.382	1.395	1.489	1.205	1.012	1.217
21	1.778	1.816	1.382	1.395	1.492	1.205	1.012	1.216
22	1.778	1.813	1.386	1.393	1.495	1.205	1.012	1.216
23	1.777	1.817	1.383	1.397	1.484	1.205	1.012	1.217
24	1.780	1.815	1.382	1.400	1.478	1.207	1.012	1.219
25	1.777	1.818	1.381	1.401	1.480	1.206	1.012	1.218
26	1.778	1.817	1.380	1.401	1.479	1.206	1.012	1.218
27	1.778	1.817	1.380	1.402	1.478	1.206	1.012	1.218
28	1.762	1.817	1.389	1.389	1.492	1.206	1.012	1.217
29	1.776	1.812	1.384	1.396	1.487	1.207	1.012	1.218
30	1.776	1.817	1.382	1.396	1.491	1.205	1.012	1.216
31	1.779	1.815	1.381	1.397	1.490	1.206	1.012	1.216
32	1.778	1.816	1.382	1.397	1.489	1.205	1.012	1.217
33	1.777	1.816	1.382	1.396	1.490	1.205	1.012	1.217
34	1.775	1.820	1.381	1.395	1.495	1.204	1.012	1.214
35	1.773	1.813	1.386	1.390	1.500	1.204	1.012	1.215

Table 5. Calculated angles (in ˚) of 2,4-thiazolidinedione derivatives obtained at B3LYP/6-31G level of theory

Angle	S1-C2-N3	N3-C4-C5	S1-C5-C9	N3-C2-O6	C5-C4-O8	C2-N3-C4	O8-C4-N3	S1-C2-O6	C2-S1-C5	O6-C2-S1-C5
Exp.	111.2	113.6	-	123.9	123.7	117.5	122.7	124.9	94.2	-
1	108.2	110.0	129.2	127.2	126.1	120.2	122.8	124.6	90.3	180.0
2	108.1	111.1	129.3	127.3	126.4	120.3	122.6	124.6	90.4	180.0
3	108.2	111.0	129.2	127.1	126.1	120.1	122.9	124.7	90.3	-180.0
4	108.1	111.0	129.1	127.2	126.3	120.2	122.7	124.7	90.3	180.0
5	108.0	111.1	129.0	127.3	126.5	120.3	122.4	124.6	90.4	-180.0
6	108.2	111.0	129.1	127.1	126.2	120.1	122.8	124.7	90.2	-179.9
7	108.2	110.9	129.3	127.2	129.9	120.1	123.1	124.6	90.2	179.9
8	108.1	111.0	129.3	127.4	126.1	120.2	122.9	124.5	90.3	180.0
9	108.2	111.0	129.4	127.3	126.0	120.2	123.0	124.6	90.3	180.0
10	108.1	111.0	129.2	127.3	126.1	120.2	122.9	124.6	90.3	180.0
11	108.2	111.0	128.4	127.0	126.4	120.2	122.7	124.7	90.1	-179.9
12	108.1	111.0	129.3	127.4	126.1	120.1	122.7	124.7	90.3	180.0
13	108.1	111.0	128.7	127.2	126.6	120.2	122.4	124.7	90.3	-180.0
14	108.1	111.0	129.0	127.4	126.1	120.3	122.9	124.5	90.3	-180.0
15	108.1	111.0	129.1	127.4	126.0	120.2	123.0	124.5	90.2	180.0
16	108.2	110.0	129.3	127.3	125.8	120.1	123.2	124.5	90.3	180.0
17	108.5	110.7	127.8	126.7	126.0	119.9	123.3	124.8	89.7	-180.0
18	108.6	110.7	128.1	126.7	126.0	119.8	123.3	124.7	89.7	-180.0
19	108.3	110.8	128.3	127.2	126.2	120.1	123.0	124.6	89.9	180.0
20	108.3	110.8	128.6	127.1	126.1	120.1	123.1	124.6	89.9	-180.0
21	108.2	111.1	129.4	127.2	126.2	120.2	122.8	124.7	90.3	180.0
22	108.5	110.8	127.8	126.7	126.0	120.0	123.2	124.8	89.9	179.5
23	108.2	110.7	126.2	127.1	126.4	120.2	122.9	124.7	89.8	180.0
24	108.1	110.7	126.8	127.1	126.7	120.3	122.6	124.7	89.9	180.0
25	108.0	110.8	127.2	127.4	126.6	120.3	122.5	124.6	90.1	180.0
26	107.9	110.8	127.2	127.4	127.0	120.3	122.5	124.6	90.1	-180.0
27	107.9	110.8	127.1	127.4	126.7	120.3	122.4	124.7	90.1	-180.0
28	108.9	110.6	127.3	126.2	125.7	119.4	123.6	124.9	89.3	180.0
29	108.3	110.9	128.4	126.8	126.4	120.0	122.7	124.8	90.0	179.2
30	108.1	111.0	129.1	127.2	126.2	120.2	122.8	124.6	90.3	180.0
31	108.1	111.1	129.3	127.2	126.5	120.3	122.5	124.7	90.4	180.0
32	108.1	111.0	129.1	127.2	126.3	120.2	122.7	124.7	90.3	-180.0
33	108.2	111.0	129.2	127.2	126.2	120.1	122.8	124.7	90.3	-180.0
34	108.0	111.1	129.6	127.6	126.0	120.3	122.9	124.4	90.4	180.0
35	108.5	110.7	128.0	126.7	125.8	120.0	123.6	124.8	89.9	-179.3

Table 6. Calculated angles (in ˚) of 2,4-thiazolidinedione derivatives obtained at B3LYP/6-31G(d) level of theory

Angle	S1-C2-N3	N3-C4-C5	S1-C5-C9	N3-C2-O6	C5-C4-O8	C2-N3-C4	O8-C4-N3	S1-C2-O6	C2-S1-C5	O6-C2-S1-C5
Exp.	111.2	113.6	-	123.9	123.7	117.5	122.7	124.9	94.2	-
1	108.5	109.5	130.2	126.8	126.8	119.5	123.7	124.8	91.9	-180.0
2	108.4	109.6	130.3	126.8	127.0	119.5	123.4	124.8	90.0	180.0
3	108.5	109.5	130.2	126.7	126.8	119.4	123.7	124.8	91.9	-180.0
4	108.4	109.5	130.0	126.8	127.0	119.5	123.5	124.8	91.9	-180.0
5	108.3	109.6	130.1	126.9	127.2	119.6	123.3	124.8	90.0	180.0
6	108.4	109.5	130.0	126.7	126.9	119.5	123.5	124.8	91.9	-179.9
7	108.5	109.5	130.2	126.8	126.6	119.9	123.9	124.7	91.8	179.9
8	108.4	109.5	130.3	126.9	126.8	119.5	123.7	124.7	92.0	-180.0
9	108.5	109.5	130.3	126.8	126.7	119.5	123.8	124.7	91.9	-180.0
10	108.4	109.5	130.2	126.8	126.8	119.5	123.7	124.8	91.9	-180.0
11	108.5	109.5	129.3	126.6	127.0	119.5	123.6	124.9	91.8	-179.7
12	108.5	109.5	130.2	126.6	126.9	119.5	123.6	124.9	91.9	180.0
13	108.3	109.5	129.7	126.8	127.2	119.5	123.2	124.9	91.9	-180.0
14	108.4	109.5	130.2	126.9	126.8	119.5	123.7	124.7	92.0	-180.0
15	108.4	109.5	130.0	126.9	126.6	119.5	123.8	124.7	91.9	-180.0
16	108.5	109.5	130.3	126.8	126.5	119.4	124.0	124.7	91.9	-180.0
17	108.8	109.2	128.7	126.4	126.7	119.3	124.1	124.9	91.4	180.0
18	108.8	109.2	128.9	126.4	126.6	119.2	124.2	124.8	91.4	180.0
19	108.5	109.3	129.1	126.8	126.9	119.4	123.8	124.7	91.6	-180.0
20	108.6	109.4	129.5	126.7	126.8	119.4	123.9	124.7	91.6	180.0
21	108.5	109.6	130.4	126.8	126.8	119.5	123.6	124.8	91.9	-180.0
22	108.8	109.3	128.6	126.2	126.6	119.3	124.1	125.0	91.6	179.5
23	108.5	109.2	127.4	126.7	126.9	119.5	123.8	124.9	91.6	-180.0
24	108.4	109.2	127.1	126.6	127.3	119.6	123.5	125.0	91.6	-180.0
25	108.2	109.4	128.3	126.9	127.2	119.6	123.4	124.8	91.8	-180.0
26	108.2	109.4	128.2	126.9	127.3	119.6	123.3	124.9	91.8	180.0
27	108.2	109.4	128.2	127.0	127.4	119.7	123.2	124.9	91.8	180.0
28	109.3	109.1	128.1	125.8	126.3	118.7	124.6	124.9	90.9	180.0
29	108.7	109.4	129.2	126.4	127.0	119.3	123.6	125.0	91.7	179.0
30	108.4	109.5	130.1	126.8	126.8	119.5	123.6	124.8	91.9	-180.0
31	108.4	109.6	130.2	126.8	127.0	119.5	123.4	124.8	92.0	179.9
32	108.4	109.5	130.1	126.8	127.0	119.5	123.5	124.8	91.9	180.0
33	108.5	109.5	130.2	126.7	126.9	119.5	123.6	124.8	91.9	180.0
34	108.5	109.5	130.1	127.0	126.6	119.5	123.9	124.6	91.9	179.7
35	108.9	109.3	130.2	126.3	126.4	119.2	124.2	124.9	91.7	178.7

Table 7. Calculated angles (in ˚) of 2,4-thiazolidinedione derivatives obtained at B3LYP/6-31G(d,p) level of theory

Angle	S1-C2-N3	N3-C4-C5	S1-C5-C9	N3-C2-O6	C5-C4-O8	C2-N3-C4	O8-C4-N3	S1-C2-O6	C2-S1-C5	O6-C2-S1-C5
Exp.	111.2	113.6	-	123.9	123.7	117.5	122.7	124.9	94.2	-
1	108.5	109.6	130.2	126.7	126.7	119.4	123.7	124.8	91.9	-180.0
2	108.4	109.6	130.3	126.8	126.9	119.5	123.4	124.8	92.0	-180.0
3	108.6	109.6	130.2	126.7	126.7	119.4	123.7	124.8	91.9	-180.0
4	108.4	109.6	130.0	126.7	126.9	119.5	123.5	124.8	91.9	-180.0
5	108.4	109.6	130.0	126.8	127.1	119.5	123.3	124.8	92.0	-180.0
6	108.5	109.6	130.0	126.7	126.9	119.4	123.6	124.8	91.9	-179.9
7	108.5	109.5	130.2	126.8	126.6	119.4	123.9	124.7	91.8	179.9
8	108.5	109.6	130.3	126.8	126.7	119.5	123.7	124.7	91.9	-180.0
9	108.5	109.6	130.3	126.8	126.6	119.4	123.8	124.7	91.9	-180.0
10	108.5	109.6	130.2	126.8	126.7	119.4	123.7	124.7	91.9	-180.0
11	108.6	109.5	129.3	126.6	126.9	119.5	123.6	124.9	91.8	-179.8
12	108.5	109.6	130.2	126.6	126.8	119.4	123.6	124.8	91.9	180.0
13	108.4	109.6	129.7	126.7	127.2	119.5	123.2	124.9	91.9	180.0
14	108.5	109.5	130.1	126.9	126.7	119.5	123.7	124.6	92.0	-180.0
15	108.5	109.6	130.0	126.9	126.6	119.4	123.9	124.7	91.9	-180.0
16	108.6	109.6	130.3	126.8	126.4	119.4	124.0	124.6	91.9	-180.0
17	108.8	109.3	128.7	126.3	126.7	119.2	124.1	124.8	91.4	180.0
18	108.9	109.3	128.9	126.3	126.5	119.1	124.2	124.8	91.4	180.0
19	108.6	109.4	129.2	126.7	126.8	119.4	123.8	124.7	91.6	-180.0
20	108.6	109.4	129.5	126.7	126.7	119.4	123.9	124.7	91.6	180.0
21	108.5	109.6	130.4	126.7	126.8	119.4	123.6	124.8	91.9	-180.0
22	108.9	109.3	128.7	126.2	126.5	119.3	124.1	124.9	91.5	179.5
23	108.5	109.3	127.5	126.6	126.9	119.5	123.8	124.8	91.5	180.0
24	108.5	109.3	127.1	126.6	127.2	119.5	123.5	124.9	91.6	-180.0
25	108.3	109.4	128.3	126.9	128.2	119.5	123.4	124.8	91.8	-180.0
26	108.3	109.4	128.2	126.9	127.3	119.6	123.3	124.8	91.8	-180.0
27	108.2	109.4	128.2	127.0	127.4	119.6	123.2	124.8	91.8	180.0
28	109.3	109.2	128.1	125.8	126.3	118.7	124.6	124.9	90.9	180.0
29	108.7	109.4	129.3	126.3	127.0	119.2	123.6	124.9	91.7	179.0
30	108.5	109.6	130.1	126.8	126.8	119.4	123.6	124.8	91.9	-180.0
31	108.4	109.6	130.3	126.8	127.0	119.5	123.4	124.8	92.0	179.9
32	108.5	109.6	130.0	126.7	126.9	119.4	123.5	124.8	91.9	180.0
33	108.5	109.6	130.1	126.7	126.9	119.4	123.6	124.8	91.9	180.0
34	108.5	109.6	130.1	127.0	126.6	119.5	123.8	124.6	91.9	179.8
35	108.9	109.4	130.2	126.2	126.4	119.2	124.2	124.9	91.7	178.7

Atomic charges of the compounds for three basis sets are described according to the Mulliken population analysis which gives information about the molecular interaction and reactivity. Mulliken charges of the selected atoms in 2,4-thiazolidinedione derivatives data set are given with Table 8-10 for 6-31G, 6-31G(d) and 6-31G(d,p) basis

sets, respectively. In Table 8, Mulliken charges of the compounds obtained with the 6-31G basis set are listed. According to the table, positive charges are concentrated on the S1, C2, H7 and C4 atoms while negative charges are concentrated on the O6, N3, O8, C5 and C9 atoms to incline positive centers. The negative charges of the O6 and O8 atoms range between (-0.389)-(-0.411) and (-0.405)-(-0.437) in the data set, respectively. N3 atoms appear to have the highest negative charge (-0.650)-(-0.660). The highest positive charge belongs to C4 (0.540-0.550) atom which is located between negatively charged N3 and C5 atoms. The C5 and C9 atoms, participate in a double bond, share the negative charge, mostly on the C5 atom (~-0.310). Negatively charged carbonyl oxygens (O6 and O8) are capable of accepting H-bond. Meanwhile, the N3 atom acts as an H-bond donor.

Table 9 represents the Mulliken charges calculated by the 6-31G(d) basis set. From the table, it is clear that there is a significant difference from the results of the 6-31G basis set. Mulliken charges are calculated according to the Mulliken population analysis (Mulliken, 1955a, b and c) and dependent on the selected basis function. In the table, O6, N3, O8, C5 and C9 atoms have negative charges and the highest negative charge is located on the N3 atom parallel with the 6-31G basis set. O6 and O8 atoms have higher negative charge values than by the 6-31G basis set. As different from Table 8, C5 and C9 atoms appear to share negative charges almost equally. S1, C2, H7 and C4 atoms possess positive charges.

Table 10 shows the selected Mulliken charges calculated with 6-31G(d,p) basis set. Compared to previously mentioned basis sets, differentiation of atoms based on the positive and negative charges resembles the other basis sets. Hereunder, S1, C2, H7 and C4 atoms own positive charges. The highest positive charge concentrates on the C4 atom (~0.620). The N3 atom has the highest negative charge (-0.555-(-0.561)).

Table 8. Selected Mulliken charges of 2,4-thiazolidinedione derivatives calculated at B3LYP/6-31G level of theory

Compound	S1	C2	O6	N3	H7	C4	O8	C5	C9
1	0.442	0.283	-0.398	-0.657	0.364	0.547	-0.420	-0.305	-0.180
2	0.434	0.282	-0.401	-0.659	0.362	0.546	-0.410	-0.303	-0.157
3	0.453	0.281	-0.398	-0.657	0.363	0.547	-0.420	-0.304	-0.185
4	0.436	0.283	-0.400	-0.658	0.362	0.546	-0.425	-0.309	-0.181
5	0.424	0.282	-0.405	-0.659	0.360	0.544	-0.424	-0.307	-0.156
6	0.445	0.281	-0.401	-0.658	0.362	0.546	-0.425	-0.307	-0.185
7	0.465	0.283	-0.389	-0.658	0.366	0.550	-0.417	-0.309	-0.180
8	0.441	0.285	-0.395	-0.658	0.365	0.548	-0.412	-0.305	0.161
9	0.448	0.284	-0.393	-0.657	0.366	0.549	-0.415	-0.306	-0.177
10	0.442	0.285	-0.394	-0.657	0.365	0.548	-0.418	-0.306	-0.180
11	0.419	0.290	-0.404	-0.658	0.360	0.544	-0.427	-0.307	-0.174
12	0.444	0.280	-0.403	-0.650	0.361	0.545	-0.426	-0.306	-0.187
13	0.423	0.281	-0.410	-0.659	0.358	0.542	-0.435	-0.313	-0.183
14	0.437	0.286	-0.394	-0.656	0.366	0.549	-0.407	-0.300	-0.123
15	0.443	0.286	-0.391	-0.657	0.367	0.550	-0.412	-0.307	-0.173

16	0.454	0.285	-0.389	-0.657	0.368	0.550	-0.410	-0.303	-0.168
17	0.470	0.284	-0.405	-0.658	0.362	0.549	-0.424	-0.334	-0.103
18	0.477	0.283	-0.404	-0.658	0.362	0.550	-0.423	-0.332	-0.118
19	0.458	0.282	-0.398	-0.656	0.363	0.544	-0.423	-0.342	-0.100
20	0.465	0.281	-0.398	-0.657	0.364	0.545	-0.422	-0.341	-0.112
21	0.442	0.282	-0.400	-0.658	0.363	0.547	-0.422	-0.309	-0.183
22	0.442	0.290	-0.400	-0.655	0.362	0.547	-0.419	-0.298	-0.167
23	0.414	0.298	-0.401	-0.657	0.362	0.546	-0.421	-0.346	-0.099
24	0.401	0.296	-0.411	-0.657	0.357	0.541	-0.433	-0.350	-0.097
25	0.405	0.288	-0.404	-0.660	0.360	0.544	-0.431	-0.329	-0.112
26	0.403	0.288	-0.406	-0.660	0.359	0.543	-0.431	-0.330	-0.109
27	0.401	0.288	-0.407	-0.661	0.359	0.542	-0.437	-0.330	-0.116
28	0.515	0.272	-0.405	-0.658	0.361	0.547	-0.425	-0.326	-0.089
29	0.438	0.285	-0.411	-0.658	0.358	0.540	-0.434	-0.305	-0.149
30	0.440	0.283	-0.399	-0.658	0.363	0.546	-0.422	-0.307	-0.180
31	0.432	0.281	-0.404	-0.659	0.360	0.544	-0.421	-0.303	-0.156
32	0.438	0.282	-0.401	-0.658	0.362	0.546	-0.424	-0.310	-0.182
33	0.450	0.281	-0.400	-0.658	0.363	0.546	-0.423	-0.306	-0.180
34	0.444	0.286	-0.390	-0.657	0.368	0.547	-0.405	-0.298	-0.185
35	0.460	0.294	-0.394	-0.655	0.365	0.550	-0.411	-0.273	-0.171

Table 9. Selected Mulliken charges of 2,4-thiazolidinedione derivatives calculated at B3LYP/6-31G(d) level of theory

Compound	S1	C2	O6	N3	H7	C4	O8	C5	C9
1	0.222	0.436	-0.451	-0.641	0.360	0.629	-0.481	-0.200	-0.211
2	0.216	0.436	-0.454	-0.642	0.358	0.628	-0.482	-0.199	-0.196
3	0.230	0.435	-0.451	-0.641	0.360	0.629	-0.481	-0.198	-0.215
4	0.215	0.436	-0.454	-0.641	0.358	0.627	-0.486	-0.206	-0.213
5	0.207	0.436	-0.458	0.643	0.356	0.626	-0.487	-0.205	-0.196
6	0.221	0.435	-0.454	-0.641	0.358	0.627	-0.486	-0.204	-0.216
7	0.239	0.436	-0.444	-0.642	0.362	0.632	-0.201	-0.201	-0.217
8	0.221	0.437	-0.449	-0.642	0.361	0.631	-0.476	-0.198	-0.203
9	0.227	0.437	-0.448	-0.641	0.362	0.631	-0.477	-0.200	-0.208
10	0.220	0.437	-0.449	-0.641	0.361	0.629	-0.481	-0.202	-0.212
11	0.207	0.440	-0.455	-0.641	0.357	0.627	-0.484	-0.198	-0.215
12	0.222	0.435	-0.455	-0.641	0.358	0.627	-0.485	-0.203	-0.211
13	0.205	0.435	-0.461	-0.641	0.355	0.624	-0.493	-0.211	-0.214
14	0.221	0.438	-0.447	-0.640	0.362	0.630	-0.470	-0.192	-0.181
15	0.223	0.438	-0.446	-0.641	0.363	0.632	-0.475	-0.200	-0.209
16	0.234	0.437	-0.443	-0.641	0.364	0.633	-0.472	-0.194	-0.203
17	0.239	0.435	-0.455	-0.642	0.358	0.631	-0.486	-0.211	-0.191
18	0.248	0.435	-0.454	-0.642	0.359	0.634	-0.483	-0.209	-0.203

19	0.233	0.436	-0.450	-0.640	0.360	0.626	-0.483	-0.227	-0.125
20	0.242	0.435	-0.450	-0.641	0.360	0.627	-0.482	-0.227	-0.131
21	0.222	0.436	-0.452	-0.641	0.359	0.629	-0.482	-0.206	-0.209
22	0.227	0.439	-0.451	-0.640	0.359	0.631	-0.480	-0.183	-0.236
23	0.208	0.443	-0.453	-0.637	0.359	0.621	-0.482	-0.222	-0.115
24	0.196	0.442	-0.461	-0.638	0.354	0.617	-0.492	-0.229	-0.113
25	0.193	0.439	-0.457	-0.643	0.357	0.527	-0.490	-0.217	-0.179
26	0.190	0.439	-0.458	-0.644	0.356	0.626	-0.491	-0.219	-0.177
27	0.187	0.439	-0.460	-0.644	0.355	0.625	-0.493	-0.221	-0.180
28	0.286	0.423	-0.455	-0.641	0.357	0.630	-0.485	-0.190	-0.199
29	0.220	0.435	-0.461	-0.643	0.354	0.626	-0.492	-0.200	-0.222
30	0.221	0.436	-0.451	-0.641	0.359	0.628	-0.482	-0.202	-0.212
31	0.213	0.436	-0.456	-0.642	0.357	0.627	-0.483	-0.199	-0.194
32	0.216	0.436	-0.455	-0.642	0.358	0.627	-0.485	-0.200	-0.209
33	0.225	0.435	-0.454	-0.641	0.358	0.627	-0.484	-0.204	-0.213
34	0.217	0.442	-0.445	-0.641	0.363	0.632	-0.470	-0.191	-0.216
35	0.245	0.438	-0.448	-0.640	0.360	0.630	-0.476	-0.167	-0.223

Table 10. Selected Mulliken charges of 2,4-thiazolidinedione derivatives calculated at B3LYP/6-31G(d,p) level of theory

Compound	**S1**	**C2**	**O6**	**N3**	**H7**	**C4**	**O8**	**C5**	**C9**
1	0.224	0.429	-0.450	-0.558	0.293	0.620	-0.480	-0.222	-0.121
2	0.218	0.428	-0.453	-0.559	0.291	0.620	-0.481	-0.225	-0.101
3	0.232	0.427	-0.450	-0.558	0.292	0.620	-0.480	-0.221	-0.124
4	0.217	0.429	-0.453	-0.558	0.291	0.619	-0.486	-0.228	-0.122
5	0.208	0.429	-0.457	-0.560	0.289	0.618	-0.486	-0.230	-0.100
6	0.223	0.427	-0.453	-0.558	0.291	0.619	-0.486	-0.227	-0.124
7	0.241	0.428	-0.443	-0.558	0.295	0.623	-0.479	-0.223	-0.125
8	0.223	0.430	-0.448	-0.559	0.294	0.622	-0.476	-0.221	-0.111
9	0.229	0.430	-0.447	-0.558	0.294	0.622	-0.477	-0.222	-0.118
10	0.222	0.430	-0.448	-0.558	0.293	0.621	-0.480	-0.224	-0.121
11	0.208	0.433	-0.454	-0.558	0.290	0.619	-0.484	-0.220	-0.127
12	0.225	0.427	-0.454	-0.558	0.290	0.619	-0.485	-0.225	-0.120
13	0.207	0.427	-0.460	-0.559	0.288	0.615	-0.493	-0.234	-0.123
14	0.223	0.430	-0.446	-0.556	0.295	0.621	-0.469	-0.214	-0.091
15	0.225	0.431	-0.445	-0.558	0.295	0.624	-0.475	-0.222	-0.120
16	0.236	0.430	-0.442	-0.557	0.296	0.624	-0.471	-0.215	-0.114
17	0.240	0.427	-0.455	-0.559	0.291	0.622	-0.485	-0.226	-0.110
18	0.249	0.427	-0.453	-0.559	0.292	0.625	-0.482	-0.224	-0.121
19	0.234	0.428	-0.449	-0.557	0.293	0.617	-0.483	-0.244	-0.048
20	0.242	0.427	-0.449	-0.557	0.293	0.619	-0.482	-0.245	-0.053
21	0.224	0.429	-0.451	-0.558	0.292	0.621	-0.482	-0.230	-0.117

22	0.228	0.431	-0.450	-0.557	0.292	0.622	-0.479	-0.200	-0.160
23	0.210	0.436	-0.452	-0.555	0.291	0.614	-0.482	-0.238	-0.054
24	0.198	0.434	-0.460	-0.555	0.287	0.609	-0.491	-0.245	-0.051
25	0.195	0.431	-0.456	-0.560	0.290	0.618	-0.490	-0.237	-0.089
26	0.192	0.431	-0.457	-0.560	0.289	0.617	-0.491	-0.239	-0.087
27	0.189	0.431	-0.459	-0.561	0.288	0.616	-0.493	-0.241	-0.089
28	0.287	0.416	-0.454	-0.558	0.290	0.621	-0.484	-0.209	-0.114
29	0.220	0.428	-0.460	-0.560	0.287	0.618	-0.491	-0.218	-0.135
30	0.223	0.429	-0.451	-0.558	0.292	0.620	-0.481	-0.224	-0.121
31	0.216	0.429	-0.454	-0.559	0.290	0.619	-0.482	-0.225	-0.099
32	0.218	0.428	-0.454	-0.558	0.291	0.619	-0.485	-0.231	-0.118
33	0.227	0.428	-0.453	-0.558	0.291	0.619	-0.484	-0.228	-0.120
34	0.220	0.434	-0.444	-0.558	0.296	0.623	-0.469	-0.216	-0.125
35	0.246	0.430	-0.447	-0.557	0.293	0.621	-0.476	-0.183	-0.144

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital are among the most known quantum chemical parameters and known frontier orbitals. HOMO describes the electron donation capability whereas LUMO describes the electron excepting capability. The high energy of the HOMO points out that the molecule has a propensity for donating an electron. Electron accepting tendency of the molecule is described with the low energy of the LUMO. The energy gap between HOMO and LUMO indicates the chemical and biological reactivity of compounds. The lower energy gap refers to the high chemical reactivity of the molecule. Energies values (in eV) of HOMO-1, HOMO, LUMO and LUMO+1 of 2,4-thiazolidinedione derivatives calculated with 6-31G, 6-31G(d) and 6-31G(d,p) basis sets are listed in Table 11, Table 12 and Table 13, respectively.

Considering the ΔE values of the 2,4-thiazolidinedione derivatives in Tables 11-13, the minimum energy gap of HOMO-LUMO is calculated for compound 24 as 2.95 eV with the 6-31G basis set. The same energy gap equals to 3.5eV for both 6-31G(d) and 6-31G(d,p) basis sets. The highest energy gap (4.04eV) belongs to compound 14 for 6-31G. Based on the magnitude of the HOMO-LUMO energy gap, it is possible to deduce the chemical reactivity of the compounds. The low HOMO-LUMO gap administrates the compound's chemical reactivity and turns it into a perfect electron acceptor. According to Table 12 and 13, the highest ΔE value was obtained as 4.10 for compound 16 and then 4.09 for compound 14. As a result, the most reactive compound in the data set is compound 24 which has 4-dimethylamino styrene group at 5-position of the 2,4-thiazolidinedione. This situation can be interpreted by the electron donation of the substituent in compound 24. Binding of such an electron-donating group at 5-position of the 2,4-thiazolidinedione ring including aromatic system increases the electron density by the conjugated double bonds in the molecule.

Dipole moment values of 2,4-thiazolidinedione derivatives obtained by the three basis sets are given in Table 14.

Table 11. Energies of frontier orbitals of 2,4-thiazolidinedione derivatives calculated at B3LYP/6-31G level of theory

Compound	E_{HOMO-1} (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{LUMO+1} (eV)	ΔE
1	-7.42	-6.49	-2.53	-0.58	3.96
2	-7.01	-6.24	-2.41	-0.50	3.83
3	-6.81	-6.41	-2.53	-0.56	3.87
4	-7.51	-6.18	-2.41	-0.65	3.78
5	-6.97	-5.96	-2.24	-0.40	3.73
6	-6.82	-6.09	-2.38	-0.49	3.70
7	-7.83	-6.72	-2.96	-2.84	3.76
8	-7.53	-6.64	-2.68	-0.75	3.95
9	-7.46	-6.73	-2.75	-0.83	3.98
10	-7.73	-6.60	-2.67	-0.91	3.94
11	-6.50	-5.70	-2.29	-0.43	3.41
12	-6.30	-5.46	-2.30	-0.36	3.16
13	-6.78	-5.41	-2.05	-0.26	3.37
14	-7.28	-6.77	-2.73	-1.12	4.04
15	-7.19	-6.82	-2.83	-1.15	3.99
16	-7.15	-7.00	-2.97	-0.99	4.03
17	-7.50	-6.24	-2.57	-0.47	3.67
18	-7.01	-6.15	-2.72	-0.75	3.43
19	-7.48	-6.31	-2.68	-0.72	3.63
20	-6.74	-6.16	-2.75	-0.84	3.41
21	-6.73	-6.14	-2.54	-1.33	3.60
22	-6.88	-5.60	-2.54	-1.76	3.06
23	-7.35	-6.10	-2.69	-0.92	3.41
24	-6.40	-5.23	-2.29	-0.51	2.95
25	-6.67	-5.81	-2.17	-0.67	3.64
26	-6.14	-5.62	-2.09	-0.70	3.53
27	-6.01	-5.61	-2.06	-0.64	3.55
28	-6.51	-6.18	-2.68	-0.60	3.50
29	-6.32	-5.67	-2.13	-1.02	3.53
30	-7.10	-6.19	-2.55	-0.89	3.64
31	-6.81	-6.07	-2.30	-0.53	3.77
32	-6.76	-6.07	-2.38	-0.50	3.69
33	-6.52	-6.04	-2.44	-0.44	3.60
34	-7.17	-6.72	-3.02	-1.88	3.70
35	-6.85	-6.40	-2.61	-1.94	3.79

Table 12. Energies of frontier orbitals of 2,4-thiazolidinedione derivatives calculated at B3LYP/6-31G (d) level of theory

Compound	E_{HOMO-1} (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{LUMO+1} (eV)	ΔE
1	-7.30	-6.32	-2.30	-0.45	4.03
2	-6.84	-6.05	-2.18	-0.25	3.87
3	-6.66	-6.21	-2.28	-0.28	3.94
4	-7.35	-5.98	-2.12	-0.56	3.86
5	-6.78	-5.76	-1.97	-0.21	3.79
6	-6.90	-5.92	-2.11	-0.41	3.81
7	-7.64	-6.47	-2.53	-2.49	3.93
8	-7.29	-6.39	-2.40	-0.50	3.99
9	-7.20	-6.49	-2.46	-0.58	4.03
10	-7.53	-6.34	-2.35	-0.77	3.99
11	-6.41	-5.77	-2.09	-0.29	3.69
12	-6.16	-5.48	-2.08	-0.11	3.41
13	-6.68	-5.33	-1.83	-0.22	3.49
14	-7.40	-6.57	-2.49	-0.98	4.09
15	-7.34	-6.59	-2.55	-1.02	4.04
16	-7.31	-6.81	-2.71	-0.70	4.10
17	-7.36	-6.01	-2.27	-0.07	3.74
18	-6.85	-5.96	-2.47	-0.50	3.48
19	-7.36	-6.12	-2.38	-0.49	3.74
20	-6.58	-5.99	-2.50	-0.59	3.50
21	-6.61	-6.01	-2.33	-1.25	3.68
22	-6.76	-5.51	-2.34	-1.60	3.17
23	-7.24	-5.95	-2.49	-0.68	3.45
24	-6.31	-5.15	-2.10	-0.32	3.05
25	-6.52	-5.66	-1.92	-0.56	3.74
26	-5.99	-5.47	-1.83	-0.58	3.64
27	-5.95	-5.37	-1.77	-0.55	3.60
28	-6.40	-5.99	-2.44	-0.35	3.55
29	-6.20	-5.55	-1.91	-0.94	3.63
30	-6.99	-6.06	-2.34	-0.73	3.71
31	-6.72	-5.94	-2.11	-0.40	3.83
32	-6.60	-5.86	-2.09	-0.33	3.77
33	-6.37	-5.81	-2.14	-0.11	3.67
34	-6.94	-6.53	-2.74	-1.71	3.79
35	-6.55	-6.21	-2.41	-1.67	3.81

Table 13. Energies of frontier orbitals of 2,4-thiazolidinedione derivatives calculated at B3LYP/6-31G (d,p) level of theory

Compound	E_{HOMO-1} (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{LUMO+1} (eV)	ΔE
1	-7.31	-6.33	-2.31	-0.47	4.02
2	-6.85	-6.05	-2.18	-0.26	3.87
3	-6.66	-6.22	-2.28	-0.28	3.94
4	-7.35	-5.98	-2.12	-0.57	3.85
5	-6.78	-5.76	-1.98	-0.22	3.78
6	-6.89	-5.92	-2.11	-0.42	3.80
7	-7.64	-6.47	-2.53	-2.49	3.93
8	-7.29	-6.40	-2.41	-0.51	3.99
9	-7.21	-6.49	-2.47	-0.59	4.03
10	-7.54	-6.34	-2.35	-0.79	3.99
11	-6.41	-5.77	-2.09	-0.30	3.68
12	-6.16	-5.48	-2.08	-0.12	3.40
13	-6.68	-5.33	-1.83	-0.24	3.49
14	-7.40	-6.58	-2.49	-0.99	4.09
15	-7.34	-6.59	-2.56	-1.03	4.04
16	-7.30	-6.81	-2.72	-0.71	4.10
17	-7.37	-6.01	-2.27	-0.08	3.74
18	-6.86	-5.96	-2.48	-0.51	3.48
19	-7.37	-6.12	-2.39	-0.49	3.73
20	-6.59	-6.00	-2.50	-0.60	3.50
21	-6.62	-6.02	-2.34	-1.27	3.68
22	-6.76	-5.52	-2.50	-1.61	3.17
23	-7.25	-5.95	-2.50	-0.69	3.45
24	-6.31	-5.16	-2.11	-0.33	3.05
25	-6.53	-5.67	-1.93	-0.58	3.74
26	-5.99	-5.48	-1.84	-0.59	3.64
27	-5.95	-5.37	-1.78	-0.57	3.60
28	-6.41	-5.99	-2.44	-0.36	3.55
29	-6.20	-5.55	-1.92	-0.95	3.63
30	-7.00	-6.06	-2.35	-0.74	3.71
31	-6.73	-5.95	-2.12	-0.41	3.83
32	-6.60	-5.86	-2.09	-0.34	3.77
33	-6.37	-5.81	-2.14	-0.11	3.66
34	-6.94	-6.53	-2.75	-1.71	3.78
35	-6.55	-6.21	-2.41	-1.68	3.80

Table 14. Dipole moment values of 2,4-thiazolidinedione derivatives

Dipole moment (Debye)			
Compound	**6-31G**	**6-31G(d)**	**6-31G(d.p)**
1	3.610	3.168	3.134
2	5.517	4.915	4.875
3	5.012	4.461	4.416
4	5.016	4.719	4.701
5	6.192	5.828	5.793
6	6.093	5.406	5.400
7	7.366	6.49	6.462
8	3.671	3.255	3.222
9	1.726	1.824	1.794
10	1.955	2.082	2.063
11	4.947	4.189	4.180
12	6.176	5.467	5.465
13	8.024	7.303	7.297
14	3.677	3.290	3.256
15	1.507	1.473	1.446
16	1.406	1.113	1.118
17	4.574	3.989	3.956
18	4.546	3.708	3.670
19	4.228	3.656	3.623
20	4.645	3.844	3.803
21	4.393	3.863	3.824
22	3.475	2.982	2.956
23	4.804	4.209	4.170
24	9.699	8.812	8.811
25	5.357	4.923	4.873
26	7.143	6.441	6.394
27	4.805	6.893	6.871
28	5.968	5.198	5.182
29	5.322	4.884	4.844
30	4.378	3.841	3.799
31	5.728	4.885	4.846
32	5.964	5.670	5.656
33	5.675	5.387	5.385
34	4.258	3.545	3.508
35	6.561	5.982	5.962

4. Conclusion

Quantum chemical analysis of a series of 2,4-thiazolidinedione derivatives was performed successfully by DFT using the B3LYP functional with 6-31G, 6-31G(d) and 6-31G(d,p) basis sets. For this purpose, each compound in the data set was geometrically optimized to find the global minimum structure. Based on the quantum chemical calculation results, geometrical parameters involving bond lengths and angles, electronic properties such as Mulliken charges and dipole moment, and energies of the frontier orbitals to define the energy of the transitions were calculated by using the mentioned basis sets. Experimental values of the geometrical parameters were taken from the literature for unsubstituted 2,4-thiazolidinedione derivatives to make a comparison. Although 5-substituted 2,4-thiazolidinedione derivatives were considered in this study, according to the computational results, calculated bond lengths agree well with the experimental data. It is observed that the deviations of bond angles are more than bond lengths due to the relatively bulky substituents at position 5 of the main structure. The calculated HOMO-LUMO gap energies promote to understand the functioning of electronic transitions. These energy values demonstrate that compound 24 is more reactive and shows less chemical stability than the others because it has the lowest HOMO-LUMO gap for three different basis sets (6-31G: 2.95; 6-31G(d) and 6-31G(d,p): 3.05). According to the DFT calculations with 6-31G, 6-31G(d) and 6-31G(d,p) basis sets, all the TZD derivatives are stable and, compound 14 and compound 16 show the lowest chemical reactivity with the relatively high HOMO-LUMO gaps. Accordingly, compound 24 is more polarizable with highest dipole moment for three basis sets compared the other compounds in the series. Substitution of different aromatic and heterocyclic units attached to 5-position of 2,4-thiazolidinedione influence the electronic and structural characters of compounds. In light of the obtained results, the present paper may be useful to comprehend the physicochemical and biochemical properties of 5-substituted 2,4-thiazolidinedione derivatives in the biochemical reactions. Moreover, this study would support the other docking, QSAR or molecular simulation studies of related data set in the future.

5. References

Alzheimer's Association (2019) Alzheimer's Disase Facts and Figures. *Alzhimers Dement,* 15(3):321-87.

Bahare, R. S., Ganguly, S., Choowongkomon, K., & Seetaha, S. (2015). Synthesis, HIV-1 RT inhibitory, antibacterial, antifungal and binding mode studies of some novel N-substituted 5-benzylidine-2,4-thiazolidinediones. *DARU, Journal of Pharmaceutical Sciences*, *23*(1). https://doi.org/10.1186/s40199-014-0086-1

Balsinha, C., Gonçalves-Pereira, M., Iliffe, S., Freitas, J. A., & Grave, J. (2019). *World Alzheimer Report 2019*. *Alzheimer's Disease International*. https://doi.org/10.1007/978-3-030-10814-4_23

Becke, A. D. (1993). A new mixing of Hartree-Fock and local density-functional theories. *The Journal of Chemical Physics*, *98*(2), 1372–1377. https://doi.org/10.1063/1.464304

Becke, A. D. (1993). Density-functional thermochemistry. III. The role of exact exchange. *The Journal of Chemical Physics*, *98*(7), 5648–5652. https://doi.org/10.1063/1.464913

Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-

development pipeline: Few candidates, frequent failures. *Alzheimer's Research and Therapy*, *6*(4), 37. https://doi.org/10.1186/alzrt269

Day, C. (1999). Thiazolidinediones: A new class of antidiabetic drugs. *Diabetic Medicine*, *16*(3), 179–192. https://doi.org/10.1046/j.1464-5491.1999.00023.x

Desai, A., & Grossberg, G. (2001). Review of rivastigmine and its clinical applications in Alzheimer's disease and related disorders. *Expert Opinion on Pharmacotherapy*, *2*(4), 653–666. https://doi.org/10.1517/14656566.2.4.653

Enchev, V., Petkov, I., & Chorbadjiev, S. (1994). Tautomerism of rhodanine. *Structural Chemistry*, *5*(4), 225–231. https://doi.org/10.1007/BF02275495

Fatma, S., Bishnoi, A., Verma, A. K., Singh, V., & Srivastava, K. (2018). Quantum chemical calculations and molecular docking studies of 5-(4-chlorobenzylidene)thiazolidine-2,4-dione(CTD) and its mannich product 5-(4-chlorobenzylidene)-3-(morpholinomethyl)thiazolidine-2,4-dione (CMTD). *Journal of Molecular Structure*, *1157*, 177–190. https://doi.org/10.1016/j.molstruc.2017.12.051

Form, G. R., Raper, E. S., & Downie, T. C. (1975). The crystal and molecular structure of thiazolidine-2,4-dione. *Acta Crystallographica Section B Structural Crystallography and Crystal Chemistry*, *31*(9), 2181–2184. https://doi.org/10.1107/s0567740875007212

Gandini, A., Bartolini, M., Tedesco, D., Martinez-Gonzalez, L., Roca, C., Campillo, N. E., … Bolognesi, M. L. (2018). Tau-Centric Multitarget Approach for Alzheimer's Disease: Development of First-in-Class Dual Glycogen Synthase Kinase 3β and Tau-Aggregation Inhibitors. *Journal of Medicinal Chemistry*, *61*(17), 7640–7656. https://doi.org/10.1021/acs.jmedchem.8b00610

González, J. F., Alcántara, A. R., Doadrio, A. L., & Sánchez-Montero, J. M. (2019). Developments with multi-target drugs for Alzheimer's disease: an overview of the current discovery approaches. *Expert Opinion on Drug Discovery*, *14:9*, 879–891. https://doi.org/10.1080/17460441.2019.1623201

Holmes, C., Wilkinson, D., Dean, C., Vethanayagam, S., Olivieri, S., Langley, A., … Damms, J. (2004). The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*, *63*(2), 214 LP – 219. https://doi.org/10.1212/01.WNL.0000129990.32253.7B

Hughes, R. E., Nikolic, K., & Ramsay, R. R. (2016). One for all? Hitting multiple Alzheimer's disease targets with one drug. *Frontiers in Neuroscience*, *10*(APR), 1–10. https://doi.org/10.3389/fnins.2016.00177

Hyde, C., Peters, J., Bond, M., Rogers, G., Hoyle, M., Anderson, R., … Moxham, T. (2013). Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: Systematic review and economic model. *Age and Ageing*, *42*(1), 14–20. https://doi.org/10.1093/ageing/afs165

Kumar, A., Tiwari, A., & Sharma, A. (2018). Changing Paradigm from one Target one Ligand Towards Multi-target Directed Ligand Design for Key Drug Targets of Alzheimer Disease: An Important Role of In Silico Methods in Multi-target Directed Ligands Design. *Current Neuropharmacology*, *16*(6), 726–739. https://doi.org/10.2174/1570159x16666180315141643

Lao, K., Ji, N., Zhang, X., Qiao, W., Tang, Z., & Gou, X. (2019). Drug development for Alzheimer's disease: review. *Journal of Drug Targeting*, *27*(2), 164–173. https://doi.org/10.1080/1061186X.2018.1474361

Lee, C., Yang, W., & Parr, R. G. (1988). Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Physical Review B*, *37*(2), 785–789. https://doi.org/10.1103/PhysRevB.37.785

Liu, Y., Nguyen, M., Robert, A., & Meunier, B. (2019). Metal Ions in Alzheimer's Disease: A Key Role or Not? *Accounts of Chemical Research*, *52*(7), 2026–2035. https://doi.org/10.1021/acs.accounts.9b00248

Masters, C. L., Bateman, R., Blennow, K., Rowe, C. C., Sperling, R. A., & Cummings, J. L. (2015). Alzheimer's disease. *Nature Reviews Disease Primers*, *1*, 1–18. https://doi.org/10.1038/nrdp.2015.56

M. J. Frisch, G., Trucks, W., Schlegel, H. B. ., Scuseria, G. E. ., Robb, M. A. ., Cheeseman, J. R., … Fox, D. J. (2009). *Gaussian 09, Revision E. 01; Gaussian*. *Gaussian, Inc.: Wallingford, CT*. https://doi.org/111

Mulliken, R. S. (1955). Electronic population analysis on LCAO-MO molecular wave functions. I. *The Journal of Chemical Physics*, *23*(10), 1833–1840. https://doi.org/10.1063/1.1740588

Mulliken, R. S. (1955). Electronic population analysis on LCAO-MO molecular wave functions. II. Overlap populations, bond orders, and covalent bond energies. *The Journal of Chemical Physics*, *23*(10), 1841–1846. https://doi.org/10.1063/1.1740589

Mulliken, R. S. (1955). Electronic population analysis on LCAO-MO molecular wave functions. III. effects of hybridization on overlap and gross AO populations. *The Journal of Chemical Physics*, *23*(12), 2338–2342. https://doi.org/10.1063/1.1741876

Naim, M. J., Alam, M. J., Ahmad, S., Nawaz, F., Shrivastava, N., Sahu, M., & Alam, O. (2017). Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship. *European Journal of Medicinal Chemistry*, *129*, 218–250. https://doi.org/10.1016/j.ejmech.2017.02.031

Patil, V., Tilekar, K., Mehendale-Munj, S., Mohan, R., & Ramaa, C. S. (2010). Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4- thiazolidinedione derivatives. *European Journal of Medicinal Chemistry*, *45*(10), 4539–4544. https://doi.org/10.1016/j.ejmech.2010.07.014

Pérez, M. J., & Quintanilla, R. A. (2015). Therapeutic Actions of the Thiazolidinediones in Alzheimer's Disease. *PPAR Research*, *2015*. https://doi.org/10.1155/2015/957248

Prati, F., Cavalli, A., & Bolognesi, M. L. (2016). Navigating the Chemical Space of Multitarget-Directed Ligands: From Hybrids to Fragments in Alzheimer's Disease. *Molecules*, *21*(4). https://doi.org/10.3390/molecules21040466

Qiu, C., & Fratiglioni, L. (2018). Aging without Dementia is Achievable: Current Evidence from Epidemiological Research. *Journal of Alzheimer's Disease*, *62*(3), 933–942. https://doi.org/10.3233/JAD-171037

Ramsay, R. R., Popovic-Nikolic, M. R., Nikolic, K., Uliassi, E., & Bolognesi, M. L. (2018). A perspective on multi-target drug discovery and design for complex diseases. *Clinical and Translational Medicine*, *7*(1), 3. https://doi.org/10.1186/s40169-017-0181-2

Rančić, M. P., Stojiljković, I., Milošević, M., Prlainović, N., Jovanović, M., Milčić, M. K., & Marinković, A. D. (2019). Solvent and substituent effect on intramolecular charge

transfer in 5-arylidene-3-substituted-2,4-thiazolidinediones: Experimental and theoretical study. *Arabian Journal of Chemistry*, *12*(8), 5142–5161. https://doi.org/10.1016/j.arabjc.2016.12.013

Reddy, K. A., Lohray, B. B., Bhushan, V., Reddy, A. S., Kishore, P. H., Rao, V. V., … Rajagopalan, R. (1998). Novel euglycemic and hypolipidemic agent. Part 2: Antioxidant moiety as structural motif. *Bioorganic and Medicinal Chemistry Letters*, *8*(9), 999–1002. https://doi.org/10.1016/S0960-894X(98)00159-0

Safi, Z. S. (2016). A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione - water complex. *Arabian Journal of Chemistry*, *9*(5), 616–625. https://doi.org/10.1016/j.arabjc.2015.03.016

Scott, L. J., & Goa, K. L. (2000). Galantamine: A review of its use in Alzheimer's disease. *Drugs*, *60*(5), 1095–1122. https://doi.org/10.2165/00003495-200060050-00008

Tahmassebi, D. (2003). Theoretical studies of the tautomerism in oxazolidine and thiazolidine heterocyclic systems. *Journal of Molecular Structure: THEOCHEM*, *638*(1–3), 11–20. https://doi.org/10.1016/S0166-1280(03)00239-2

Ulep, M. G., Saraon, S. K., & McLea, S. (2018). Alzheimer Disease. *Journal for Nurse Practitioners*, *14*(3), 129–135. https://doi.org/10.1016/j.nurpra.2017.10.014

Yiannopoulou, K. G., & Papageorgiou, S. G. (2013). Current and future treatments for Alzheimer's disease. *Therapeutic Advances in Neurological Disorders*, *6*(1), 19–33. https://doi.org/10.1177/1756285612461679