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Computational Study of the Antioxidative Potential of Substituted Hydroxy-2-arylbenzothiazole Derivatives

MUSA ELBALLA MOHAMED BABIKER

Department of Chemistry, Faculty of Science, Albaha University, Albaha 65779, Saudi Arabia

*Corresponding author: Tel: +966 558841537; E-mail: musa.elballa@gmail.com

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This study use density functional theory B3LYP/6-31+G(d) methods to examine theoretically the electrical and structural characteristics of substituted hydroxy-2-arylbenzothiazole derivatives, which contribute to their ability to scavenge free radicals. It was found that the antioxidant activities increase with small the energy gap ΔE (E_L–E_H), lower ionization potential (IP), lower hardness (η), higher softness (S), higher dipole moment, higher negative total energy of optimization and high the net charge. These values are interpreted with experimental equivalent antioxidant values. Two series of compounds, series one, compounds **1-6** (hydroxyl groups attached to aryl ring) and series two *viz*. compounds **7-10** (substituent to *ortho*-position of phenyl ring) were studied. It was observed that in series one, compound **6** with three hydroxy substituent had the lowest energy gap ΔE, lowest IP, lowest hardness (η), highest softness (S), highest dipole moment, highest total negative energy of optimization and compound **1** with no substituent had highest energy gap ΔE, highest IP, highest hardness (η), lowest softness (S), lowest dipole moment, lowest negative total energy of optimization. The results of the antioxidant activity are in the following order: **6 > 5 > 4 > 2 > 3 > 1**. The introduction of the strongly electron-withdrawing substituent, $-NO_2$ and –CN groups attached to phenyl ring of hydroxy-2-arylbenzothiazole nucleus improve the effect of antioxidant activity. On the basis of these findings, a novel antioxidant compound that possesses enhanced activity can be developed.

Keywords: Substituted hydroxy-2-arylbenzothiazoles, Antioxidant activity, DFT calculations, Energy gap.

INTRODUCTION

Among nitrogen heterocycles, benzothiazoles consist of important fundamental structural motifs in a wide variety of naturally occurring and artificially produced drugs with physiological activity [1]. Both heterocycles (benzene and thiazole) have attracted a lot of attention in medicinal chemistry as potential building blocks for various physiologically active derivatives, which could have pharmacological, chemical or industrial uses [2,3]. Their derivatives exhibit a wide range of biological activities, including anti-inflammatory, anticancer, antiviral, antibacterial and antifungal activities [4-6].

The intriguing pharmacological characteristics of benzothiazole derivatives have resulted in the emergence area of study. Extensive research on the antibacterial, anticancer and antiviral effects of benzothiazole analogues revealed a wide range of structural diversity [7]. Central rings and connected substituents have a significant impact on binding affinity and selectivity, in addition to the benzothiazole core and its many possible biological effects. A number of 2-arylbenzothiazole derivatives have been synthesized and shown anticancer activity [8-10]. The research on structural-activity relationships (SAR) intriguingly demonstrate that altering the structure of substituent group at the C-2 position typically leads to a corresponding change in its bioactivity.

The antiproliferative activity of 2-phenylbenzothiazole derivatives is significantly influenced by position and type of the amidino group on the targeted molecule [11]. Currently, medicinal chemists are primarily interested in developing new antioxidative medicines. This interest has grown due to the new findings that oxidative damage to essential biomacromolecules is directly linked to the pathogenesis of various diseases [12,13]. Thus, reactive oxygen species (ROS) can contribute significantly to the development of cancer, atherosclerosis, aging and rheumatoid arthritis by damaging cellular biomacromolecules such as proteins, lipids and DNA/RNA [14,15]. Lipid peroxidation, a chain process triggered by ROS, can produce mutagenic substances that have carcinogenic qualities [16].

Several natural and synthetic compounds have the ability to act as antioxidants and are being investigated as potential agents that can decrease the formation of reactive oxygen species (ROS) and the oxidation of biomacromolecules [17]. Several articles have been documented the antioxidative activity and promise of benzothiazole derivatives as agents with antioxidative activities. Additionally, a several benzothiazoles with 2-aryl substitution has demonstrated antioxidative properties and significant ability to scavenge radicals, which may be attributed due to the presence of electron donating substituents [18]. Based on the different types of substitutions, it was clear that increasing the number of hydroxy groups linked to the phenyl ring led to an improvement in scavenging activity [19]. The antioxidative activity is highly controlled by the varying amount of hydroxy groups linked to the phenyl ring, with the trihydroxy substituted derivatives exhibiting the highest level of activity [19].

Computational chemistry has emerged as a compelling field for investigating chemical challenges or issues using a laptop or modern computer [20]. It is a rapidly growing and stimulating field that focuses on the visual representation and theoretical computation of various systems, including medicines, polymers, biomolecules, organic and inorganic compounds, and biomolecules [21]. Theoretical methodologies, specifically density functional theory (DFT), have proven effective in predicting the physico-chemical descriptors associated with various mechanisms of radical scavenging activity [22-27]. Moreover, DFT has been utilized to establish structure-activity relationships (SARs) for phenolic antioxidants [28-31]. As far as we know, there have been no theoretical studies conducted on the antioxidant properties of substituted hydroxy arylbenzothiazoles or their derivatives.

Based on the aforementioned findings, it is suggested to design subsituted hydroxyl-2-arylbenzothiazoles derivatives to assess their antioxidant potential. The data obtained were analyzed in relation to SAR (structure-activity relationship) to determine the influence of the position and number of hydroxy groups, as well as the kind of substituent group linked to the phenyl ring of hydroxy-2-arylbenzothiazole nucleus, on the antioxidative activity of derivative models.

COMPUTATIONAL METHODS

The calculations for the title compounds were performed using the Gaussian 09 program package [32]. The substituted hydroxy-2-arylbenzothiazole derivatives, including neutrals and radical cations, have undergone geometry optimization and frequency analysis in the gaseous phase. The electrical ground states of the system were thoroughly optimized using the B3LYP/6-31+G(d) level of theory [33,34], which is confirmed by absence of any imaginary frequencies. Unrestricted computations have been performed for open shell systems, such as radical cations, without any interference from spin impurities. The frontier molecular orbitals *e.g.* HOMO and LUMO, have been depicted for both neutral molecules and radical cations, following the same level of structural optimization. Additionally, global reactivity descriptors have been computed. The Gaussian calculations were conducted at the standard conditions of 298 K and 1 atm.

The accuracy of this computational setup in modeling the processes of several antioxidants was another factor that influenced its choice [35]. Several mechanisms are associated with a molecule's antioxidative capabilities, as reported in the literature [36]. The two most common and thermodynamically preferred antioxidant mechanism are hydrogen atom transfer (HAT) and single electron transfer (SET), often accompanied by proton transfer (SET-PT). All of these methods lead to the formation of the identical antioxidant radical.

RESULTS AND DISCUSSION

Two series of compounds were studied *i.e.* series one contains compounds **1-6**, as they have hydroxyl groups attached to aryl ring (positions and numbers) and series two (compounds **7-10**) consist of substituent to *o*-position of phenyl ring of nucleus compound (Fig. 1).

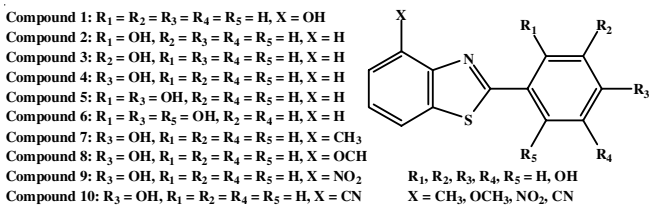

Fig. 1. Substituted 2-aryl benzothiazole derivatives with antioxidative activity

Energy difference of HOMO and LUMO (ΔE); ionization potential and dipole moment: In recent times, FMO analysis has emerged as a crucial tool for understanding the electrical properties and reactivity of substances. The transfer of electrons from the ground state to the excited state primarily occurs from the frontier molecular orbitals. The kinetic stability and reactivity of the compounds can also be explained by the energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (ΔE). A higher value of ΔE indicates that the chemical is less reactive and has a more stable kinetically. A less stable and more reactive molecule is the result of an electron mobility from the HOMO to the LUMO that is facilitated by a low ΔE [37]. According to the computational details, the systems with lower ΔE exhibit superior antioxidant properties through the H-atom transfer pathway, while lower ionization potential values suggest the stronger antioxidants through the single electron transfer mechanism.

The energies of HOMO and LUMO, energy gap (ΔE), ionization potential (IP), energy values and the calculated dipole moment values, the hardness (η) and softness (S) of the studied compounds are given in Tables 1 and 2. In present work, the unsubstituted parent compound **1** will serve as a reference point for subsequent derivatives as its ΔE value is 0.162 a.u., which is much greater than all substituted derivatives.

The ΔE values of all substituted hydroxyl-2-arylbenzothiazole derivatives (**1-6**) were in the range 0.153-0.162 a.u. It was observed that compound **6** consisted of three -OH groups attached to aryl ring of benzothiazole nucleus had the lowest energy gap (ΔE) value of 0.153 a.u., so it was the least stable and more reactive compound among this series. According to

TABLE-1
ENERGY PARAMETERS FOR THE OPTIMIZED STRUCTURES OF SUBSTITUTED HYDROXYL-2-ARYL BENZOTHIAZOLE DERIVATIVES (**1-6**)[(a)] AT THE B3LYP/6-31+G(d) LEVEL OF THEORY

Compd.	E_{LUMO} (a.u.)	E_{HOMO} (a.u.)	E_L-E_H (a.u.)	Dipole moment (D)	Ionization potential (a.u.)	Total energy (a.u.)	Hardness (η)	Softness (S)
1	-0.0702	-0.2318	0.162	0.811	0.2824	-0953.7835	0.081	12.34
2	-0.0657	-0.2237	0.158	1.880	0.2736	-1028.9965	0.079	12.65
3	-0.0702	-0.2307	0.161	2.028	0.2809	-1029.0044	0.080	12.50
4	-0.0641	-0.2215	0.157	2.294	0.2706	-1029.0059	0.078	12.82
5	-0.0594	-0.2169	0.157	2.558	0.2652	-1104.2194	0.078	12.82
6	-0.0658	-0.2189	0.153	3.701	0.2269	-1179.4500	0.076	13.16

[(a)]All atomic parameters are in atomic unit.

TABLE-2
GLOBAL REACTIVITY DESCRIPTORS, FOR THE OPTIMIZED STRUCTURES OF SUBSTITUTED HYDROXY 2-ARYL BENZOTHIAZOLE DERIVATIVES (**7-10**)[(a)]

Compd.	E_{LUMO} (a.u.)	E_{HOMO} (a.u.)	E_L-E_H (a.u.)	Hardness (η)	Softness (S)	Total energy (a.u.)
7	-0.0637	-0.2189	0.155	0.077	12.98	-1068.3253
8	-0.0593	-0.2117	0.152	0.076	13.15	-1143.5289
9	-0.0856	-0.2352	0.149	0.074	13.51	-1233.5043
10	-0.0846	-0.2342	0.149	0.074	13.51	-1121.2505

[(a)]All parameters are in atomic unit.

the findings conducted on antioxidant activity, the identical results were obtained with compound **6** containing three hydroxyl groups [19]. Compounds **2**, **3** and **4** with hydroxyl group at *ortho*-, *meta*- and *para*-positions with ΔE value equal 0.158, 0.161 and 0.157 a.u., respectively. This indicate that compound **4** more reactive than compound **2** and compound **2** more reactive than compound **3**. Compound **5**, with two hydroxyl group at *ortho*- and *para*-positions with ΔE value of 0.157 a.u. is same as that for compound **4**. The order of reactivity of compounds of series one with hydroxyl groups attached to aryl ring to benzothiazole nucleus as follows: **6 > 4 = 5 > 2 > 3 > 1**.

As can be seen from Gaussian calculations (Table-1), compound **6** has lower ionization potential (IP) value of 0.2269 a.u., thus less stable and more reactive one in the series. The order of IP as follows: **6 > 4 > 5 > 2 > 3 > 1**. Whereas the dipole moment order is presented as: **6 > 5 > 4 > 3 > 2 > 1**. Hence, the polarity of compound **6** with three hydoxy groups is better than the others.

The addition of a hydroxyl group (-OH) and electron-donating substituents on the phenyl ring greatly enhances the antioxidative properties and exhibits favorable behaviour. The preferred location for H-atom abstraction shifts towards the hydroxy moiety due to the O-H group's tendency to undergo homolytic cleavage more easily [38]. This highlights the need to focus on designing antioxidants that are more efficient. This concept coincides completely with the demonstrated antioxidative properties of several phenols and polyhydroxy aromatics that have been documented in other sources [39].

In order to examine the impact of electron-donating and electron-withdrawing groups on the reactivity of compound **4** (*para*-hydroxy substituent), these groups were introduced in the *ortho*-position to the phenyl ring of benzothiazole nucleus. This was done based on the hydroxyl groups present on the aryl ring attached to the benzothiazole nucleus (series two). As observed from Table-2, compounds **9** and **10** consist of nitro and cyano group, respectively at *ortho*-position have same, energy gap (ΔE) value of 0.149 a.u. lower than that of compound **4** (0.157 a.u.). Compounds **8** and **7** containing methoxy and methyl group have (ΔE) value equal 0.152 and 0.155 a.u., respectively. The introduction of the strongly electron-withdrawing substituent, NO_2 and CN groups in compounds **9** and **10**, improve their activity compare to compounds **7** and **8** and made their ΔE smaller, thus making it the most reactive one. Thus the order of reactivity in series two as follows: **10 = 9 > 8 > 7 > 4**.

Mullikan atomic charge: The site with the highest negative electronic charge is the most favourable location for electrophilic attack. The regions with strong negative electronic charges are found close to the oxygen of hydroxyl groups. In benzene rings, all the carbon atoms should be negatively charged, but some aromatic ring carbons are positively charged. This could be because the nitrogen atom N20 is attached to these carbons in the five-membered ring (Table-3). Similar to other hydrogen atoms in the compounds, all of the hydrogen atoms in the molecules under study are determined to be somewhat positively charged.

The highest negative atomic charges are present in the 23th position oxygen atom of hydroxyl group in compound **4** (O_{23} = -0.699), compound **3** (O_{23} = -0.690) and compound **2** (O_{23} = -0.607) (Table-3). These theoretical values highly correlated with the metal binding properties of hydroxy 2-arylbenzothiazoles compounds. Comparison of the present results with those compounds, the atomic charges are in the order of **4 > 3 > 2**. From these results, it is concluded that 23th oxygen atom (-OH) in 2-arylbenzothiazole compounds have higher charges, hence chelation by metal occur in the 23th position hydroxy group. The significant negative charge is due to the increased number of hydroxyl oxygen atoms in compounds **5** and **6**. Compound **6** consisting three hydroxyl groups has a negative

TABLE-3
MULLIKAN CHARGES OF THE OPTIMIZED STRUCTURES OF SOME BENZOTHIAZOLE DERIVATIVES BY B3LYP/6-31+G(d)

Compound **2**		Compound **3**		Compound **4**		Compound **5**		Compound **6**		Compound **9**	
Type	Charge	Type	Charge	Type	Charge	Type	Charge	Type	Charge	Type	Charge
C1	-0.441	C1	-0.205	C1	-0.245	C1	-0.423	C1	-0.511	C1	-0.562
C2	0.915	C2	0.553	C2	0.580	C2	0.924	C2	0.989	C2	0.685
C3	-0.881	C3	-0.622	C3	-0.629	C3	-0.875	C3	-0.875	C3	-0.465
C4	0.128	C4	0.089	C4	0.095	C4	0.116	C4	0.155	C4	0.004
C5	-0.310	C5	-0.260	C5	-0.271	C5	-0.309	C5	-0.318	C5	0.115
C6	-0.343	C6	-0.381	C6	-0.386	C6	-0.410	C6	-0.328	C6	-0.299
C7	0.791	C7	0.094	C7	0.231	C7	0.784	C7	0.999	C7	0.308
C12	0.563	C12	0.406	C12	0.472	C12	0.804	C12	0.618	C12	-0.457
C13	-0.876	C13	-0.228	C13	-0.603	C13	-1.200	C13	-0.920	C13	-0.643
C14	-0.270	C14	-0.826	C14	-0.672	C14	-0.408	C14	0.577	C14	-0.142
C15	-0.143	C15	-0.641	C15	-0.014	C15	0.192	C15	-0.834	C15	-0.053
C16	0.075	C16	0.458	C16	0.042	C16	0.102	C16	-0.444	C16	-0.082
C17	-0.525	C17	0.192	C17	0.030	C17	-0.226	C17	-0.074	H17	0.173
H18	0.183	H18	0.185	H18	0.170	H18	0.170	H18	0.150	H18	0.203
H19	0.165	H19	0.168	H19	0.197	H19	0.180	H19	0.177	N19	-0.025
H20	0.185	N20	-0.098	N20	-0.114	N20	-0.154	N20	-0.148	S20	0.181
N21	-0.148	S21	0.153	S21	0.146	S21	0.081	S21	0.507	H21	0.189
S22	0.084	H22	0.184	H22	0.189	H22	0.191	O22	-0.686	O22	-0.662
O23	-0.607	O23	-0.690	O23	-0.699	O23	-0.678	H23	0.482	H23	0.480
						H24	0.483	O24	-0.611	H24	0.230
						O25	-0.608	H25	0.525	N25	-0.388
								O26	-0.700	O26	0.015
								H27	0.537	O27	0.015

charge of -0.920 on C-13 and -0.834 on C-15, which is higher than the negative charges of any other C-13 or C-15 type in any other molecule.

Hardness (η) and softness (S): The molecule stability is directly related to the hardness parameter (η), while chemical reactivity can be understood by looking at the softness parameter (S). The values of global reactivity descriptors are given in Table-1. In present studies, the calculated chemical hardness (η) of molecule **6** is lowest in series one in the gasous phase reflecting their lower stabilities. The order of softness parameter for series one is **6 > 4 = 5 > 2 > 3 > 1**, the same results can be obtained from the energy gap, revealing that molecule **6** are more favourable in the charge-transfer mechanism than other molecules.

The scavenging activity of phenolic antioxidants is determined by the O-H bond dissociation energy (BDE) [40], which is primarily governed by the stability of the phenoxyl free radical formed following H-abstraction for the antioxidant. In general, factors that improve the stability of free radicals increase antioxidant activity. The polar effect, which includes inductive and resonance stabilization, is responsible for the stability of the parent molecule (SPM), whereas the spin delocalization of the unpaired electron determines the stability of the phenoxyl radical (SPR) [41]. The radical resonance structure of substituted hydroxy-2-arylbenzothiazoles is stabilized by the resonance effect, which converts it into a phenoxyl radical species that is more stable due to electron delocalization between adjacent benzene rings and the benzothiazole nucleus (compound **2**) has ten resonance structures (Fig. 2).

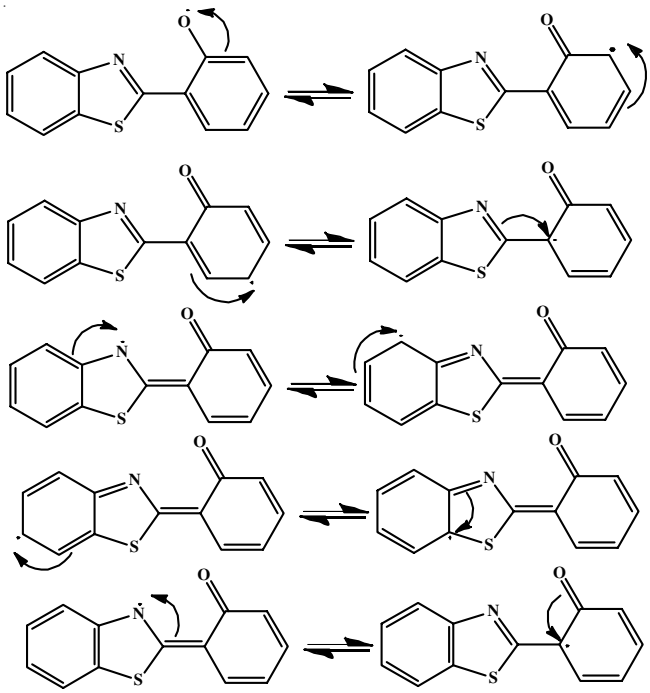

Fig. 2. Resonance structures of *ortho*-hydroxy-2-arylbenzothiazole radical

Conclusion

The antioxidant activity of substituted hydroxy-2-arylbenzothiazoles derivatives was studied by the density functional theory (DFT) method in gaseous phase. The main energy parameters responsible for antioxidant potential in this work, are

the energy gap ΔE, ionization potential (IP), Mullikan net charge of oxygen atom (-OH), the hardness (η) and the softness (S). The results obtained from the used calculations of antioxidative parameters indicated that the number and the position of hydroxy groups strongly influenced the antioxidative activity of studied compounds. Trihydroxy substituted 2-arylbenzothiazole compound **6**, was found to be the most power one as antioxidant and compound **1** with no substituent hydroxyl group, the lowest one as antioxidant. It is also found that strongly electron withdrawing substituent, $-NO_2$ and –CN groups attached to the phenyl ring of 2-arylbenzothiazole improve their antioxidant activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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