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Draft

Calculated antioxidant activity of selected Phenolic Compounds

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ABSTRACT. Determination of the corresponding bond dissociation enthalpy, ionization potential and proton affinity, dipole moment values, highest occupied molecular orbital eigenvalues, and spin density along with the bioactivity score is central to the antioxidant activity evaluation in this paper. Molecular geometries were optimized with DFT using B3LYP and UB3LYP for parent, ionic, and radical species, and 6-311+G(d,p) basis set. Bioactivity, drug-likeness, and drug-scores were calculated using freely available cheminformatics programs for data visualization and analysis. Overall, the values revealed two structures as promising molecules because of good reaction enthalpies (ΔH_r). Lipinski rules were fully satisfied for all molecules.

Key words: Antioxidant activity, Reaction enthalpies, Bioactivity scores

INTRODUCTION

Essential oils have attracted the interest of the scientific community because of their properties.¹ Numerous studies to highlight their importance are conducted each year. Discovery of efficient antimicrobial compounds against multidrug-resistant microbes is needed. Plants naturally produce secondary metabolites for protection against these infectious agents. Efforts are being made to identify such antimicrobial substances from plants and use them as therapeutic agents.² These natural products also exert anticancer activities in vivo. Cancer suppressive activities of essential oils have been demonstrated using human cancer cells, including glial, colon, gastric, hepatic, pulmonary, breast, and blood cells.³ The essential oil of *Myristica fragrans* contains myristicin as the major component, which shows hepatoprotective activity against carcinogenesis.⁴

Essential oils are complex mixtures of organic compounds, such as alkaloids, phenolic compounds, quinones, flavonoids, tannins, coumarins, and terpenoids. Eugenol and thymol are reported to exhibit the highest antioxidant activity against low density lipoprotein oxidation.⁵ The essential oils of *Artemisia arborescence* are reported to be cytotoxic against HSV-1 and HSV-2 viruses; therefore, they are used for the treatment of malaria, hepatitis, cancer, inflammation, and fungal and bacterial infections.⁶ These previously discussed medicinal uses of essential oil components have attracted further research in this field. Moreover, industrial applications of these components also contribute to the importance of this natural resource; fragrance and flavor industries have been using these essential oils and natural products since the nineteenth century.⁷ Haarmann and Reimer manufacturers produced synthetic aroma chemicals in 1876 for the first time.⁷ Nowadays, perfumes, toiletries, detergents, household chemicals, cosmetics, etc. contain natural essential oils or their synthetic constituents.

2-Propenyl-benzene and chalcone derivatives are phytochemicals found as main components of these essential oils. The profile of this class of compounds directed structure–activity relationship (SAR) studies^{8,9} with promising results. Figure 1 illustrates the general structure of these compounds as 1,3-diarylprop-2-en-1-ones, known as chalcones 1, and 1,4-diarylbut-3-en-2-ones 2. These are highly oxidized substances with great potential uses. Their wide use and applications, along with the risk of high toxicity, have rendered the identification of bioactive substances with analogous properties to those mentioned below, a promising research area.¹⁰⁻¹³ Bioactivity of such compounds greatly depends on conjugation and substituent electrophilicity¹⁴ as well as inductive and mesomeric effects on α,β -unsaturated ketone moiety.¹⁵

Lipid peroxidation by free radicals, which are responsible for various diseases, can be counteracted if antioxidant

bioactive compounds are used.¹⁶ Studies have found that oxidative damage and inflammatory conditions are correlated.¹⁷ Therefore, the design of antioxidants is a promising field of research. Prediction of antioxidant activity improves the bioactivity of new compounds with low toxicity.

Antioxidant activity depends on the substitution pattern of the two aryl rings of chalcones. The hydroxyl substituent is proven to enhance the antioxidant activity of chalcones through a hydrogen atom transfer mechanism.¹⁸ The antioxidant activity of this type of molecules is based on the formation of phenoxy radicals owing to the high reactivity of phenolic hydroxyl groups. The mechanism of action of phenolic antioxidants is considered to involve the scavenging of free radicals.¹⁹ The most accepted mechanisms involve hydrogen atom transfer (HAT) (Eq. 1) and single-electron transfer, followed by proton transfer (SET-PT) (Eq. 2a and 2b).

Another mechanism, sequential proton-loss electron-transfer (SPLET), has been discovered and confirmed on the basis of kinetic experiments²⁰⁻²¹ (Eq. 3a and 3b).

Reaction enthalpies (ΔH_r) related to the above mentioned mechanisms are usually denoted as bond dissociation enthalpy (BDE), ionization potential (IP), proton dissociation enthalpy (PDE), proton affinity (PA), and electron transfer enthalpy (ETE). The corresponding calculated reaction enthalpies correlate well with the experimental results of antioxidant activity; with higher antioxidant activity, the reaction enthalpy would be lower.²²⁻²⁵

In this study, 12 structural variants of 1,3-diarylprop-2-en-1-ones and 1,4-diarylbut-3-en-2-ones (Chart 1) were examined as radical scavengers by thermodynamics on a theoretical basis. The estimation of the corresponding gas-phase ΔH_r values for BDE, IP, and PA mechanisms; dipole moment values; highest occupied molecular orbital (HOMO) eigenvalues; and spin density surfaces along with the bioactivity score was central to the antioxidant activity evaluation in this study. DFT method with B3LYP²⁶⁻²⁷ functional was used in this study as this method

produces accurate structural geometries of phenolic antioxidants²⁸⁻²⁹

EXPERIMENTAL

Molecular geometries were optimized with DFT using B3LYP and UB3LYP for parent, ionic, and radical species, and 6-311+G(d,p) basis set.^{30,31} For all calculations and comparisons in this study, only the most stable conformations were considered. The double bond in the molecules had trans configuration, which are thermodynamically and biologically favored. No imaginary frequencies were found; therefore, the calculated geometries were local minima in a potential energy surface. Calculations were performed using Gaussian09 software.³² Reaction enthalpies, ΔH_r , were estimated from the calculated enthalpies of all gas-phase products and reactants $H(X)$, as the following equation illustrates.³³

$$H(X) = E_0 + ZPE + E_{trans} + E_{rot} + E_{vib} + RT$$

$$\Delta H_r = \sum H_{products} - \sum H_{reactants}$$

where E_0 is the total electronic energy, ZPE is the zero-point energy, and E_{trans} , E_{rot} , and E_{vib} are translational, rotational, and vibrational contributions to enthalpy, respectively. The calculated gas-phase enthalpy of proton, $H(H^+)$, and electron, $H(e^-)$, is 6.2 and 3.1 kJ mol⁻¹, respectively.³⁴ Drug-likeness and drug scores were calculated with OSIRIS Property Explorer³⁵ and bioactivity scores were calculated using Molinspiration Cheminformatics software.³⁶

RESULTS AND DISCUSSION

BIOAVAILABILITY AND BIOACTIVITY ASSESSMENT

The in silico drug-relevant properties obtained with OSIRIS, such as mutagenic (M), tumorigenic (T), irritant (I), and reproductive effects (RE) as well as ClogP, S (solubility), MW, TPSA, drug-likeness (DL), and drug-score (DS), nON = number of hydrogen bond acceptors; nOHNH = number of hydrogen bond donors are presented in Table 1. Drug-likeness³⁷ of bioactive compounds is calculated by OSIRIS Property Explorer³⁵ program using a database of marketed drugs and commercially available compounds (Fluka) to assess the occurrence of structural fragments. Drug-likeness³⁷ was calculated as the sum of the scores for the fragments present in the molecule under study. These scores were determined as the logarithm of the quotient of frequencies of fragments present in the marketed drugs versus Fluka chemicals. A distribution diagram of drug-likeness of the fragments from marketed drugs and Fluka

chemicals showed that 80% of the fragments of the marketed drugs have a positive drug-likeness score, whereas those from Fluka chemicals have negative values.³⁷ Thus, a positive drug-likeness value calculated by the OSIRIS program indicates that the molecule under investigation contains structural fragments that are frequently present in commercial drugs.

Drug-score combines ClogP, LogS, MW, toxicity risks, and drug-likeness to evaluate the potential of a compound as a drug candidate. A compound's overall potential as a drug depends mainly on hydrophobicity, electronic distribution, hydrogen bonding, molecular volume, conformation, and pharmacophoric patterns. Table 1 shows that Molecule 08 had the highest drug-likeness score and molecule 06 and 08 had the highest drug-score.

Lipinski rules are a guide to evaluate bioavailability in humans.³⁸ Absorption, distribution, metabolism, and excretion (ADME) are important aspects of drug pharmacokinetics³⁹ that Lipinski rules take into account. According to Lipinski's rule of five, an ideal drug candidate for in vivo administration has a ClogP value under 5, molecular weight under 500 g/mol, number of hydrogen bond donors (nOHNH) less than five, and number of hydrogen bond acceptors (nON) less than ten. ClogP values of 2.76–4.21 indicated that the compounds in this study are lipophilic and can cross biological membranes. Molecular weights of 268–412 were within the Lipinski limit of 500; molecules 01–12 fulfill nOHNH and nON limits. All the molecules considered in this study followed Lipinski's rules (Table 1).

Another important descriptor of bioavailability in medicinal chemistry is the total polar surface area (TPSA),⁴⁰ which ranged between 46.53 and 83.45 Å² for molecules 01–12. TPSA directs human intestinal absorption, permeability, and blood-brain barrier penetration. Molecules with TPSA greater than 140 Å² do not adequately permeate cell membranes⁴¹, whereas TPSA less than 90 Å² indicates good cell membrane permeability⁴¹; molecules 01–12 also exhibited TSPA under 90 Å². However, low water solubility (*S*) also results in reduced absorption; therefore, poorly soluble compounds are not recommended. *S* distribution analysis in marketed drugs showed that more than 80% of the commercially available drugs have an *S* value greater than -4.0.³⁵ Table 1 shows that molecules 01–12 have water solubility ranging between -4.08 and -3.03. An adequate water solubility indicates a favorable ClogP, and molecules 01–12 could be predicted to cross cell membranes.

Based on toxicity risk assessment shown in Table 1 in terms of mutagenicity (M), tumorigenicity (T), irritation potential (I), and reproductive effects (RE), molecules 04 and 05 were shown to possess structural fragments that may have reproductive effects. All molecules showed favorable bioavailability and safety profiles. However,

molecules 04 and 05 were associated with the risk of causing reproductive effects.

Bioactivity score calculated using Molinspiration Cheminformatics software uses Bayesian statistics to calculate a score by comparing with G protein-coupled receptor (GPCR) ligands, ionic channel modulators, kinase inhibitors, DNA ligands, proteases inhibitors, and enzyme inhibitors.³⁶ If the score is (>0) the compound is active, if ($-5.0-0.0$) slightly active, and (<-5.0) inactive. GPCR ligands are involved in many diseases and represent 40% of modern therapies.³⁶ The compounds evaluated in this study have higher similarity to enzymatic inhibitors and GPCR ligands (Table 2). None of the molecules were inactive, and interestingly, molecule 06 was the most active as an enzyme inhibitor and as a GPCR ligand.

Thus far, molecules 06 and 08 are promising compounds in terms of predicted bioactivity and pharmacokinetics; similar structural features among them could explain the proximity to previously reported results. Surprisingly, molecules 06 and 08 showed superior bioactivity to chalcone type molecules 01 and 03. When comparing molecule 08 to molecule 06, the only differentiating fragment was a methoxy group in place of a hydroxy group, which is a stronger electron donor than the methoxy group. This could imply that the interaction of molecule 06 with biological targets requires strong electrostatic interactions. From the electrostatic potential maps in Figure 2, the intense two positive areas in blue developing upon hydroxyl hydrogens in molecule 06 can be clearly seen, in contrast to the unique hydroxyl hydrogen in molecule 08, which is an area of minor intensity. This is hindered by the proximity of the bulky methoxy group, as shown in the optimized geometries in Figure 2.

EQUILIBRIUM GEOMETRY

Gas phase frequency values of the most characteristic groups matched the calculated ones.⁴² The harmonic frequencies, $\nu(\text{O-H})_{\text{phenyl}}$ and $\nu(\text{C=O})$, were chosen on the basis of the importance of the bond. All calculated frequency values, $\nu(\text{O-H})_{\text{phenyl}} = 3743-3849 \text{ cm}^{-1}$ and $\nu(\text{C=O}) = 1718-1790 \text{ cm}^{-1}$, are in agreement with the characteristic gas phase values of $\nu(\text{O-H})_{\text{phenyl}} = 3651 \text{ cm}^{-1}$, and $\nu(\text{C=O}) = 1762 \text{ cm}^{-1}$. This could account for the correctness of the equilibrium geometries.

Phenolic O-H bond length was considered as an important descriptor of hydrogen donating ability however the proximity of the calculated O-H bond-lengths values is unsuitable to compare antioxidant activity of phenolic compounds.²⁸ Dipole moments for the antioxidants under study are provided in Table 3. Molecule 09 and 05 showed the lowest ($\mu=2.689$) and the highest ($\mu=6.405$) dipole moments, respectively. Molecules with low hydrophilicities

and therefore high logP values cause poor distribution in the lipid bilayer of the cell membranes. Dipole moment do not sufficiently account for absorption or permeation. However, as shown in Table 1, *S* values correlated with ClogP. Our data showed that molecules with *S* values greater than -4 have ClogP values of around 2.76–3.79, corresponding to the lower range of ClogP values indicated in the Lipinski rule. Moreover, a high ClogP value is not recommended because it indicates low hydrophilicity and poor absorption. Therefore, it was concluded that the hydrophilicity of molecules 01–12 is adequate for human absorption.

ANTIOXIDANT ACTIVITY

HOMO-LUMO eigenvalues are parameters that allow the prediction of molecular electron-donating ability; the lower the *E*_{gap}, the higher the antioxidant activity.⁴³ With a low magnitude of the energy band gap, molecules 12, 11, 04, and 08 hold high antioxidant potential (Table 3). They have a higher HOMO orbital energy indicating stronger electron donating abilities; HOMO orbitals in these molecules are mainly localized on the phenolic oxygen atom.

Another method to predict the free radical scavenging activity of phenolic compounds is based on the stability of their phenoxyl radicals. Radicals stabilize as the spin density is delocalized through the structure. Delocalization of the spin density occurs when the spin density (SD) is small at every atom of the radical.⁴⁴ When SD is close to 1, the unpaired electron on that atom does not get distributed over the radical structure. In this study, we found that the unpaired electron mainly distributed over radical structures, and SDs ranged between 0.31 and 0.63 (Table 4). Radicals of molecules 11, 01, and 08 exhibited large spin delocalization, and those of molecules 05, 06, and 07 had their spin delocalization focused on the benzene ring (Figure 3). Radicals of molecules 11, 01, and 08 demonstrated to be the most stable, indicating that they have good free radical scavenging activities. Although the radical of molecule 02 exhibited a large spin delocalization (Figure 3), it showed a high SD (0.56). This could be due to the high SD exhibited by the oxygen atom at which the radical was formed; the unpaired electron mainly focused on this oxygen atom, making the radical highly reactive.

Several studies have explored substances based on the calculated electronic and molecular properties to understand the mechanism underlying the antioxidant activity.^{45–48} The reaction enthalpy (ΔH_r) values are related to the ease of hydrogen donation and it is a useful descriptor of free radical scavenging activity. The calculated ΔH_r values of all

antioxidants studied are shown in Table 4. The values ranged from 313.6 to 358.9 kJ/mol for BDE mechanism. It is clear that the lower the BDE, the easier the dissociation of the phenolic O-H bond.

Molecule 10 had the lowest BDE value and molecule 02 the highest. Molecules 10, 11, and 06 showed an improvement in antioxidant activity compared with chalcone molecules 01 and 03. A substantial improvement in the reaction enthalpy of about 40.3 kJ/mol was observed when an OH was added to molecule 06 compared with molecule 02. Structure–activity studies reveal that the number and position of aromatic hydroxyl group have a strong impact on the activity of phenolic antioxidants.⁴⁹⁻⁵² Functional group exchange in molecule 04 and molecule 05 favored BDE compared with molecule 05 at 26.2 kJ/mol. The replacement of an OH in molecule 06 with OCH₃ in molecule 08 increased BDE. Evaluation of molecules 10, 11, and 12 showed that molecule 12 is sterically more congested than molecules 10 and 11 (Δ BDE = 31.2 kJ/mol for molecules 12 and 10). On comparing molecules 02 and 01, we observed that the addition of a CH₂ and a methoxy group reduced antioxidant activity in molecule 02 compared with molecule 01. In general, molecules 06, and 10 with good BDE values contained two strong electron-donating groups (OH) at both ends of the molecular frame stabilizing the resulting phenoxy radicals through inductive or resonance effects.

The lower the IP, the easier was the electron abstraction. Molecule 12 showed the lowest IP and molecule 01 the highest. (Δ IP = 72.3 kJ/mol). Molecules 12, 11 and 08 showed good IP values. On comparing molecules 02, 03, and 04, we observed that the double bond in molecule 03 favored IP due to conjugation. Molecules 04 and 05 had similar IP values. The replacement of OH with OCH₃ did not significantly affect IP values when comparing molecules 08 and 06; molecules 09 and 07 also followed the same trend. The IP values of structurally related compounds were similar i.e., molecules 04 and 05 (Δ IP = 5.9 kJ/mol); molecules 06 and 08 (Δ IP = 7.8 kJ/mol); and molecules 11 and 12 (Δ IP = 7.0 kJ/mol). IP values for molecules 12, 11, and 08 correlated with their HOMO eigenvalues.

PA values ranged from 1363.2 to 1580.3 kJ/mol. Molecule 11 had the lowest value and molecule 06 the highest (Δ PA = 217.0 kJ/mol). The general structure of chalcone in molecule 01 favored the antioxidant activity by PA mechanism compared with molecule 06 (Δ PA = 48.5 kJ/mol). The addition of an OH in molecule 06 reduced PA activity compared with molecule 02. The addition of the alkyl chain to molecule 12 reduced PA activity compared to molecule 11.

From Table 4, it can be seen that the calculated gas-phase PA values are significantly higher than BDE and IP values, indicating that from the thermodynamic point of view, HAT represents the preferred reaction pathway in the gas phase.

CONCLUSION

Quantum thermochemical calculations characterized antioxidant activity but no particular structural trends could be deduced. The structural effects of conjugation, electrophilicity, inductive and mesomeric effects on the α,β -unsaturated ketone moiety that is responsible for antioxidant activity cannot be correlated as independent variables but as a summation of all. The higher amount of delocalized spin in molecules 08 and 11 supports the possibility of them readily initiating radical chain reactions. The trend for calculated BDE, IP and PA values are different from each other, this is understood since the mechanism is also governed by the structure of the scavenged radical. However, the overall calculated descriptors demonstrated molecules 08 and 11 as promising antioxidants. Taking into account both bioactivity and antioxidant activity at the same time, molecule 08 can be considered as the best potential drug candidate under study owing to its drug-likeness, drug-score, and similarity with enzyme inhibitors and GPCR ligands.

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01		07
02		08
03		09
04		10
05		11
06		12

Chart1. Chemical structures

Molecule	M	T	I	RE	ClogP	S	Mw	TPSA	DL	DS	nON	nOHNH
01					3.18	-3.30	268.0	46.53	0.19	0.64	3	1
02					3.11	-3.32	298.0	55.76	1.82	0.77	4	1
03					4.21	-4.02	308.0	46.53	-2.16	0.38	3	1
04				X	3.29	-4.01	312.0	64.99	2.11	0.43	5	1
05				X	3.29	-4.01	312.0	64.99	2.24	0.43	5	1
06					2.76	-3.03	314.0	75.99	2.92	0.83	5	2
07					3.86	-3.72	324.0	66.76	-0.38	0.52	4	2
08					3.04	-3.34	328.0	64.99	4.28	0.81	5	1
09					4.14	-4.03	338.0	55.76	-0.55	0.47	4	1
10					3.79	-3.74	354.0	75.99	0.78	0.61	5	2
11					3.15	-4.05	372.0	83.45	1.37	0.66	7	1
12					4.18	-4.076	412.0	83.45	-0.95	0.37	7	1

M = Mutant = Tumorigenic; I = Irritant; RE = Reproductive effect; ClogP = calculated partition coefficient, S = Solubility; MW = Molecular weight; TPSA = total polar surface area; DL = drug-likeness; DS = Drug- score; nON = number of hydrogen bond acceptors; nOHNH = number of hydrogen bond donors.

Table 1. Toxicity risks and physicochemical properties predicted by OSIRIS Property Explorer

Molecule	GPCR	Ion-Mod	KI	NR	PI	EI
01	0.00	-0.16	-0.14	-0.03	-0.08	0.14
02	-0.02	-0.08	-0.43	-0.04	-0.32	0.06
03	0.03	-0.21	-0.15	-0.13	-0.10	0.11
04	0.03	-0.21	-0.15	-0.13	-0.10	0.11
05	0.03	-0.14	-0.11	-0.02	-0.05	0.14
06	0.12	-0.05	-0.25	0.05	-0.09	0.20
07	0.03	-0.14	-0.10	-0.01	-0.03	0.13
08	0.08	-0.07	-0.28	0.00	-0.08	0.17
09	0.09	-0.06	-0.25	0.01	-0.09	0.18
10	-0.04	-0.25	-0.29	-0.23	-0.13	0.00
11	-0.01	-0.23	-0.25	-0.18	-0.15	0.04
12	0.03	-0.16	-0.38	-0.15	-0.20	0.07

GPCR = GPCR ligand; Ion-Mod = Ion channel modulator; KI = Kinase inhibitor; NR = Nuclear receptor ligand; PI = Protease inhibitor; EI = Enzyme inhibitor

Table 2. Calculated bioactivity predicted by Molinspiration Cheminformatics Software

Molecule	μ	HOMO	LUMO	Gap
01	3,159	-0,216	-0,080	0,136
02	2,735	-0,212	-0,070	0,142
03	6,149	-0,216	-0,079	0,294
04	4,206	-0,207	-0,074	0,133
05	6,405	-0,211	-0,072	0,140
06	3,651	-0,207	-0,072	0,135
07	5,140	-0,214	-0,072	0,143
08	5,115	-0,205	-0,071	0,134
09	2,689	-0,215	-0,070	0,144
10	3,745	-0,208	-0,065	0,143
11	4,759	-0,206	-0,073	0,133
12	4,797	-0,201	-0,070	0,131

Table 3. Calculated dipole moments (Debye), HOMO, LUMO eigenvalues, and HOMO-LUMO gap

Molecule	BDE	IP	PA	SD
01	322,2	706.7	1380.5	0.34
02	358,9	676.5	1385.4	0.56
03	344,5	698.3	1436.4	0.36
04	324,8	667.6	1447.2	0.37
05	351,0	673.5	1464.7	0.37
06	318,6	663.5	1580.3	0.38
07	345,1	681.3	1441.8	0.63
08	340,8	655.7	1401.4	0.34
09	335,2	677.8	1425.9	0.36
10	313,6	660.9	1457.3	0.37
11	313,8	641.4	1363.2	0.31
12	344,8	634.4	1438.3	0.36

Table 4. Calculated BDE, IP, PA and SD

Figure Captions

Figure 1. General structure of phenolic compounds

Figure 2. Calculates optimized structures and electrostatic potential maps of molecules 06 and 08.

Figure 3. Calculated spin density surfaces

Draft

Figure 1

Draft

Figure 2.

Figure 3.

GRAPHICAL ABSTRACT