1st International Conference
on Chemo and BioInformatics
ICCBIKG 2021

ICCBIKG

1st International Conference on
Chemo and BioInformatics

BOOK OF PROCEEDINGS

October 26-27th, 2021,
Kragujevac, Serbia

www.iccbikg.kg.ac.rs

Ministry of Education, Science and Technological Development of the Republic of Serbia

SHIMADZU
Excellence in Science

KEFO
SINCE 1949

Alfamed

UNI-CHEM

SUPERLAB
Your Lab - Our Passion

ART WINE

1st International Conference on Chemo and BioInformatics
ICCBIKG 2021

BOOK OF PROCEEDINGS

October 26-27, 2021
Kragujevac, Serbia

Sponsored by

Ministry of Education, Science and Technological Development of the Republic of Serbia

1st International Conference on Chemo and BioInformatics, Kragujevac, October 26-27, 2021 Serbia

Editors:

Professor Zoran Marković

Professor Nenad Filipović

Technical Editors:

Vladimir Simić

Izudin Redžepović

Nikola Srećković

Illustrations:

Igor Stanković, „Vector Alchemist“ d.o.o.

Publisher:

Institute for Information Technologies, University of Kragujevac, Serbia, Jovana Cvijića bb, 2021

Press:

„Grafo Ink“, Kragujevac

Impression:

120 copies

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

54:004(048)(0.034.2)
57+61]:004(082)(0.034.2)

INTERNATIONAL Conference on Chemo and BioInformatics (1 ; 2021 ; Kragujevac) Book of Proceedings [Elektronski izvor] / 1st International Conference on Chemo and BioInformatics, ICCBIKG 2021, October 26-27, 2021 Kragujevac, Serbia ; [editors Zoran Marković, Nenad Filipović]. - Kragujevac : University, Institute for Information Technologies, 2021 (Kragujevac : Grafo Ink). - 1 USB fleš memorija ; 3 x 2 x 1 cm

Sistemski zahtevi: Nisu navedeni. - Nasl. sa naslovne strane dokumenta. - Tiraž 120. - Bibliografija uz svaki rad.

ISBN 978-86-82172-01-7

a) Хемија - Информациона технологија - Зборници b) Биомедицина - Информациона технологија - Зборници

COBISS.SR-ID 48894473

doi:10.46793/ICCBI21.458A

ANTIOXIDATIVE POTENCY AND RADICAL SCAVENGING ACTIVITY OF SELECTED COUMARIN-HYBRIDS

Antonijević R. Marko[1], Milanović B. Žiko[1], Simijonović M. Dušica[1], Marković S. Zoran[1] Snežana Bogosavljević-Bošković[2]

[1]Institute for Information Technologies, University of Kragujevac, Jovana Cvijica bb, 34000 Kragujevac, Serbia;
e-mail: mantonijevic@uni.kg.ac.rs, ziko.milanovic@uni.kg.ac.rs, dusicachem@kg.ac.rs, zmarkovic@uni.kg.ac.rs
[2]Faculty of Agronomy in Čačak, University of Kragujevac, Cara Dušana 34, 32102 Čačak, Serbia
e-mail: sbb@kg.ac.rs

Abstract:

In previous studies, it was found that coumarins with hydrazide moiety show good antioxidative potential, while similar coumarins with hydrazone moiety are good anticancer agents. In this paper, the antioxidative potency and radical scavenging activity of two coumarin hydrazone derivatives were investigated. For this purpose, density functional theory method M062X with 6-311G++(d,p) basis set was implemented. It was found that investigated compounds exhibit good antioxidative potency, with very similar BDE values regardless of the position involved. On the other hand, PA values show that a preferable functional group for proton loss depends on the position of the OH group. In *ortho* position, OH group shows lower antioxidative potency than NH group, while in the same time in *para* position OH group is favourable position for antioxidative activity reactions. A similar situation is obtained by investigation of radical scavenging mechanisms, with the more pronounced difference in BDE between the positions in favour of the NH group. While SPLET is the most probable mechanism which is in competition with HAT in some cases (hydroxy radical) SET-PT was found to be a non-operative mechanistic pathway.

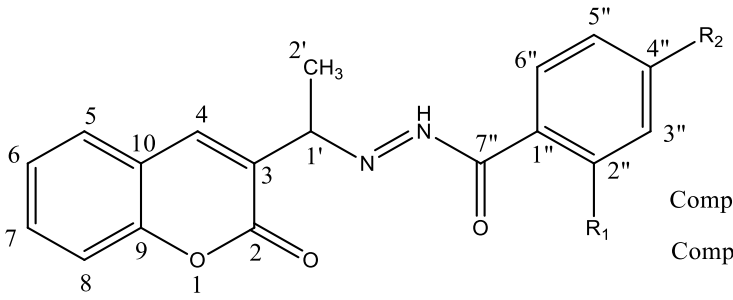
Keywords: Coumarin derivates, DFT, antioxidative potency, radical scavenging activity

1. Introduction

Oxidative stress, and the consequences it causes, are one of the most common problems in modern medicine. Although organisms have the ability to fight free radicals to a certain extent, compounds that exhibit antioxidant activity and prevent the occurrence or reduce the damage caused by prolonged exposure of the organism to oxidative stress are gaining in importance. [1] Of special importance would be a discovery of non-toxic, water-soluble, easily obtainable compounds that can act as antioxidative agents to inactivate the free radicals and prevent damage induced by oxidative stress, with the ability to prevent the proliferation of the existing cancer cells.

In previous studies, it was found that coumarins with hydrazide substituents show good antioxidative potential. [2] Additionally, in a study conducted by Angelova et al., it was found that some coumarin-hydrazone derivates show low *in vitro* DPPH radical scavenging ability, but at the same time excellent anticancer activity on different cell lines [3]. In this paper, the antioxidative and radical scavenging activity of some coumarin hydrazone derivates,

structurally similar to compounds from two aforementioned studies, was investigated. Structures of investigated compounds are presented in Scheme 1.



	R_1	R_2
Compound **A**	OH	H
Compound **B**	H	OH

Scheme 1: Structures of investigated compounds

2. Materials and methods

All calculations were carried out by using the Gaussian 09 software package. [4] The geometry optimization was obtained using the Density Functional Theory (DFT) method M06-2X with basis set 6-311G++(d,p) and CPCM solvation model. Calculations were performed in ethanol, as a polar medium. First, the mechanistic pathway of antioxidative activity was investigated. Three main mechanisms are described by the following equations:

$$\text{HAT:} \quad \text{Ar-OH} \rightarrow \text{Ar-O}^{\bullet} + \text{H}^{+} \tag{1}$$
$$\text{SET-PT:} \quad \text{Ar-OH} \rightarrow \text{Ar-OH}^{\bullet+} + e^{-} \tag{2}$$
$$\text{Ar-OH}^{\bullet+} \rightarrow \text{Ar-O}^{\bullet} + \text{H}^{+} \tag{3}$$
$$\text{SPLET:} \quad \text{Ar-OH} \rightarrow \text{Ar-O}^{-} + \text{H}^{+} \tag{4}$$
$$\text{Ar-O}^{-} \rightarrow \text{Ar-O}^{\bullet} + e^{-} \tag{5}$$

The values of thermodynamic parameters that describe the antioxidative activity of investigated compounds are calculated from total enthalpies by applying the equations 6-10:

$$\text{BDE} = H(\text{Ar-O}^{\bullet}) + H(\text{H}^{+}) - H(\text{Ar-OH}) \tag{6}$$
$$\text{IP} = H(\text{Ar-OH}^{\bullet+}) + H(e^{-}) - H(\text{Ar-OH}) \tag{7}$$
$$\text{PDE} = H(\text{Ar-O}^{\bullet}) + H(\text{H}^{+}) - H(\text{Ar-OH}^{\bullet+}) \tag{8}$$
$$\text{PA} = H(\text{Ar-O}^{-}) + H(\text{H}^{+}) - H(\text{Ar-OH}) \tag{9}$$
$$\text{ETE} = H(\text{Ar-O}^{\bullet}) + H(e^{-}) - H(\text{Ar-O}^{-}) \tag{10}$$

Radical scavenging properties of the investigated compounds were investigated against the various radicals such as hydroxy ($^{\bullet}$OH), methoxy ($^{\bullet}$OCH$_3$), ethoxy ($^{\bullet}$OCH$_2$CH$_3$), isopropiloxy ($^{\bullet}$OCH(CH$_3$)$_2$), terc-butoxy ($^{\bullet}$OC(CH$_3$)$_3$), and peroxy ($^{\bullet}$OOH) radical. Mechanisms of radical scavenging activity are described by the following equations:

$$\text{HAT:} \quad \text{Ar-OH} + \text{RO}^{\bullet} \rightarrow \text{Ar-O}^{\bullet} + \text{ROH} \tag{11}$$
$$\text{SET-PT:} \quad \text{Ar-OH} + \text{RO}^{\bullet} \rightarrow \text{Ar-OH}^{\bullet+} + \text{RO}^{-} \tag{12}$$
$$\text{Ar-OH}^{\bullet+} + \text{RO}^{-} \rightarrow \text{Ar-OH}^{\bullet} + \text{ROH} \tag{13}$$
$$\text{SPLET:} \quad \text{Ar-OH} + \text{RO}^{-} \rightarrow \text{Ar-O}^{-} + \text{ROH} \tag{14}$$
$$\text{Ar-O}^{-} + \text{RO}^{\bullet} \rightarrow \text{Ar-O}^{\bullet} + \text{RO}^{-} \tag{15}$$

where RO$^{\bullet}$ denotes reactive oxygen species and where Ar-OH, Ar-O$^{\bullet}$, Ar-OH$^{\bullet+}$, and Ar-O^{-} denote antioxidant, its radical, radical-cation and anion, respectively.

Thermodynamic parameters that describe radical scavenging activity of investigated compound are calculated from total Gibbs energies using the following equations:

$$\Delta_r G_{BDE} = G(\text{Ar-O}^{\bullet}) + G(\text{ROH}) - G(\text{Ar-OH}) - G(\text{RO}^{\bullet}) \tag{16}$$
$$\Delta_r G_{IP} = G(\text{Ar-OH}^{\bullet+}) + G(RO^{-}) - G(\text{Ar-OH}) - G(\text{RO}^{\bullet}) \tag{17}$$
$$\Delta_r G_{PDE} = G(\text{Ar-O}^{\bullet}) + G(\text{ROH}) - G(\text{Ar-OH}^{\bullet+}) - G(\text{RO}^{-}) \tag{18}$$
$$\Delta_r G_{PA} = G(\text{Ar-O}^{-}) + G(\text{ROH}) - G(\text{Ar-OH}) - G(\text{RO}^{-}) \tag{19}$$

$$\Delta_r G_{ETE} = G(\text{Ar-O}^\bullet) + G(RO^-) - G(\text{Ar-O}^-) - G(\text{RO}^\bullet) \quad (20)$$

3. Results and discussion

3.1. Antioxidative activity

It can be expected from two compounds with similar structures to exhibit similar antioxidative activity. By investigation of the BDE values from Table 1, that statement could be confirmed. The only significant difference is present in position C2"-OH because hydrogen loss from this position is aggravated by the presence of a hydrogen bond between C2"-OH and carbonyl group in position C7". However, if PA values are being examined it could be seen that the position of the OH group can make a significant difference.

Firstly, it is important to notice that loss of a proton from an OH group is noticeably easier in position C4" than C2". Partly it is a consequence of better charge delocalization, but mostly it is a consequence of the aforementioned hydrogen bond. A second important conclusion is that proton loss from the NH group is favoured in the case of the *ortho* positioned OH group. The reason is that hydrogen bond formation at the same time allows better charge delocalization, which leads to molecule stabilization, and prevents proton loss from the OH group.

It is important to emphasize that a dominant mechanism of antioxidative activity will be SPLET followed by HAT, while SET-PT is a non-operative mechanism judging by the values of thermodynamic parameters that describe these mechanisms.

Table 1. Thermodynamic *para*meters describing the mechanisms of antioxidative activity of investigated compounds (kJ/mol)

Position	**HAT**	**SET-PT**		**SPLET**	
	BDE	*IP*	*PDE*	*PA*	*ETE*
Compound **A**					
C7"-NH	343	542	36	185	393
C2"-OH	361		53	219	377
Compound **B**					
C7"-NH	345	532	48	209	371
C4"-OH	344		47	190	389

3.2. Radical scavenging activity

As can be expected from the results presented in the previous section, and according to the results from Table 2, SET-PT is not an operative mechanistic pathway of radical-scavenging reactions. That being said, negative ΔG_{BDE} and ΔG_{PA} values indicate that HAT and SPLET are thermodynamically possible mechanisms. The preferred mechanistic pathway depends on the structure of the radical species that are being inactivated, as well as the structure of the investigated antioxidant molecule. For hydroxy radical HAT and SPLET mechanisms are in competition, especially in the case of the inactivation by compound **A**. In the case of compound **B**, SPLET is a slightly less favourable mechanism.

That being said SPLET is the dominant mechanism in the case of the inactivation of other investigated radical species. By careful examination of the ΔG_{BDE} values, it can be noted that the favoured position for radical inactivation is C7"-NH. Interestingly, the differences between C7"-NH and hydroxy group are lower in the case when this group is found in *para* position, which makes these positions thermodynamically very similar. The situation is even more interesting when ΔG_{PA} values are investigated. In the case of radical inactivation by compound **A**, C7"-NH is favoured, while the situation is reversed in the case of compound **B**.

All alkoxy radicals preferably follow SPLET although the reactions are exothermic even by HAT mechanism. The ease of alkoxy radical inactivation increases with an increase in the number of methyl groups on the α-carbon atom, which is to be expected.

Hydroperoxy radical can only be inactivated by following the SPLET mechanism.

Table 2. Thermodynamic *para*meters describing radical scavenging activity of investigated compounds

Radical	Position	HAT	SET-PT		SPLET		Position	HAT	SET-PT		SPLET	
		ΔG_{BDE}	ΔG_{IP}	ΔG_{PDE}	ΔG_{PA}	ΔG_{ETE}		ΔG_{BDE}	ΔG_{IP}	ΔG_{PDE}	ΔG_{PA}	ΔG_{ETE}
		*Compound **A***						*Compound **B***				
HO•	C7”-NH	-224	153	-377	-226	2	C7”-NH	-225	142	-367	-200	-26
	C2”-OH	-207		-360	-192	-15	C4”-OH	-222		-364	-220	-2
HOO•	C7”-NH	18	240	-222	-71	89	C7”-NH	17	229	-212	-44	61
	C2”-OH	35		-205	-37	72	C4”-OH	20		-208	-65	85
MeO•	C7”-NH	-54	217	-271	-120	66	C7”-NH	-56	205	-261	-94	38
	C2”-OH	-37		-254	-86	48	C4”-OH	-52		-257	-114	62
EtO•	C7”-NH	-55	215	-270	-119	64	C7”-NH	-56	204	-260	-93	36
	C2”-OH	-38		-253	-85	47	C4”-OH	-53		-257	-113	60
IpO•	C7”-NH	-62	209	-271	-120	58	C7”-NH	-63	198	-261	-93	30
	C2”-OH	-45		-254	-86	41	C4”-OH	-59		-257	-114	54
tBuO•	C7”-NH	-66	208	-274	-123	57	C7”-NH	-68	197	-264	-97	29
	C2”-OH	-49		-257	-89	40	C4”-OH	-64		-261	-117	53

4. Conclusions

The antioxidative potential and preferred radical scavenging pathways of coumarin hydrazone derivatives were theoretically investigated by the density functional theory. The obtained results revealed that investigated compounds exhibit good antioxidative activity. *In silico* calculations indicated that for both examined compounds SPLET is the most probable mechanism and that this mechanism is in competition with HAT, while SET-PT was found to be a non-operative mechanistic pathway.

References

[1] Droge, Wulf. *Free radicals in the physiological control of cell function*. Physiological reviews 82, no. 1 (2002) 47-95.

[2] Antonijević, Marko R., Dušica M. Simijonović, Edina H. Avdović, Andrija Ćirić, Zorica D. Petrović, Jasmina Dimitrić Marković, Višnja Stepanić, and Zoran S. Marković. *Green One-Pot Synthesis of Coumarin-Hydroxybenzohydrazide Hybrids and Their Antioxidant Potency.* Antioxidants 10, no. 7 (2021) 1106.

[3] Angelova, Violina T., Nikolay G. Vassilev, Boryana Nikolova-Mladenova, Jasmina Vitas, Radomir Malbaša, Georgi Momekov, Mirjana Djukic, and Luciano Saso. *Antiproliferative and antioxidative effects of novel hydrazone derivatives bearing coumarin and chromene moiety.* Medicinal Chemistry Research 25, no. 9 (2016) 2082-2092.

[4] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, et al., *Gaussian 09*, (2009) http://www.gaussian.com