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Graphical Abstract

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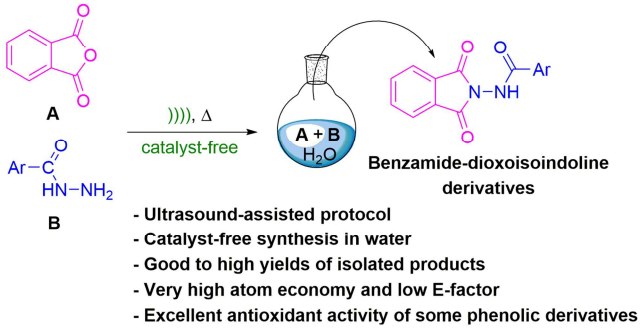

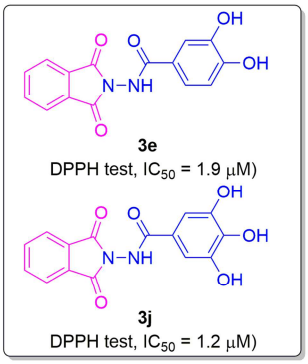

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ABSTRACT

A series of benzamide-dioxoisoindoline derivatives **3** was obtained, starting from phthalic anhydride and different benzoyl hydrazides **2**, by ultrasound irradiation in water as solvent and without any catalyst. Five obtained compounds have been reported in this study for the first time and crystal structure of compound **3h** was determined. All compounds were subjected to experimental determination of their antioxidative potential. DPPH test revealed that newly synthesized phenolic compounds **3d**, **3e**, and **3j** are the best antioxidants. Additionally, probable radical scavenging pathway was analysed for reactions of the most active compounds and some radicals that can be found in living cells.

1. Introduction

Heterocyclic compounds containing isoindoline moiety have been of great interest to the researchers for many years. Isoindoline nucleus is known to be an integral part of many compounds that exert wide spectra of biological and pharmaceutical activities.[1] It was shown that this compound class possesses anticancer,[2,3] anti-inflamatory,[4] sedative,[4] analgesic,[5] antihyperglycemic,[6] antipsychotic,[7] antihypertensive,[8] and cytotoxic[9] activity. Commercial drugs, such as lenalidomide,[2] apremilast,[4] indoprofen,[5] (s)-pazinaclone,[4] contain isoindoline scaffold. These compounds exert affinities for dopamine, serotonine[10] and GABA receptors,[11] and therefore they have been known as potential anti-Alzheimer's agents.[12,13] They also exert similar effect as L-DOPA in Parkinsonism treatment.[14] In addition, isoindolines have found industrial application as a dye, such as pigment yellow 139, which belongs to the class of highly resistant dyes.[4] The most common method for the synthesis of 1,3-dioxoisoindoline derivatives involves condensation of phthalic anhydride with different substituted primary amines in the presence of acids or bases as catalysts.[15–17] The literature also claims a procedure for the synthesis of a range of 1,3-dioxoisoindoline derivatives by palladium-catalyzed carbonylation reactions of *o*-dihaloarenes, *o*-halobenzoic acids and their esters, and with primary amines.[18,19]

All previously mentioned methods for the synthesis of 1,3-dioxoisoindolines have one or more deficiency, such as high temperature, a multistep synthesis, low yields, transition metal catalysts, usage of CO gas, usage of toxic materials such as some mineral acids, NEt_3, MeOH, etc., and the feature of not following green chemistry principles. Also, the usage of microwave irradiation for the synthesis of 1,3-dioxoisoindolines, requires the use of organic solvents and additives.[20–22]

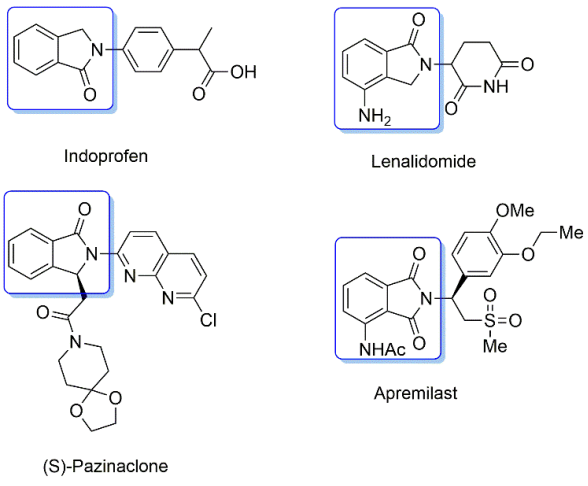


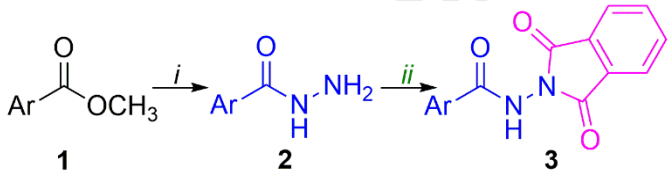
Figure 1. Some commercially available drugs with isoindoline moiety.

Ultrasound irradiation has become significant green and cheap methodology in the syntheses of various organic compounds.[23-33] It is important to emphasize that literature fails with ultrasound assisted green synthesis of *N*-(1,3-dioxoisoindolin-2-yl)benzamide derivatives. In addition, ultrasonic methodology has found application in pharmacy, biotechnology, food industry and environmental engineering. Compared to the traditional synthetic methods, ultrasound irradiated reactions have more advantageous such as: cheap and fast chemical activation which does not require any catalyst, increasing of reaction rate, product selectivity, yield and purity of the products, etc.[34–37]

In the present study we report green ultrasound assisted methodology for the synthesis of benzamide-dioxoisoindoline derivatives in water, in the absence of any catalyst and toxic organic solvents. This research involved determination of the structures of reaction products, experimental investigation of their antioxidative potential using DPPH test and theoretical investigation of the effects of some medically relevant radicals on the antioxidative activity and reaction mechanism of the most active compounds.

2. Results and Discussion

For the synthesis of benzamide-dioxoisoindoline derivatives **3**, differently substituted methyl esters **1** were transformed to corresponding benzoyl hydrazides **2**, which were used for further reactions. The reactions of **2** and phthalic anhydride were performed in water and without any catalyst (Scheme 1). In order to optimize reaction conditions, the reaction between phthalic anhydride and benzohydrazide (**2a**) in water was used as a model reaction for optimization of reaction conditions (Table 1). Firstly, the reaction was performed at room temperature, but the reaction did not occur. The product was detected upon reaction mixture being heated under reflux for 1h, and good yield of product was obtained after 5h. In order to accelerate the reaction, ultrasound irradiation was used and heating to 80 □. In that case, satisfactory yield of benzamide-dioxoisoindoline derivatives **3** was obtained after 2h (Scheme 1, Table 1).



Scheme 1. Synthesis of benzamide-dioxoisoindoline derivatives (**3**): (*i*) hydrazine monohydrate, esters (**1**), reflux, (*ii*) phthalic anhydride, benzoyl hydrazides (**2**), water, heating to 80 ℃, ultrasound irradiation.

Table 1. Optimization of reaction conditions

Entry	Temperature (□)	Time (h)	Yield (%)
1	rt[a]	10	nr
2	100[a]	1	25
3	100[a]	3	65
4	100[a]	5	82
5	rt[b]	5	nr
6	80[b]	0.5	40
7	80[b]	1	65
8	80[b]	2	84

Reaction conditions: phthalic anhydride (1 mmol), **2a** (1 mmol), 2 mL H_2O; [a]Reaction performed by heating under reflux; [b]Reaction performed under ultrasound irradiation by heating to 80 □; nr = no reaction.

Therefore, optimal conditions for the synthesis of benzamide-dioxoisoindoline derivatives **3** are heating to 80 □ and ultrasound irradiation for 2h in water as solvent (Table 2). Products **3a** and **3b-j** (with electron donating substituents) were simple isolated by precipitation and filtration, in good to excellent yields (70-89%). However, when benzoyl hydrazides with electron withdrawing groups (**2k-n**) were used, the yields of the reactions were lower. Prolongation of reaction time to 12h provided good yields of the reaction products (Table 2), whose structures are reported on the Fig. 2. It is important to emphasize that five obtained products have been reported in this study for the first time (**3d-f**, **3i** and **3j**). All products were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. For newly synthesized compounds elemental analysis was done. In addition, crystal structure of *N*-(1,3-dioxoisoindolin-2-yl)-3,4,5-trimethoxybenzamide (**3h**) was determined.

Table 2. Yields of isolated benzamide-dioxoisoindoline derivatives **3**

Compound	Time (h)	Yield (%)
3a	2	84
3b	2	73
3c	2	85
3d	2	80
3e	2	78
3f	2	74
3g	2	89
3h	2	74
3i	2	72
3j	2	70
3k	12	71
3l	12	87
3m	12	70
3n	12	71

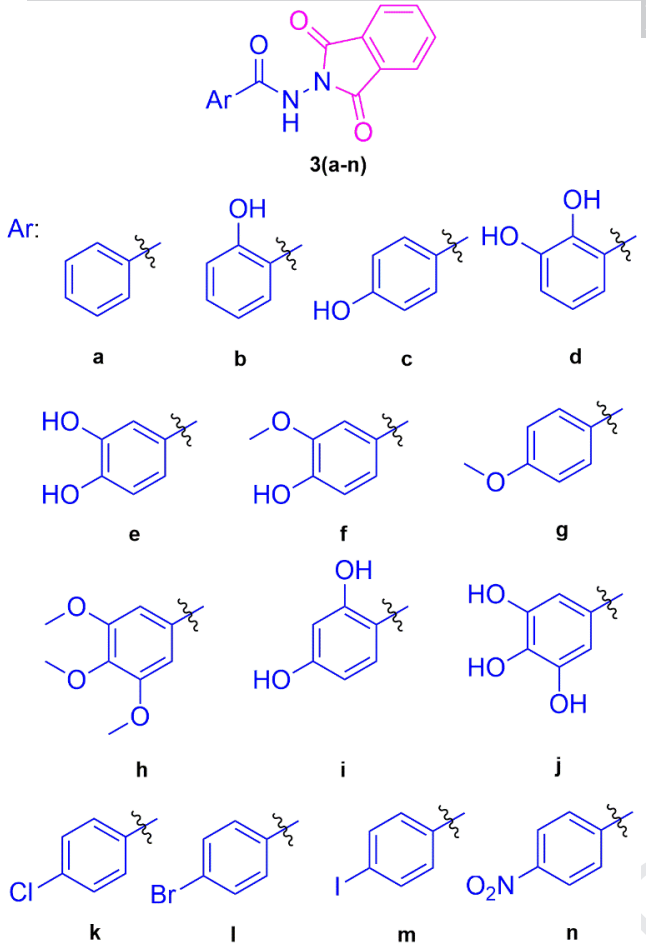
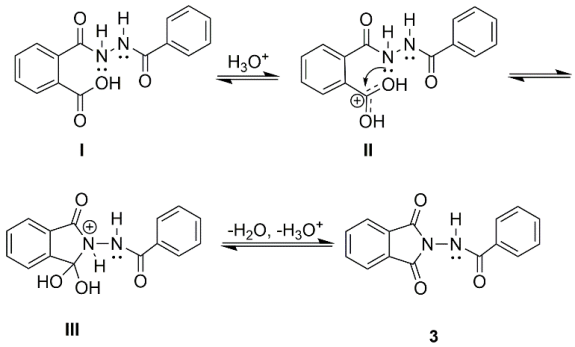


Figure 2. The structures of isolated benzamide-dioxoisoindoline derivatives **3**.

Mechanism of the reaction for the synthesis of **3** was proposed and analysed.[38] The reaction starts with nucleophilic attack of nitrogen from hydrazide **2** to the carbonyl group of phthalic anhydride. In this way, 2-(benzoylhydrazine-carbonyl)benzoic acid (intermediate **I**) is formed (Scheme 2). It is important to emphasize that this intermediate is observed in cases of reactions with lower yield after 5h, and isolated from the reaction where electron accepting nitro group was presented. Spectral characterisation of this intermediate is given in SI. In this acid medium, oxygen of carbonyl group within carboxylic group of intermediate **I** is subjected to protonation to form intermediate **II**. This way, carbon atom is more electrophilic, and therefore subjectable to nucleophilic attack of the nitrogen. This enables cyclisation and formation of intermediate **III**. The final step in this reaction is dehydration and deprotonation of intermediate **III**, which yields the corresponding benzamide-dioxoisoindoline derivatives **3**.



Scheme 2. Proposed mechanism for the synthesis of benzamide-dioxoisoindoline derivatives **3**.

The environmental acceptability and efficiency for the used reaction method were determined. For that purpose, green chemistry metrics, such as atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME), EcoScale, mass intensity (MI), and environmental factor (E-factor) were determined (Table S1).[39–41] The graphical presentation of the values calculated for the green mass metrics on the basis of which is estimated incorporation of atoms of reagents into the product (AE, AEf, CE, RME, and EcoScale) and green mass metrics for estimating waste minimization (MI and E-factor) are presented in Fig. 3. The obtained results reveal that AE is very high and goes in range from 93.7% to 95.6%. The monitored reactions have high values for AEf and CE (up to 84% and 89%). The scores of RME in range of 66,2-83,9% label this method as green synthetic route for preparation of benzamide-dioxoisoindoline derivatives. The values obtained for EcoScale (73-83%), indicate that the compounds **3a-n** are synthesized in good to high yield, using low cost chemicals, under safety conditions and isolated without any purification. Additionally, the obtained results for MI and E-factor (1.62-1.12 and 0.62-0.12) convincingly confirm the green features of the method used.

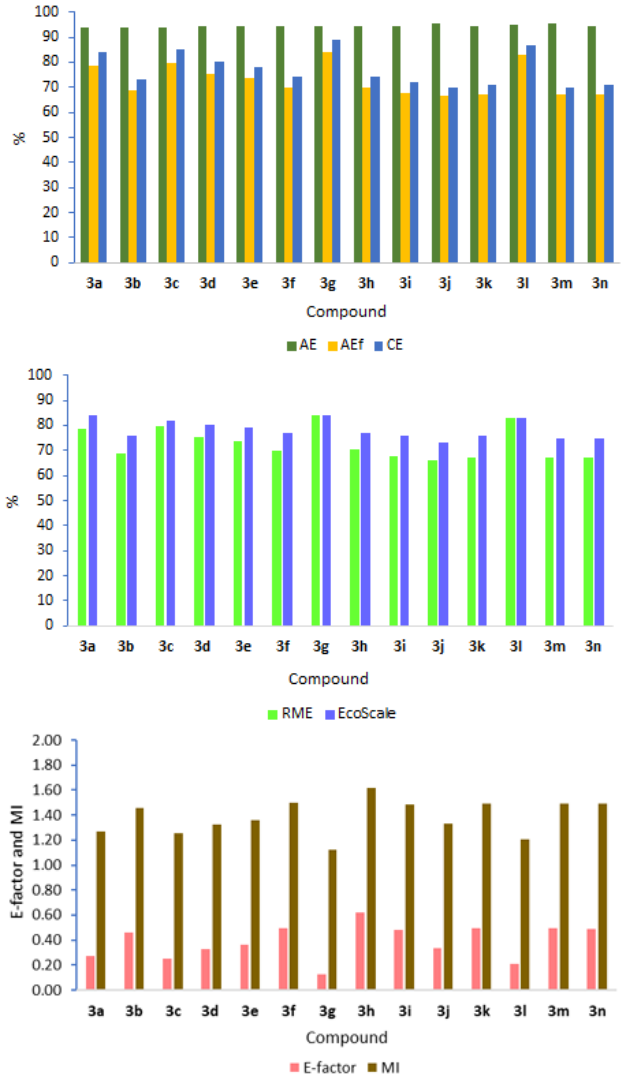


Figure 3. Green chemistry metrics calculated for the synthesized compounds **3a-n**.

*2.1. Crystal structure of **3h***

Molecular structure of **3h**, determined by single-crystal X-ray analysis, is shown in Fig. 4.

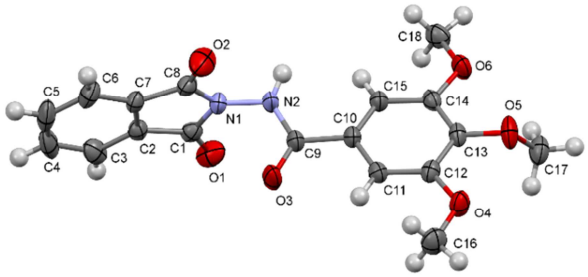


Figure 4. Crystal structure and atom-numbering scheme of **3h**. Displacement ellipsoids are drawn at the 40% probability level.

All non-H atoms in **3h** (except C17 methyl group) are placed in three planes. The first plane is defined by two fused rings together with the O1 and O2 atoms (root-mean-square deviation of all 11 atoms is 0.023 Å). The N2 atom is displaced from this plane for 0.133 (2) Å. The second plane is defined by the N1-N2-C9-O3 fragment (rms deviation of four atoms is 0.011 Å). Dihedral angle between these two planes is 86.56 (7)°. The third plane is defined by phenyl ring and the atoms bonded to this ring (rms deviation of all 10 atoms is 0.026 Å). Two methyl groups, the C16 and C18, are roughly seated in this plane. Dihedral angle between the last two planes is only 11.56 (9)°, therefore, we can say overall that the molecule **3h** is divided into two halves approximately orthogonal to each other and connected through the N1-N2 bond. The N2-C9 bond is somewhat shorter than corresponding N-C bonds formed by the N1 nitrogen atom but generally all bonds in **3h** molecule have expected values (Table 3).

Table 3. Selected bond lengths (Å) for **3h**

O1-C1	1.208(2)
O2-C8	1.197(2)
O3-C9	1.213(2)
O4-C12	1.365(2)
O4-C16	1.423(2)
O5-C13	1.366(2)
O5-C17	1.393(2)
O6-C14	1.361(2)
O6-C18	1.418(2)
N1-N2	1.375(2)
N1-C1	1.388(2)
N1-C8	1.402(2)
N2-C9	1.361(2)
C1-C2	1.473(2)
C7-C8	1.480(2)
C9-C10	1.489(2)

The only significant H bond donor in **3h** is the N2-H group. Via the N2-H…O1 hydrogen bonds, it forms a chain along the c axis of unit cell (Fig. 5). The molecules in the chain are additionally interconnected through the C3-H…O2 weak H-bonds. The C2-C7 phenyl ring participates in π…π interaction with the same ring of neighboring molecule. Two rings are ideally parallel and form centrosymmetric dimer with perpendicular distance between the rings of only 3.37 Å (Distance between ring centroids is 3.71 Å). This π…π interaction and some additional weak C-H…O intermolecular hydrogen bonds (Table 4) interconnect to form the above described chains of molecules **3h**.

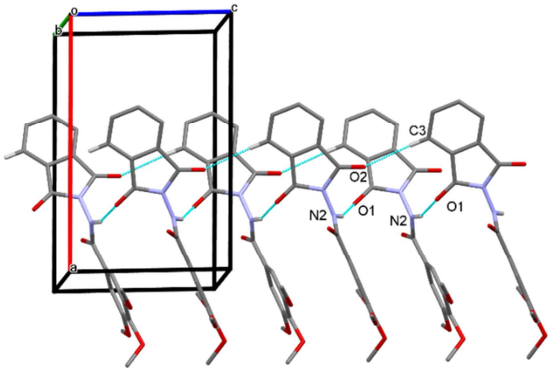


Figure 5. The molecules of **3h** are mutually interconnected into the chains using hydrogen bonds which are shown in light blue dashed lines. All H atoms not involved in hydrogen bonding are omitted for clarity.

Table 4 Hydrogen bonding geometry in crystal structure of **3h**

D–H...A	D–H (Å)	D...A (Å)	H...A (Å)	D–H...A (°)	Symmetry codes:
N2–H1...O1	0.83(2)	2.841(2)	2.05(2)	159(2)	x,-y+0.5,z+0.5
C3-H3...O2	0.93	3.408(2)	2.49	170	x,y,z-1
C4-H4...O4	0.93	3.509(3)	2.59	169	x-1,y,z-1
C5-H5...O3	0.93	3.350(2)	2.50	153	-x+1,-y,-z+1

2.2. Radical scavenging activity

All synthesized benzamide-dioxoisoindoline derivatives (**3a-n**) were tested for their *in vitro* antioxidative activity, Tables 5, S2, and S4. Their scavenging ability was screened using stable free radical 1,1-diphenyl-2-picryl-hydrazyl (DPPH). The most probable radical scavenging pathway was analysed using thermodynamical parameters and reaction enthalpies for the reactions of the most active compounds with the some medically relevant radicals (Scheme 3, Tables 5, and S4).

In this investigation nordihydroguaiaretic acid (NDGA) and quercetin were used as reference compounds. The results of this test showed that compounds *N*-(1,3-dioxoisoindolin-2-yl)-3,4,5-trihydroxybenzamide (**3j**), *N*-(1,3-dioxoisoindolin-2-yl)-3,4-dihydroxybenzamide (**3e**), and *N*-(1,3-dioxoisoindolin-2-yl)-2,3-dihydroxybenzamide (**3d**) expressed the best antioxidant activity with IC_{50} values of 1.2 µM, 1.9 µM, and 2.6 µM, respectively. Furthermore, stoichiometric factor has been determined for the most active compounds.[42,43] Taking into account this parameter, compounds **3d**, **3e**, and **3j** can be considered as significant radical scavengers, since stoichiometric factor amounts 4.8, 6.6, and 10.4 respectively (Table 5). Based on the fact that good antioxidants have value for this parameter more than 2,

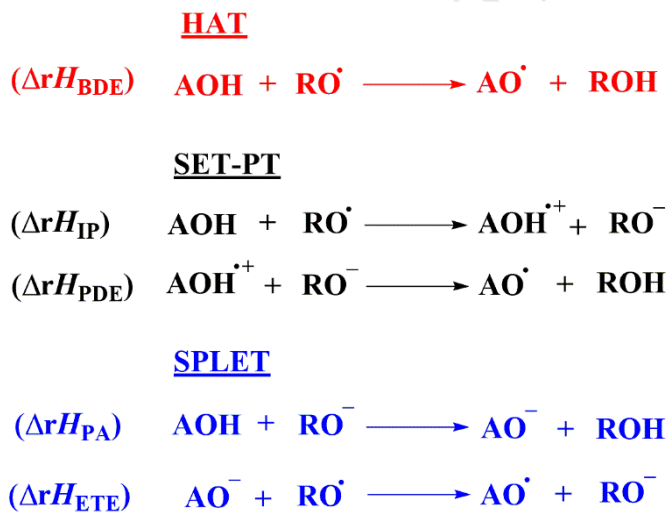
investigated compounds, especially **3j**, can be considered as excellent antioxidants.[42,43]

Table 5. Interaction of compounds **3d**, **3e**, and **3j** with the stable radical DPPH, calculated thermodynamical parameters (kJ mol^{-1}) of antioxidant mechanisms and reaction enthalpies (kJ mol^{-1}) for the reactions of these compounds with the selected radicals in methanol using B3LYP functional and the 6-311+G(d,p) basis set.

	3d					**3e**					**3j**				
IC_{50} (μM)	2.6±0.1					1.9±0.1					1.2±0.1				
Stoichiometric factor	4.8					6.6					10.4				
	HAT	SET-PT		SPLET		HAT	SET-PT		SPLET		HAT	SET-PT		SPLET	
Thermodynamical parameters (kJ mol^{-1})															
	BDE	IP	PDE	PA	ETE	BDE	IP	PDE	PA	ETE	BDE	IP	PDE	PA	ETE
	329	486	4	115	375	334	488	8	127	368	349	510	1	122	389
	330		6	125	367	335		9	118	379	328		-20	106	384
											348		0	121	389
Reaction enthalpies (kJ mol^{-1})															
Radical	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}	ΔH_{BDE}	ΔH_{IP}	ΔH_{PDE}	ΔH_{PA}	ΔH_{ETE}
$^{\bullet}OCH_3$	-99	109	-207	-97	-2	-93	111	-204	-84	-9	-78	133	-211	-90	12
	-97		-205	-86	-11	-92		-203	-94	2	-99		-231	-106	7
											-79		-211	-90	12
$^{\bullet}OC(CH_3)_3$	-107	109	-216	-106	-1	-102	111	-213	-93	-8	-87	133	-220	-99	12
	-105		-214	-95	-10	-101		-212	-103	2	-107		-240	-114	7
											-87		-220	-99	12
$^{\bullet}OH$	-170	30	-200	-89	-81	-165	32	-197	-77	-88	-150	54	-203	-83	-67
	-168		-198	-79	-89	-164		-196	-86	-77	-170		-224	-98	-72
											-150		-204	-83	-67
$^{\bullet}OOH$	-30	131	-161	-51	21	-25	133	-158	-38	14	-10	155	-165	-44	34
	-28		-159	-40	12	-24		-157	-48	24	-30		-185	-60	29
											-10		-165	-44	34
$^{\bullet}OOCH_3$	-23	139	-163	-52	29	-18	141	-159	-40	22	-3	163	-166	-45	42
	-22		-161	-41	20	-17		-158	-49	32	-23		-186	-61	37
											-4		-167	-46	42
$^{\bullet}OO\text{-}CH{=}CH_2$	-22	118	-140	-30	7	-17	120	-137	-18	1	-2	142	-144	-23	21
	-21		-139	-19	-1	-16		-136	-27	11	-23		-164	-39	16
											-3		-144	-24	21
DPPH	6	109	-103	8	-2	11	111	-99	20	-9	26	132	-106	15	12
	8		-101	19	-11	12		-98	11	1	6		-126	-1	7
											26		-107	14	11
$O_2^{\bullet-}$	42	298	-256	21	21	47	300	-253	34	14	62	322	-259	28	34
	44		-254	32	12	48		-252	24	24	42		-280	12	29
											62		-260	28	34

It is well known that compounds with several hydroxy groups bonded to aromatic ring, exert excellent antioxidative activity,[44] and compounds with catechol and pyrogallol moiety present significant antioxidants.[45–49] This can be explained by stabilisation of formed phenoxy radical (after dehydrogenation) through intramolecular hydrogen bonding with the neighbouring hydroxy groups.[50] This is in agreement with obtained results for an excellent antioxidant activity of 1,3-dioxoisoindolin-benzamide with pyrogallol moiety (**3j**), which is even better than the activity of positive controls quercetin and NDGA. Compounds **3d** and **3e** have one catecholic moiety, i.e. one hydroxy group less than **3j**, and therefore they are less active. Lower activity of **3d** can be explained by position of hydroxy groups. Namelly, hydroxy groups in **3d** are ortho and meta positioned relative to the amide group (-$CONH_2$) with electron-withdrawing effect. This effect of amide group makes it difficult to build a radical in ortho hydroxy group. Summarizing all previously mentioned facts, it can be concluded that the number of hydroxy groups and their position in aromatic ring present the most important factor for expressed antioxidative scavenging activity.

In addition to *in vitro* DPPH radical scavenging activity, compounds **3d**, **3e**, and **3j** were subjected to thermodynamic investigation in the absence and in the presence of free radicals (Schemes 3 and S1, Tables 5, and S4). To get insight which of the mechanism Hydrogen Atom Transfer (HAT), Single Electron–Proton Transfer (SET-PT), and Sequential Proton-Loss Electron-Transfer (SPLET) prevails in the absence of free radicals, appropriate thermodynamic parameters (Bond Dissociation Enthalpy (BDE), Ionisation Potential (IP), and Proton Abstraction (PA) energies, respectively) were calculated with functionals B3LYP and M06-2X (Schemes S1, Tables 5 and S4).[51–56] It is worth pointing out that the energies obtained with M06-2X are generally slightly higher than those with B3LYP functional, but with the same outcome. Here, the results obtained with B3LYP functional are presented and discussed, while those obtained with M06-2X are provided in Table S4 of ESI. For the examination of the preferred mechanism of radical scavenging in the presence of free radicals, enthalpies of the reactions of examined phenolics with selected free radicals ($\Delta_r H$) were calculated using same DFT functionals. Here, HAT, SET-PT, and SPLET mechanisms are presented with ΔH_{BDE}, ΔH_{IP} and ΔH_{PDE}, ΔH_{PA} and ΔH_{ETE} reaction enthalpies, respectively (Scheme 3, Tables 5, and S4).[51–56] The HAT mechanism is presented with the hydrogen atom transfer to radical species, and enthalpy of this reaction ($\Delta_r H_{BDE}$) can be calculated according to the Eq. 1 (Scheme 3). The SET-PT mechanism is two-step process, where in the first step, electron transfer takes place, and enthalpy of this reaction ($\Delta_r H_{IP}$) can be determined via Eq. 2. In the second step, formed radical cation is deprotonated, where enthalpy of this reaction ($\Delta_r H_{PDE}$) is calculated according to, Eq. 3. The SPLET mechanism is two-step process, also. Here, in the first step, antioxidant is being deprotonated (Eq. 4, $\Delta_r H_{PA}$), and in the second step electron transfer takes place (Eq. 5, $\Delta_r H_{ETE}$). All above mentioned mechanisms have the same net thermodynamic balance, owing to the same reactants and products, Eq. 6.[56]



Scheme 3. Thermodynamical parameters in the presence of free radical species

$$\Delta_r H_{BDE} = [H(AO^{\bullet}) + H(ROH)] - [H(AOH) + H(RO^{\bullet})] \quad (1)$$
$$\Delta_r H_{IP} = [H(AOH^{\bullet+}) + H(RO^{-})] - [H(AOH) + H(RO^{\bullet})] \quad (2)$$
$$\Delta_r H_{PDE} = [H(AO^{\bullet}) + H(ROH)] - [H(AOH^{\bullet+}) + H(RO^{-})] \quad (3)$$
$$\Delta_r H_{PA} = [H(AO^{-}) + H(ROH)] - [H(AOH) + H(RO^{-})] \quad (4)$$
$$\Delta_r H_{ETE} = [H(AO^{\bullet}) + H(RO^{-})] - [H(AO^{-}) + H(RO^{\bullet})] \quad (5)$$
$$\Delta_r H_{BDE} = \Delta_r H_{IP} + \Delta_r H_{PDE} = \Delta_r H_{PA} + \Delta_r H_{ETE} \quad (6)$$

In both cases (absence and presence of free radicals), the lowest amount in energy suggests preferred route of radical scavenging. Thermodynamic parameters and reaction enthalpies were obtained by optimisation of all relevant species in methanol, the same solvent which was used in experimental DPPH assay. Selection of radicals (hydroxy ($^{\bullet}OH$), hydroperoxy ($^{\bullet}OOH$),methylperoxy ($CH_3–O–O^{\bullet}$), superoxide radical anion ($O_2^{\bullet-}$), methoxy ($^{\bullet}OCH_3$), tert-butoxy ($^{\bullet}OC(CH_3)_3$), vinyl peroxy ($CH_2=CH–O–O^{\bullet}$), and DPPH) for reaction with the examined compounds was made based on their appearance and behaviour in the living cell.[47,57,58]

Based on the obtained values for BDE, IP, and PA (the absence of free radicals) one can undoubtedly conclude that the preferred mechanism of antiradical action is SPLET Namely, PA is significantly lower than BDE and IP. On the other hand, obtained reaction enthalpies in the presence of free radicals imply that the reaction routes are highly influenced by reacted radical.[47,57] Here, SET-PT can be eliminated as possibility for all examined compounds and for all radicals, since ΔH_{IP} is considerably higher than ΔH_{BDE} and ΔH_{PA}. The only pronounced difference between ΔH_{BDE} and ΔH_{PA} is in the case of the reaction with $^{\bullet}OH$ radical. Here, ΔH_{BDE} values are significantly lower, labelling HAT as preferred mechanism of $^{\bullet}OH$ radical quenching. Not so evident difference between ΔH_{BDE} and ΔH_{PA} for the reactions with alkoxy and peroxy radicals ($^{\bullet}OCH_3$, $^{\bullet}OC(CH_3)_3$, $^{\bullet}OOH$, $CH_3–O–O^{\bullet}$, $CH_2=CH–O–O^{\bullet}$) points out competition between HAT and SPLET mechanisms. The similar trend is obtained for the reactions with the DPPH radical. However, ΔH_{BDE} and ΔH_{PA} are presented by low positive values, which implies slow reactions. Similarly to previously published results for other phenolic compounds, enthalpies for the reactions with $O_2^{\bullet-}$ are the highest.[47,55,56,59,60]

3. Conclusions

Catalyst-free and ultrasonic assisted synthesis of benzamide-dioxoisoindoline derivatives, in water as a solvent, is reported in this paper. Five of fourteen products have been presented in this study for the first time (**3d-f**, **3i**, **3j**). All compounds were obtained in high yields and characterized by melting points, NMR, IR, elemental analysis for new compounds, and crystal determination for product **3h**. Additionally, the mechanism for the synthesis of benzamide-dioxoisoindoline derivatives **3** was proposed and analysed. According to the calculated values of green chemistry metrics, it can be concluded that this synthesis fulfills the principles of green chemistry. All products were tested for their antioxidative potential. The obtained *in vitro* results reveal that compounds with catecholic moiety (**3d**, **3e** and **3j**) exerted excellent activities comparing to NDGA and quercetin as reference compounds, and that benzamide-dioxoisoindoline derivatives with pyrogallolic scaffold (**3j**) displays the best antioxidant activity with IC_{50} value 1.2 μM. In addition, based on thermodynamicall parameters, in the absence of free radicals, the preferred radical scavenging pathway is SPLET. On the other hand, enthalpies of the reactions of investigated compounds with the free radicals denote competition of HAT and SPLET mechanisms. The only difference is in the case of the reaction with $^{\bullet}OH$ radical, where the HAT reaction pathway is significantly

more exergonic, clearly pointing it out as preferred route of radical quenching.

4. Experimental Section

4.1. Materials and Methods

Chemicals used for the synthesis were acquired from Sigma Aldrich with purities above 98%. The IR spectra were obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer using the KBr disc. The NMR (^{1}H and ^{13}C) spectra were determined on a Varian Gemini spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C) using $CDCl_3$ and DMSO. The UV-Vis measurements were recorded on Agilent Technologies, Cary 300 Series UV/Vis Spectrophotometer. Ultrasonication was performed with ultrasonic bath (BandelinSonorex RK 52 H, Bandelin electronic GmbH & Co. KG, Berlin, Germany) at 35 kHz frequency and 150 W power. Melting points were done on a Mel-Temp capillary melting points apparatus, model 1001. Elemental (C, H, N) microanalysis were determined at the University of Belgrade, Faculty of Chemistry.

4.2. Synthetic procedures

*4.2.1. General procedure for the synthesis of hydrazides **2***

Hydrazides **2** were obtained in reaction of methyl esters **1** (1 mmol), which synthetized from corresponding acids,[61] and hydrazine monohydrate (6 mmol) by heating under reflux for 4h.[62]

*4.2.2. General procedure for the synthesis of benzamide-dioxoisoindoline derivatives **3***

A mixture of phthalic anhydride (1 mmol) and corresponding hydrazide (1 mmol) in water as a solvent (2 mL), was heated to 80 □, using an ultrasound bath. Reaction progress was monitored using TLC. In all reactions, the formed precipitation was filtrated and washed with water. All 1,3-dioxoisoindolin-benzamide products (**3a-n**) were characterized with melting points, ^{1}HNMR, ^{13}CNMR and IR spectra. For the newly synthetized compounds **3d-f**, **3i** and **3j**, purity was confirmed by elemental analysis, too. In addition, crystal structure of **3h** was determined in this study for the first time. The spectral characterization of new benzamide-dioxoisoindoline derivatives (**3d-f**, **3i** and **3j**) is given in main part of the manuscript, while for other compounds in Electronic Supplementary Information, as well as copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds.

*4.2.2.1. N-(1,3-dioxoisoindolin-2-yl)-2,3-dihydroxybenzamide (**3d**)*

Beige powder, m.p. 220 □; Isolated yield: 85 (80)%; ^{1}H NMR (200 MHz, DMSO) δ: 6.82 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 8.06-7.90 (m, 4H), 9.95 (s, 1H), 11.04 (s, 1H), ^{13}C NMR (50 MHz, DMSO) δ: 114.60, 118.86, 119.22, 119.96, 123.97, 129.63, 135.49, 146.37, 148.18, 165.22, 167.43; IR (cm^{-1}): ν_{max} = 3289-3503 (NH/OH), 1644-1787 (3C=O); $C_{15}H_{10}N_2O_5$ (FW = 298.25): C, 60.41; N, 9.39; H, 3.38%; found: C, 59.95; N, 9.46; H, 3.63%.

*4.2.2.2. N-(1,3-dioxoisoindolin-2-yl)-3,4-dihydroxybenzamide (**3e**)*

Beige powder, m.p. 230-232 □; Isolated yield: 81 (78)%; ^{1}H NMR (200 MHz, DMSO) δ: 6.87 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.30 (m, 2H), 8.06 – 7.89 (m, 4H), 9.42 (s, 1H), 9.83 (s, 1H), 10.96 (s, 1H), ^{13}C NMR (50 MHz, DMSO) δ: 115.37, 115.51, 120.10, 121.83, 123.89, 129.61, 135.44, 145.32, 149.98, 165.18, 165.64; IR (cm^{-1}): ν_{max} = 3301-3535 (NH/OH), 1674-1790 (3C=O); $C_{15}H_{10}N_2O_5$ (FW = 298.25): C, 60.41; N, 9.39; H, 3.38%; found: C, 60.22; N, 8.99; H, 3.71%.

*4.2.2.3. N-(1,3-dioxoisoindolin-2-yl)-4-hydroxy-3-methoxybenzamide (**3f**)*

White powder, m.p. 233-235 □; Isolated yield: 76 (74)%; ^{1}H NMR (200 MHz, DMSO and $CDCl_3$) δ: 3.86 (s, 3H), 6.88 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.44 (m, 2H), 8.00 – 7.80 (m, 4H), 9.75 (s, 1H), 10.95 (s, 1H), ^{13}C NMR (50 MHz, DMSO and $CDCl_3$) δ: 55.72, 111.57, 115.00, 121.54, 121.79, 123.48, 129.64, 134.81, 147.26, 150.85, 164.84, 165.29; IR (cm^{-1}): ν_{max} = 3395 (NH/OH), 1672-1794 (3C=O), 1219-1277 (OCH_3); $C_{16}H_{12}N_2O_5$ (FW = 312.28): C, 61.54; N, 8.97; H, 3.87%; found: C, 61.22; N, 9.07; H, 3.90%.

*4.2.2.4. N-(1,3-dioxoisoindolin-2-yl)-2,4-dihydroxybenzamide (**3i**)*

Brown powder, m.p. 230-232□; Isolated yield: 75 (72)%; 1H NMR (200 MHz, DMSO) δ: 6.49 – 6.34 (m, 2H), 7.79 (d, *J* = 8.6 Hz, 1H), 8.05 – 7.90 (m, 4H), 10.37 (s, 1H), 10.73 (s, 1H), 11.54 (s, 1H), ^{13}C NMR (50 MHz, DMSO) δ: 102.78, 105.86, 108.15, 123.79, 129.53, 131.02, 135.33, 160.80, 163.21, 165.32, 166.62; IR (cm^{-1}): ν_{max} = 3307 (NH/OH), 1648-1790 (3C=O); $C_{15}H_{10}N_2O_5$ (FW = 298.25): C, 60.41; N, 9.39; H, 3.38%; found: C, 60.05; N, 9.70; H, 3.56%.

*4.2.2.5. N-(1,3-dioxoisoindolin-2-yl)-3,4,5-trihydroxybenzamide (**3j**)*

Yellow powder, m.p. 226-228 □; Isolated yield: 72 (70)%; ^{1}H NMR (200 MHz, DMSO) δ: 6.97 (s, 2H), 8.04 – 7.91 (m, 4H), 9.00 (s, 1H), 9.32 (s, 2H), 10.88 (s, 1H), ^{13}C NMR (50 MHz, DMSO) δ: 107.38, 120.74, 123.78, 129.52, 135.34, 137.85, 146.71, 165.40, 165.53; IR (cm^{-1}): 3363 (NH/OH), 1652-1786 (3C=O); $C_{15}H_{10}N_2O_6$ (FW = 314.25): C, 57.33; N, 8.91; H, 3.21%; found: C, 57.10; N, 9.05; H, 3.26%.

4.3. X-ray crystal structure determination

Single-crystal X-ray diffraction data for compound **3h** were collected at Oxford Gemini S diffractometer, using monochromatized Mo*K*α radiation (λ = 0.71073 Å). Data reduction and empirical absorption correction were performed with CrysAlisPRO.[63] The structure was solved by direct methods using SHELXS and refined on F^2 by full-matrix least-squares using SHELXL.[64] All non-hydrogen atoms were refined anisotropically. H atoms bonded to C atoms were placed in geometrically calculated positions and refined using the riding model with U_{iso} values constrained to $1.2U_{eq}$ or $1.5U_{eq}$ of the parent C atoms. H atom bonded to N atom was found in a difference Fourier synthesis and refined isotropically. The PLATON[65] software was used to perform geometrical calculation and the Mercury[66] was employed for molecular graphics. Crystallographic details are summarized in Table S3. CCDC 1965239 contains the supplementary crystallographic data for compound **3h**.

4.4. DPPH free radical scavenging assay

The free radical scavenging activity of synthetized compounds was measured by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay method.[67] The examined compound (20 μL of different concentrations dissolved in DMSO and 980 μL of methanol) was mixed with 1mL solution of DPPH in methanol (0.05 mM). The reaction mixture was shaken well and incubated in the dark for 20 and 60 minutes at room temperature. Then, absorbance was acquired at 517 nm using the spectrophotometer. In this assay, methanol was used as a blank control. The tests were run in triplicate and averaged. As reference compounds, NDGA and quercetin were used. For compounds which exert good activity, IC_{50} values were determined. IC_{50} is defined as the concentration necessary to determine 50% of a maximum antioxidative activity. The results are presented as mean ± SD. The stoichiometric factor was calculated using the equation:

$$\text{stoichiometric factor} = [DPPH]_0/(2\times IC_{50}).$$ [42,44]

4.5. Density functional theory calculations

All calculations were performed using The Gaussian 09 program package.[68] B3LYPfunctional with D3 dispersion term using Becke–Johnson damping function[69] and M06-2X functionals[70] and the 6-311+G(d,p) basis set were employed to calculate equilibrium geometries of all compounds and all relevant species that participate in the reactions.[71,72] To simulate the influence of methanol (ε = 32.6) as solvents SMD solvation model was used as implemented in Gaussian 09.[68,73] Frequency calculations were done, and the absence of any imaginary frequency confirmed that all structures are local minima. For the calculations of open-shell systems unrestricted spins were used. All relative enthalpies were calculated at 298.15 K. The solvation enthalpies of proton and electron in methanol were used from literature.[74]

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Highlights

- *N*-(1,3-dioxoisoindolin-2-yl)benzamide derivatives were obtained.
- “On water” ultrasonic assisted methodology is presented.
- Used method presents green approach according to green chemistry parameters.
- Five compounds have been reported in this study for the first time.
- All obtained compounds were tested for their *in vitro* antioxidative activity.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: