Natural dihydroisobenzofuran derivatives as a template for promising radical scavengers: theoretical insights into structure–activity relationships, thermochemistry and kinetics

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Received: 6 September 2022 / Accepted: 26 September 2022 / Published online: 10 October 2022 © The Author(s) 2022

Abstract
Dihydroisobenzofuran heterocycle is a structural motif found in a number of medications with anti-tumour, anti-diabetic, and antibacterial activities. It is also found in a slew of natural substances, most notably fungus metabolites, which have been shown to possess credible radical scavenging activity. Density functional theory studies on three different derivatives were conducted to investigate their electronic structures as well as thermochemical and kinetic behaviour against ·OOH, ·OH, and ·OCH3 in biologically relevant solvents, with the goal of elucidating structure–activity relationships and discussing the potential role of the scaffolds as a template for new semisynthetic antioxidants. The importance of resonance and inductive effects, and also hydrogen bonding, has been underlined, but most importantly, it has been demonstrated that all structures have considerable scavenging potential against all studied radicals, with reactions rates close to the diffusion limit.

Keywords Dihydroisobenzofuran · Radical scavenging · Density functional theory · Structure–activity relationship · Kinetics · Thermochemistry

1 Introduction

When it comes to conducting precise research at the atomic resolution, computational chemistry gives powerful tools. With the ability to generate data on interactions with membranes, enzymes, or other pharmaceuticals; to describe the underlying mechanisms of action; and to project new substances, it speeds up the drug-development process by reducing study time and costs. Today, when there is a strong quest for radical scavengers emerging from their excessive accumulation in body, it can be utilized once more with the goal of proposing scaffolds that might serve as a backbone for novel semisynthetic radical scavengers of senolytic properties [1].

Despite being minuscule particles with at least one unpaired electron on their valence shell, radicals comprise a huge class of chemical entities. Reactive oxygen, nitrogen or carbon species accounts for an oxidative deterioration of organic and inorganic matter. They cause peroxidation of lipids, saccharides and amino acids, oxidize metals, and disrupt the carbon structures, resulting in a food spoilage, materials breakdown, or cell and tissue malfunctioning. However, their nature is twofold and hence, cannot be deemed entirely undesirable; for example, cells produce and release ·OH, NO· and O2– in course of normal metabolic activities, such as inflammation during immune response or wound healing, intracellular signalling, or vasodilatation [2].

An elevated and sustained concentration of prooxidants, known as oxidative stress, has detrimental impact on health and has been linked to the development of severe conditions such as cardiovascular diseases, arthritis, diabetes and cancer [2–4]. The brain is particularly vulnerable to oxidative stress because its cells require continuous and substantial amount of oxygen to produce radical neurotransmitters involved in brain cell growth, neuroplasticity and cognitive functioning. Thereby, their excess may cause damage to dopaminergic neurons, eventually leading to necrosis and development of Parkinson’s disease; free radicals are also known to interact with amyloid-β peptides, whose modifications contribute to the deposition of amyloid plaques, key markers of Alzheimer’s disease [3, 5, 6]. Prolonged oxidative stress has also

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been related to accelerated and premature ageing and cell senescence [4]. Finally, oxidative stress can also trigger a vicious circle in which physiologically desired inflammatory response further increases free radicals’ level, enhancing inflammation.

Several factors contribute to development of oxidative stress, including high-fat and high-sugar diet, drug abuse, lifestyle (especially smoking and alcohol consumption), and environmental factors such as exposure to pesticides, pollution and radiation. Although the latter are not directly bounded, they mutually influence on each other, and for example, \( \text{OH}, \text{NO}^- \) and \( \text{Cl}^- \) sourcing majorly from wastes participate in ozone depletion chain reactions, increasing the amount of UV radiation that reaches Earth [7]; exposure to it is observed in a greater number of integumentary neoplasms incidences and unpleasant ecosystem changes [8].

Internal antioxidants, the most well-known of which are glutathione, lipoic acid, and uric acid, maintain oxidants concentration in vivo. Unfortunately, the presence of that system appears to be insufficient in our times, and thin line proceeding oxidative damage is often extended, unveiling the harmful consequences of havoc radicals do. Because many natural products, such as fruits and vegetables, are high in vitamins and polyphenols, which the body cannot make on its own and have sturdy antioxidative potential, a diet rich in them is a crucial aspect of maintaining the balance between prooxidants and their scavengers.

From chemical standpoint, as an antioxidant can be considered any substance that may neutralize free radicals. This can be achieved in a variety of ways, including direct radical scavenging, chelation of metals involved in Fenton’s reaction, up- or down-regulation of certain enzymes, regeneration of biological antioxidants, and others [9]. The first one of the listed is the most broadly discussed in this manner what stems from the presence of aromatic hydroxyl groups, which stabilize radicals thanks to their chemical properties: typically strong electron delocalization, present in the excellent degree among carotenoids [10], non-covalent interactions of intra- or inter-molecular character such as hydrogen bonds, and hyperconjugation effects.

Isobenzofuran, isobenzofuran-1(3H)-one and 3-hydroxyisobenzofuran-1(3H)-one heterocycle rings are structural motifs building up important pharmaceuticals and naturally occurring substances evidenced to have plausible radical scavenging potential [11]. These have been shown to possess bunch of therapeutic properties, such as anti-tumour [12, 13], anti-diabetic [14, 15], antimyocytic [16], antibacterial [17–20], cytotoxic [17, 19, 21] and antioxidative [15, 16, 18, 20, 22–26]. Fungi provide virtually endless natural source of that class of compounds [16, 27–30], with many of them already being successfully used, as for example griseofulvin.

In their recent papers, She et al. [15, 20, 26] comprehensively explored the antiradical activity of several fungal metabolites by measuring their DPPH/ABTS$^+$ radical scavenging capacity. The results showed that isobenzofuran and isobenzofuran-1(3H)-one derivatives had the most promising IC$_{50}$ values when compared to other structures investigated. Meng et al. [31] reported a 2-benzofuran-1(3H)-one compound with an IC$_{50}$ of 1.23 ug/mL, which is exceptionally low when compared to reference antioxidants like ascorbic acid (30.6 ug/mL [32], 43.2 ± 10.3 ug/mL [33]) or Trolox (6.3 ug/mL [33]). The experimental results obtained by Li et al. [34] against DPPH$, \cdot\text{OH}$, and $\text{O}_2^-$ speciesimply that the heterocyclic backbone may play an essential role in such potent radical scavenging activity.

While many experiments have been carried out to assess the antiradical activity of specific benzofuran derivatives, no computational elaborations on their common chemical structures are available. To address this gap, three Epicoccum sp. derivatives (Fig. 1) with established radical scavenging activity.

![Fig. 1 The molecular structures of the substances under consideration. The violet colour represents uncommon parts. The common backbone is represented by the bolded fragments in the IUPAC nomenclature](image-url)
activities were chosen [26] and thoroughly investigated using density functional theory in terms of the electronic structure, thermochemistry and kinetic behaviour against some common oxidants such as ·OOH, ·OH and ·OCH₃, with discussions on structure–activity relationships responsible for that activities provided at each step.

2 Results and discussion

2.1 Acid–base equilibria

Because aromatic hydroxyl groups have a slightly acidic character, the reactivity of phenolic antioxidants is sensitive to pH changes and shall be assessed at the outset of the investigation to assert reliable outcomes. Dissociation rearranges electronic structure, altering chemical behaviour of the species not only as a consequence of the reduced number of available hydroxyl groups that would participate in hydrogen-related pathways, but also due to the feasibility of electron-related redox processes [35]. This is particularly relevant aspect because certain radicals are scavenged much easier by hydrogen atom acceptance than electron transfer [9].

To account for all the species present at the environment of interest, pKₐ values for water solvent at physiologically appropriate pH = 7.4 have been established and are included in Supplementary Information along with the deprotonation routes and distribution diagrams (Table S1). The results show that the most prevalent forms of each component in water are: M⁻¹ (85.5%, diss. at C3), M⁻² (98.5%, diss. at C5) and M₃ (96.2%). M₁ (7.8%), M¹⁻ (6.7%, diss. at C3 and C6), M₂ (1.5%) and M³⁻ (3.8%, diss. at C6) although present at relatively much smaller fraction, still can be detected at considerable amounts and so were studied as well (Fig. 2).

In case of pentyl ethanoate, all neutral forms were examined. After all, given that diffusion through the membrane bilayer is preferred for small, uncharged particles, the results obtained for water milieu are encouraging.

To begin with deprotonation appears to have an unusual effect on M₁. It occurs at C3 hydroxyl, starts at pH ≈ 4, has a corresponding proton dissociation enthalpy ΔG° = 35.9 kcal/mol, and results in decomposition of 3-hydroxyfuran-1(3H)-one ring into separated aldehyde and carboxylate residues. With C3–O2 bond frozen, another optimization was carried out, and it appears that the relative energy difference between the expected C3-dissociated form and the actual one results in 10.7 kcal/mol more stable structure in favour of the latter.

Recruiting second-order perturbation theory analysis of the Fock matrix in NBO basis (Table S2) LP₂(O₁₈) → σ*(C₁₄–O¹₆) interaction found in case of undissociated species and corresponding to the move of lone pair from hydroxyl oxygen to C–Oₐₙₙ bond and destabilizing it by 20.9 kcal/mol, is no longer in the intermediate product; instead, a new one, LP₃(O₁₈) → σ*(C₁₄–O₁₆), with an energy of roughly 35.0 kcal/mol, originating from the oxygen lone pair, and resulting from dissociation, appears.

2.2 Frontier molecular orbitals

The distribution and energies of frontier molecular orbitals, highest occupied (HOMO) and lowest occupied (LUMO), can be directly related to antioxidative activity of an isolated species via the set of indices matching to their electron donating and electron accepting properties.

The outcomes shows that the electron density is spread mainly on the aromatic hydroxyl groups and phenyl ring of the isobenzofuran backbone, as expected and as illustrated in Fig. 3, and exhibiting properties typical of π-type conjugated bonds. A tiny fraction is also present on furan scaffold.

While MOs do not differ considerably between examined substances or solvents, three observable traits are worth mentioning:

(1) The π-electron density is visible on the furan site after the second dissociation of M₁ and the first dissociation of M₂, both of which are connected with hydroxyl at position C5. This suggests that the lactone scaffold exhibits strong inductive character.
(2) The electrons from C5 oxygen of $M_1$ participate in the HOMO-delocalized system, but furan ring opening breaks this contribution, whereas subsequent deprotonation from C6 restores it.

(3) Unlike the former, electrons from C5–OH of $M_2$ and $M_3$ are not implicated in $\pi$-resonance, what shifts upon deprotonation from the same (higher contribution) or C4 site (lower contribution), respectively.

A structure of low HOMO eigenvalue, according to the frontier molecular orbitals theory, is considered as a poor electron donor. In contrast, low LUMO eigenvalue suggests that the molecule will most likely take the electrons. HOMO is especially interesting in this pair since antiradical activity of antioxidants is majorly dependent on electron donating abilities [35]. In this regard, the neutral forms of the compounds examined have comparable activity in both solvents (ranging from $-7.84$ eV for $M_1$ in pentyl ethanoate to $-7.29$ eV for $M_3$ in the same environment). After first dissociation, the energies of HOMO shift for $M_2$ (from $-7.64$ to $-6.52$ eV) and $M_3$ (from $-7.64$ to $-6.25$ eV), but not for $M_1$, as previously identified in the context of furan ring crumbling. LUMO energies are relatively high and do not vary much despite of the solvent or the chemical structure of the species, showing that the chemicals under investigation are unwilling to attract electrons.

The presence of carboxyl and carbonyl residues resulting from the opening of lactone ring alters the aromaticity of the system via $+M$ (relative meta positions) and $-I$ effects. The former has a superior impact, as evidenced by virtually
identical MO energies and fundamental gaps between $M_1$ and $M_1^-$, suggesting approximately comparable chemical stability between them. Simultaneously contrasting to other mono-ionized species. Furthermore, the newly created –COO– group is only 1.57 Å away from the adjacent hydroxyl hydrogen, indicating the presence of hydrogen bond interactions. With the help of Multiwfn [36], three (3, – 1) bond critical points were identified, as were non-covalent interactions (Fig. 4). There are several of them in the structure, and the previously mentioned hydrogen bond has been estimated to equal −14.2 kcal/mol, explaining the observations.

The difference in energies between HOMO and LUMO also allows for a preliminary estimation of kinetic stability for radical reactions—the smaller the difference, the faster the process. Thereby, ionic species are expected to react more readily with radicals. This impact becomes much stronger after the second deprotonation, as evidenced by the lowest $\Delta E = 5.88$ for $M_1^{2−}$.

In any case, whether compared to other natural [38, 39], semisynthetic [40] or synthetic [41] compounds with a benzofuran motif, the chemicals studied here are less likely to give electrons. Using TD-DFT simulations, Kumar et al. [42] found the HOMO−LUMO gap of vitamin E to be 5.17 eV, indicating that all species presented in this work will react substantially slower in radical reactions than tocopherol. They should also react slower than the flavonoid quercetin, which has an optical gap of 5.90 eV [43].

### 2.3 Electronic structure descriptors

Electronegativity ($\chi$), global hardness ($\eta$) and electrophilicity index ($\omega$) were determined to assess the electron acceptor/ donor properties of the examined species. The findings are summarized in Table 1.

#### Table 1 Electronic Structure Descriptors Values for $M_1$–$M_3$ Species in Pentyl Ethanoate and Water, in eV

| Specie | Solvent          | $\chi$ | $\eta$ | $\omega$ |
|--------|------------------|--------|--------|----------|
| $M_1$  | Pentyl ethanoate | 4.18   | 3.67   | 2.38     |
|        | Water            | 4.29   | 3.59   | 2.56     |
| $M_1^-$| Pentyl ethanoate | 3.96   | 3.51   | 2.23     |
|        | Water            | 3.38   | 2.94   | 1.94     |
| $M_2$  | Pentyl ethanoate | 4.06   | 3.60   | 2.29     |
|        | Water            | 4.11   | 3.54   | 2.39     |
| $M_2^-$| Pentyl ethanoate | 3.28   | 3.25   | 1.66     |
|        | Water            | 3.73   | 3.56   | 1.95     |
| $M_3$  | Pentyl ethanoate | 3.84   | 3.57   | 2.07     |
|        | Water            | 2.92   | 3.34   | 1.28     |

Electronegativity, or the system’s readiness to attract electrons, ranges from 3.28 eV ($M_1^-$ in water) to 5.83 eV ($M_1^-$ in water). As demonstrated, aqueous environment favours electron uptake, which can be attributed to the higher solvation of the subsequently produced charged species in water than in aprotic pentyl ethanoate. When switching to ionic species, the expected behaviour of decreasing $\chi$ value is also observable. Its values have been found to drop in pattern: $M_1^→M_1^- (0.33 \text{ eV}) < M_2^→M_2^- (0.83 \text{ eV}) < M_3^→M_3^- (0.92 \text{ eV})$. The observed shift in molecule electronegativity might be linked to the furan ring residues. The highest values are associated with $M_1^-$, which contains an electron-donating lactone scaffold that, when opened, generates carboxyl and carboxyl groups, which common and mutually amplified -I effect stabilizes the electron density, explaining smaller shift in electronegativity than among other species.

Global hardness values are thoroughly consistent among the examined substances and, unlike electronegativity, do not vary appreciably between solvents or charged states. In pentyl ethanoate, they are all around 3.60 eV; in water, except for the $M_1^{2−}$ (2.94 eV), they are all around 3.25–3.59 eV (boundary values were found for $M_2^-$ and $M_1^-$, respectively). Because this descriptor serves two purposes: it assesses the relative stability of structures and their resistance to charge transfer; it is safe to presume that both properties are equivalent.

To recap, oxygen radicals having electrophilic properties, such as OH, OOH or OCH$_3$, react with antioxidants by the interaction of their SOMOs with HOMO of the scavenger. Although the indices presented allow for a brief description of the molecule’s reactivity and relative feasibility in electrons involving channels, a much better descriptor is electrophilic index, which simultaneously encompasses both the properties of the electrophile to acquire an additional electronic charge, which is driven by the $\chi^2$ term, and the resistance of the system to exchange electronic charge with the environment, which is described by $2\eta$, accounting also...
for the stabilization effects. Furthermore, by comparing the electrophilicity indices of the reacting species, not only the expected direction of electron flow, but also the magnitude of such interaction may be determined.

The electrophilicity indices of the studied isobenzofuran derivatives follow the trend of \( \eta \), which in relation to their mathematical formulation, implies that chemical hardness, which can be associated with delocalization degree, has a much greater influence than the electron-attracting character of MOs following previous discussion. Again, the values found for pentyl ethanoate and water differ insignificantly (0.13 eV on average); however, deprotonation from \( M_2 \) and \( M_3 \) affects \( \omega \) significantly, providing differences of 0.73 eV and 0.79 eV, respectively. Interestingly, the second dissociation of \( M_1 \) leads to the decrease in chemical hardness from 3.51 to 2.94 eV, and electronegativity from 3.96 to 3.38 eV, as well as a decrease in electrophilicity index value from 2.23 to 1.94 eV. This behaviour ought to be associated with the stability of LUMO, which is more important for electron acceptance properties, and which energy remains constant. The acquired charge is further stabilized due to the presence of two electroaccepting groups, carboxylate and carbonyl.

With electrophilicity indices of 2.46 eV for \( \text{OH} \) [44], 1.98 eV for \( \text{OOH} \) and 1.97 eV for \( \text{OCH}_3 \), it appears that the hydroxyl radical is an electron acceptor in all situations except reactions with \( M_1 \). In contrast, hydroperoxide appears to be converted to \( \text{OOH} \) mostly by ionic species. The same is true for \( \text{OCH}_3 \). Nonetheless, these predictions are based on isolated species properties that, while sufficient to provide insight into structure–activity correlations, are frequently inappropriate to determine reaction direction, especially when such modest energy differences across activating species are displayed.

### 2.4 Intrinsic reactivity indices

Similarly to electronic structure descriptors, those described in this section of the paper represent a viable way for identifying structural elements that improve or diminish antiradical activity. While the radical scavenged has no effect on these calculations, they do allow for a preliminary assessment of preferred reaction routes of isolated species, selection of the most promising ones in a certain objective, and comparison.

As of now, antioxidants are acclaimed to exhibit five general mechanisms of action: formal hydrogen atom transfer (f-HAT), radical adduct formation (RAF), sequential proton loss-electron transfer (SPLLET), sequential proton loss-hydrogen atom transfer (SPLHAT) and sequential electron transfer-proton transfer (SETPT) [35].

Considering that in a multistep antiradical mechanism, the first step drives the reaction and is thermodynamically relevant, a set of reactivity indices can be specified. Because deprotonation, which initiates the SPLLET pathway, is already included indirectly by investigating various species at the given chemical equilibrium, this process can be described satisfactorily purely in terms of single electron transfer (SET) energies. The presence of ionic species is not taken into account in the case of pentyl ethanoate due to the lack of proton solvability, which evidences that the entire process is unwilling to be possible in that solvent. As a result, SET computations are skipped in that medium. Furthermore, because electron transfer from reactive oxygen species to antioxidant is unlikely, electron acceptance capacity of the latter is frequently overlooked in computations [45]. As a result, bond dissociation enthalpy (BDE) for the formal hydrogen atom transfer (f-HAT), ionization potential (IP) for SET, and proton dissociation enthalpy (PDE) for the second phase of SETPT have all been computed (Table 2).

#### 2.4.1 Ionization potential

The calculated IP values match the widely reported pattern of being higher in pentyl ethanoate than in water, and decreasing with subsequent dissociation. The greatest values are recorded for \( M_1 \) species, followed by \( M_2 \), and \( M_3 \) for which ionization undergoes the most easily. Assuming that ionization potentials are exclusively determined by available electron density and that the methoxy group is equal to hydroxyls in terms of electrodonating characteristics, the species differs only in the furan motif. Because \( M_1 \) and \( M_2 \) have such comparable structures, it is fair to presume that the presence of any residue in the furan ring should increase system’s IP value.

The previous pictures of MOs explain this by demonstrating their participation in LUMO, with a minimal contribution to HOMO. However, with deprotonation, the electron density gradually extends onto them, as indicated by the decrease in IP value. As shown in the electronic structure section, the vertical ionization potential can be approximated to the negative of HOMO, which pattern agrees with existing data. The presence of water not only decreases these values due to the stabilization effect, but also normalizes them, making the differences less noticeable—142.7 kcal/mol, 139.6 kcal/mol and 127.0 kcal/mol in pentyl ethanoate, and 117.6 kcal/mol, 115.7 kcal/mol and 111.0 kcal/mol in water, for \( M_1 \), \( M_2 \) and \( M_3 \), respectively. This leads to another observation: the electronic structure of the provided species is less impacted by a solvent, as shown by differences in 25.1 kcal/mol; 23.9 kcal/mol and 16 kcal/mol, in the same sequence.

#### 2.4.2 Bond dissociation enthalpy

According to Table 2, the lowest BDE has been discovered in \( M_2 \) structure. By comparing index values of \( C_6–\text{OH} \), which is present in all species, it is clear that \( M_1 \) and \( M_3 \) have relatively adequate radical scavenging potential by hydrogen atom donation from that site, with \( M_3 \) benefiting just slightly.
While various factors, including radical scavenged, are important for proclivity of $f$-HAT, the emphasis will be given on internal factors such as spin density delocalization in the generated species, inductive influence of substituents, and intramolecular hydrogen bond interactions. To begin, resonance structures for each species have been drawn (Fig. 5), and based purely on these, the lowest BDE should be connected with either C5 or C7 hydroxyl, which is capable of delocalizing to the largest extent, namely up to the furan scaffold. In contrast, spin density resulting from hydrogen atom removal from C4 or C6 hydroxyl is confined in the benzene ring. Indeed, the lowest value of bond dissociation enthalpy reported for C5 hydroxyl of $M_2$ coincides with that, but not with $M_1$. If the resonance is the most important factor in benzofurans antiradical viability by $f$-HAT, the obtained BDE values should reflect this.

As a result, the polar effects have been taken into account, and electronic surface potentials have been mapped onto the electron density, as shown in Fig. 6. The electronegativity between the atoms is highly related to covalent bond fission, and decreasing values account for reduced stability and hence a higher change of its breakage during the reaction. The computed polarity values of the examined species' hydroxyl O–H bonds ($\Delta\delta$) equal:

- for $M_1$: $\Delta\delta_{3O-H} = 0.064$; $\Delta\delta_{5O-H} = 0.032$; $\Delta\delta_{6O-H} = 0.010$; $\Delta\delta_{7O-H} = 0.008$
- for $M_2$: $\Delta\delta_{4O-H} = 0.005$; $\Delta\delta_{5O-H} = 0.570$; $\Delta\delta_{6O-H} = 0.009$
- for $M_3$: $\Delta\delta_{4O-H} = 0.017$; $\Delta\delta_{4O-H} = 0.007$

In the case of those species, it appears that the inductive effect plays a significant role. It renders C3 hydroxyl as the most polar residue and most likely to undergo deprotonation not only in terms of antibonding interactions, and can now be used to support the earlier debate on lactone ring opening. After all, the BDE and IP values obtained are comparable to those observed for moracin T [38] or viniferifuran [39], two naturally occurring antioxidants with benzoferan motifs that have been proved to exhibit notable radical scavenging properties.

### 2.5 Thermochemistry and kinetics

To end the research, thermochemistry and kinetic computations against the common radicals were conducted. After all, without taking into account reaction rates, it is assumed that the Bell–Evans–Polanyi principles hold true [46, 47], which is not always the case, and for unknown systems, such as these, may lead to incorrect conclusions about the correlation between obtained Gibbs free energies and activation barrier or reaction rate.

Using the reaction equations below, the Gibbs free energies ($\Delta G^\circ$) for the scavenging of a radical $R^\cdot$ by an
antioxidant $\text{M(OH)}_n$ via $f$-HAT, RAF, and SET mechanisms were calculated:

$$f\text{-HAT} : \quad M(\text{OH})_n + R \rightarrow M(\text{OH})_{n-1}O^- + RH$$
The outcomes for \(M_1\), \(M_2\) and \(M_3\) are collected in Table S3, S4 and S5, respectively. The results reveal that any of the derivatives and species can easily scavenge \(\cdot\text{OH}\) by the f-HAT and RAF pathways. With each deprotonation, these processes become increasingly simpler. In contrast, the obtained SET values are noticeably positive, especially for neutral forms in water.

Moving on to \(\cdot\text{OCH}_3\), while not all \(\Delta G^\circ\) values obtained for RAF are negative, they are in most cases lower than the recommended threshold of 10 kcal/mol, implying that these routes may still be meaningful. \(\cdot\text{OCH}_3\) is likewise more easily neutralized in SET—lower \(\Delta G^\circ\) values are reported in water than phenylethane; the opposite is true for \(\cdot\text{OH}\). Another possible mechanism for neutralizing these radicals is f-HAT. With the exception of a few isolated examples and positions of \(M_2^-\), RAF does not appear to be a viable method the investigated compounds utilize to get rid of \(\cdot\text{OOH}\). Neither is SET, which has been proven to have the lowest Gibbs free energy of 33.9 kcal/mol (\(M_2^-\)). f-HAT, on the other hand, stands out as a feasible option.

For reactions with negative or moderately positive Gibbs free energy, apparent rate constants (\(k_{\text{app}}\), corresponding to the reaction rate of the thermodynamically plausible mechanism, were computed. They were then used to calculate: total reaction rate (\(k_{\text{total}}\), Eq. 1), which is the sum of the \(k_{\text{app}}\) of reactions between the antioxidant species and the given radical in the studied solvent; and overall reaction rate (\(k_{\text{overall}}\), Eq. 2), which is the summed product of the previously estimated \(k_{\text{total}}\) the molar fraction (\(M_f\)), is formulated as:

\[
k_{\text{overall}} = \sum (k_{\text{total}} \times M_f)
\]

The results are shown in Table S6, S7 and S8. There are also activation energies (\(\Delta G^\ne\)) and branching ratios (\(\Gamma\)), computed as a \(k_{\text{app}}/k_{\text{total}}\). \(\Delta G^\ne\) was frequently negative, or the transition state could not be determined. Relaxed scans were used in the latter situation to analyse the potential energy surface of the radical approaching the studied species. The lack of the saddle point was confirmed and estimated as a determinant of the barrierless reaction, the rate constant of which is simply restricted by diffusion. This is a common characteristics of potent radical scavengers [39, 48–50]. Figure 7 displays the localized transition states associated with hydrogen atom transfer.

It was found that \(\cdot\text{OCH}_3\) is most easily scavenged by \(M_2\) in pentyl ethanoate (\(k_{\text{overall}} = 1.24 \times 10^9\) M\(^{-1}\) s\(^{-1}\)) and, at nearly 6 times greater reaction rate, in water (\(k_{\text{overall}} = 7.03 \times 10^9\) M\(^{-1}\) s\(^{-1}\)). Although f-HAT if the primary pathway pursued by both of them, the importance of SET cannot be overstated. It is worth noting that, while RAF is possible, the reaction rates are significantly lower, resulting in a negligible contribution to the \(\cdot\text{OCH}_3\) overall scavenging activity of that compound. \(M_1\) and \(M_3\), on the other hand, represent valuable reactivity towards that radical in both pentyl ethanoate (\(k_{\text{overall}} = 7.98 \times 10^5\) M\(^{-1}\) s\(^{-1}\) and \(k_{\text{overall}} = 1.96 \times 10^6\), respectively) and water (\(k_{\text{overall}} = 4.13 \times 10^9\) M\(^{-1}\) s\(^{-1}\) and \(k_{\text{overall}} = 2.91 \times 10^9\), respectively).

Moving to the \(\cdot\text{OH}\), its scavenging is the quickest for \(M_1\). The overall reaction rate in pentyl ethanoate was found to be equal 2.94 \(\times 10^9\) M\(^{-1}\) s\(^{-1}\), while it is 2.38 \(\times 10^{10}\) M\(^{-1}\) s\(^{-1}\) in water. In contrast to \(\cdot\text{OCH}_3\), hydroxyl radical can be scavenged by either RAF or f-HAT to the same extent in water, as evidenced by similar branching ratios. However, in pentyl ethanoate, f-HAT is still the only way to neutralize that radical. When compared to other compounds studied, similarly high values are observed: \(M_3\) scavenges \(\cdot\text{OH}\) with the \(k_{\text{overall}} = 2.76 \times 10^9\) M\(^{-1}\) s\(^{-1}\) in pentyl ethanoate.
and \( k_{\text{overall}} = 2.04 \times 10^{10} \) in water, and \( M_3 \) with \( k_{\text{overall}} \) of \( 5.88 \times 10^8 \text{ M}^{-1} \text{ s}^{-1} \) and \( 1.90 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1} \), respectively.

The superoxide radical, \( \cdot \text{OOH} \), appears to be most effectively neutralized by \( M_2 \) in pentyl ethanoate, with a reaction rate of \( 1.49 \times 10^3 \text{ M}^{-1} \text{ s}^{-1} \), and water, with a reaction rate of \( 5.56 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} \). This species, like the hydroxyl radical, is scavenged by \( f^{-}\text{HAT} \) and \( \text{RAF} \). Nonetheless, \( M_1 \) and \( M_3 \) preferably neutralize it solely by hydrogen atom transfer, with \( k_{\text{overall}} \) of \( 9.39 \times 10^0 \text{ M}^{-1} \text{ s}^{-1} \) in pentyl ethanoate and \( 3.39 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} \) in water for the former; and \( 6.23 \times 10^1 \text{ M}^{-1} \text{ s}^{-1} \) and \( 1.05 \times 10^8 \text{ M}^{-1} \text{ s}^{-1} \), respectively, for the latter. It is worth noting that no reaction barriers have been discovered for the reaction of any of the studied compounds with hydroperoxyl radical, which, given its destructive nature, is very plausible observation.

### 3 Conclusions

The computational chemistry methods were used to investigate the antioxidative activity of three natural isobenzofuran derivatives and explain the observed behaviour by mean of structure–activity relationships. The investigations into their electronic structure enabled to assess their poor electrodonating character. The intrinsic reactivity indices confirmed that hydrogen atom transfer, relying on the bond...
dissociation enthalpy, is affordable and may be a common mechanism of action. This was confirmed by thermochemical and kinetic studies of these compounds’ reactions with OCH₃, OH, OOH. The studied derivatives react with them without barriers in many cases, and thus, the reaction is limited solely by the diffusion–limit. During the study, it was discovered that M₁ is the best scavenger of OH, whereas M₂ most readily neutralizes both OCH₃ and OOH. The kinetic data obtained, particularly of ·OH, are similar to those established by Van Trang et al. for the reaction of stemofurans, the natural stilbenoid-type 2-phenylbenzofuran derivatives with well-known activities [51], against DPPH radical [40]. After all, the reaction rate constants of the studied compounds do indicate that all of the studied isobenzofurans are effective antioxidants, and thereby, further modifications in furan motif are able leading to the development of derivatives with desired safety profiles, allowing for the wider application.

4 Computational details

The computations were carried out using Gaussian16 (rev. C.01) and M06-2X/6-311 + G(d,p) [52–54] level of theory, the reliability of which in electronic, thermochemical and kinetic calculations has been evidenced for the radical-involving reactions produced by this functional in radical-involving reactions [55–58]. At each stage of studies, total spin has been confirmed not to differ significantly from the perfect one [59]; similarly, the number of imaginary frequencies was asserted to equal 0 for ground states, and exactly 1 for transition states.

To account for different position and conformation of the hydroxyl group originating from the environmental factors [60, 61], the initial structures at normal conditions were generated using conformational search tool implemented in Gabedit software [62] and the least energetical conformers were submitted for quantum-mechanical studies. Water (ε = 78.35) and pentyl ethanoate (ε = 4.73) solvents were chosen to mimic biologically relevant media in the framework of solvation model based on density (SMD) [63]. Furthermore, owing to the acidic character of aromatic hydroxyl groups, fitting parameters method [64] was used to establish most favourable deprotonation pathways in water, as well as their corresponding dissociation constants which were next utilized to assess molar fractions; only species with non-negligible populations (Nf > 0.1%) at pH = 7.4 were considered for the detailed investigations.

The electronic structure indices—electronegativity, global hardness and electrophilicity index—were approximated in relation to Koopman’s theorem [65, 66] which, although functional and basis set dependent, has been evidenced from the recent benchmark [56] to yield energies with error not greater than 0.5 eV from the experimental data.

The intrinsic reactivity indices, bond dissociation enthalpy (BDE) and ionization potential (IP), which correspond to the three main mechanisms of action presented by antioxidants: formal hydrogen transfer (f-HAT), sequential electron transfer–proton transfer (SETPT) and sequential proton loss–electron transfer (SPLPT), were obtained in an adiabatic manner for preliminary assessment of the antiradical activity of the isolated species. Thermochemical computations served to test the ability to scavenge free radicals, against OH, OCH₃ and OOH in f-HAT, SET and RAF mechanisms. Following kinetic studies were conducted in accordance with quantum mechanics-based test for overall radical scavenging activity (QM-ORSA) which has been shown to produce reliable results [45]: Marcus theory [67, 68] was used within it to establish the reaction barrier of a single electron transfer (∆G°SET, Eq. 3) from the reorganization enthalpy (λ, Eq. 4), computed as a difference between vertical and adiabatic ionization enthalpies.

\[
\Delta G_{\text{SET}}^\# = \frac{\lambda}{4} \left( 1 + \frac{\Delta G_{\text{SET}}^\circ}{\lambda} \right)^2 \]  

\[
\lambda \approx \Delta E_{\text{SET}} - \Delta G_{\text{SET}}^\circ \]  

Collins-Kimball [69] theory (k_{\text{app}}, Eq. 5), steady-state Smoluchowski rate constant for an irreversible bimolecular diffusion-controlled reaction (k_D, Eq. 6) [70] and Stokes–Einstein equation (D, Eq. 7 and Eq. 8) are used to account for diffusion-limited reactions.

\[
k_{\text{app}} = \frac{k_{\text{TST}}k_D}{k_{\text{TST}} + k_D} \]  

\[
k_D = 4\pi R_{\text{AB}} D_{\text{AB}} N_A \]  

\[
D_{\text{AB}} = D_A + D_B \]  

\[
D = \frac{k_B T}{6\pi \eta a} \]  

where R_{AB} is the reaction distance, N_A is the Avogadro constant, and D_{AB} = D_A + D_B is the sum of the mutual diffusion coefficients of the reactants A and B. Mutual diffusion coefficient, D, is calculated from the viscosity of the solvent, \( \eta \), (herein: \( \eta (\text{H}_2\text{O}) = 8.91 \times 10^{-4} \text{ Pa s} \); \( \eta (\text{pentylethanoate}) = 8.62 \times 10^{-4} \text{ Pa s} \) and the radius of the solute (a).

Thermal rate constants were computed using conventional transition state theory with the Eckart zero–curvature tunnelling correction (Eq. 9), which involves the Boltzmann average ratio of quantum and classical probabilities [71, 72]
\[ k_{\text{TST}} = \sigma k \frac{k_B T}{h} e^{-(\Delta G^r)/RT} \]  

(9)

where \( \sigma \) is the reaction path degeneracy, \( k \) is tunnelling correction calculated, \( k_B \) is the Boltzmann constant, \( h \) is the Planck constant, and \( \Delta G^r \) is the activation free energy.

The results were combined to establish total and overall rate constants, and branching ratios for individual reactions, with activation energies no greater than 10.0 kcal/mol—this is because, while the endergonic reaction may occur at a significant rate, the products would not be observed due to its reversibility.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00124-022-02922-5.

**Acknowledgements** The computational studies were carried out in Wroclaw Centre for Networking and Supercomputing, Grant No. 527.

**Author contributions** Conceptualization was contributed only by MS; Resources were contributed by MS and ZS; Supervision was contributed by MS; Formal analysis, investigation and methodology were contributed by MS; Resources were contributed by MS and ZS; Supervision was contributed by MS; Validation, visualization and writing were contributed by MS.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

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