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Original article

New isatin derivatives with antioxidant activity

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ABSTRACT

The reaction between isatin and 2,5-dimethoxyaniline is described. The main product was identified as 3,3-bis(4-amino-2,5-dimethoxyphenyl)-1,3-dihydroindol-2-one. The antioxidant activity of the compounds isolated was evaluated with two methods. Three published antitumor *E*-3-(2-chloro-3-indolylmethylene)1,3-dihydroindol-2-ones entered the same tests to search whether they are endowed with antioxidant activity too. 3,3-Bis(4-amino-2,5-dimethoxyphenyl)-1,3-dihydroindol-2-one and the three antitumor agents showed a good chemical antioxidant activity.

1. Introduction

Most of our research is devoted to the synthesis of new antitumor agents and some of them have been prepared by means of the Knoevenagel reaction between an aldehyde and an oxindole. A recent example of this research is a paper describing antitumor activity and effect on cell cycle of some substituted *E*-3-(2-chloro-3-indolylmethylene)1,3-dihydroindol-2-ones **3** (Scheme 1) prepared by means of the above mentioned reaction with the aldehyde **1** and the oxindole **2** as the starting compounds [1].

In other papers we considered different aldehydes [2,3] and we also planned the synthesis of compounds bearing bridges different from the usual methine group for the connection of the two moieties. The mechanism of action of these compounds has not been completely understood but we believe they act by means of multiple mechanisms [3].

2. Chemistry

To obtain a deeper insight into structure–activity relationships of this class of compounds, we designed the replacement of the methine by a nitrogen. We thought that the reaction between isatin **4** (Scheme 2) and an aniline bearing selected substituents, could be the right route since the reaction between isatin and *p*-anisidine **5** is well documented in the literature under different experimental conditions and leads always to the expected imine **6** [4–9]. This reaction gave always the related imine even when employed with different methoxy anilines such as 2-methoxy [10], 3-methoxy [11] and 2,4-dimethoxyaniline [12] but when we attempted the reaction of isatin with 2,5-dimethoxyaniline **7** to obtain the imine **8**, we were able to isolate only one compound whose spectroscopic data were not in agreement with the structure of **8** and was later identified as 3,3-bis(4-amino-2,5-dimethoxyphenyl)-1,3-dihydroindol-2-one **9**. Under the same experimental conditions, when isatin was replaced by N-acetylisatin **10**, the reaction proceeded with nucleophilic attack at the C-2 carbonyl leading to heterocyclic ring cleavage and formation of 2-(2-acetamidophenyl)-N-(2,5-dimethoxyphenyl)-2-oxoacetamide **11** in agreement with previous reports [13].

For the structure determination of compound **9** we planned to use X-ray crystallography since any crystal was apparently shiny but unfortunately it was not a single crystal but an agglomerate of microcrystals useless for this kind of analysis. After several crystallization attempts with different solvents we decided to leave this approach.

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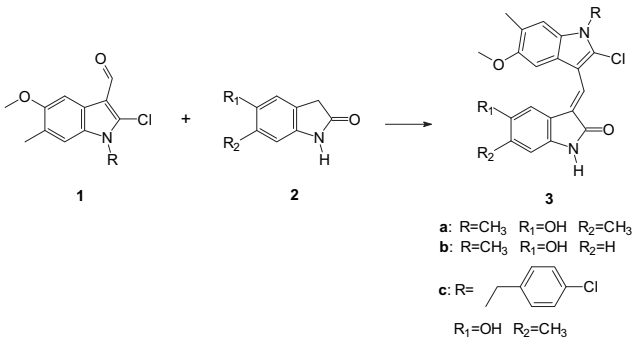


Scheme 1. Substituted *E*-3-(2-chloro-3-indolylmethylene)1,3-dihydroindol-2-ones.

The mass spectrum of compound **9** ($m/z = 435$) indicates that one molecule of isatine reacted with two molecules of 2,5-dimethoxyaniline **7** by loss of two protons and one oxygen.

The NMR data in d_6-DMSO (298 K) and $CDCl_3$ (298 and 263 K) show that one aromatic proton is missing from each of the two 2,5-dimethoxyaniline moieties and an aliphatic quaternary carbon at 59.8 ppm replaces the carbonyl at C_3 of the parent isatin, thus forming a diaryloxindol similar to those reported in ref. 14.

A rough molecular mechanics calculation (Chemsketch 12, ACD, Inc., Toronto, CA) shows that the two aryls are tilted with respect to each other, thus making the molecule chiral and the atoms of each 2,5-dimethoxyaniline moiety diastereotopic. The two aryls undergo a dynamic phenomenon (most probably a rotation about the C_1' – C3 and C_1'' – C3 bonds) that broadens the proton and carbon signals of the two 2,5-dimethoxyaniline moieties. The dynamic phenomenon stops (on the NMR time scale) at 263 K.

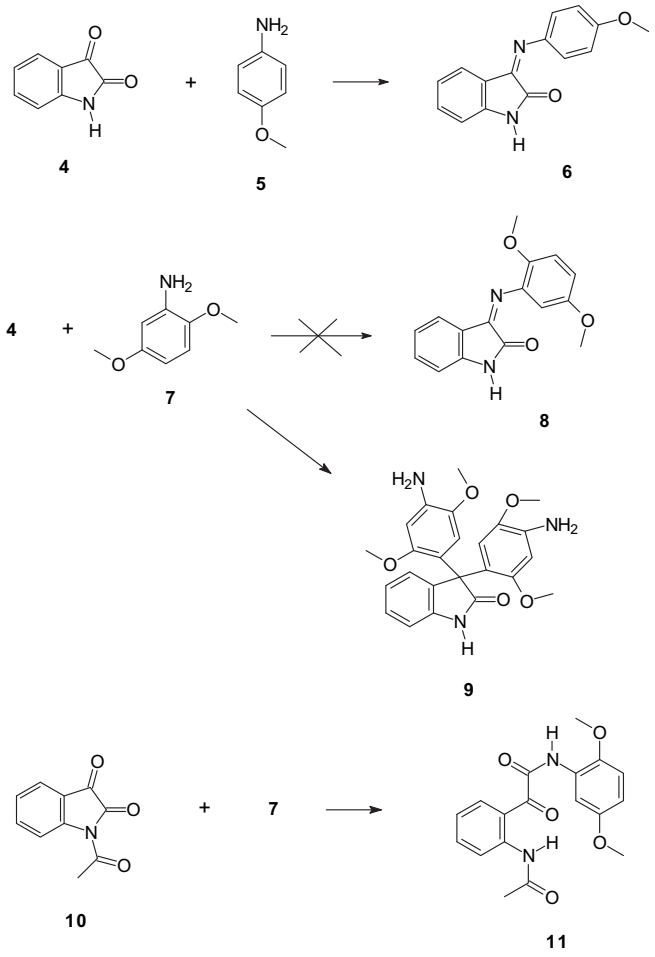
The proposed structure of **9** (where each 2,5-dimethoxyaniline moiety is bonded to the C_3 of the aryloxindol *via* the former C_4 of 2,5-dimethoxyaniline) is confirmed at 263 K by strong HMBC connections between both H_6', H_6'' and C_3 and by the presence of ROESY cross peaks only between each of the 2,5-dimethoxyaniline aromatic protons and a different methoxy group. This rules out the possibility of the 2,5-dimethoxyaniline moieties being bonded to C_3 of the aryloxindol *via* the former C_3 of 2,5-dimethoxyaniline (one methoxy would give ROESY cross peaks with two aromatic protons, while the other would give none) or *via* the former C_6 (each aromatic proton would give ROESY cross peaks with the nearby proton and methoxy group): see Experimental section and Supplementary data.

From a literature survey we found that, notwithstanding the numerous aforementioned citations of the reaction between isatin and methoxy anilines, no mention was reported about the reaction between isatin and 2,5-dimethoxyaniline. Nevertheless it has been reported that isatin may give Friedel–Crafts adducts [13–16]. We believe that the different behavior of 2,5-dimethoxyaniline **7** (compared to other methoxy anilines) is due to the combined electronic effect of the amino group and the methoxy groups which activate the 4-position.

Therefore the reaction proceeds with nucleophilic attack at the C-3 carbonyl of isatin leading to compound **9** according to Scheme S1. A similar mechanism could explain the reaction products of isatin with alifatic secondary diamines [17].

3. Antioxidant activity

As we wrote in the introduction, compounds **3a–c** showed antitumor activity [1] whereas the compounds resulting from the above described reactions did not show any activity when subjected to the standard antitumor tests performed by the National Cancer Institute (NCI, Bethesda, MD). Both these groups of compounds were evaluated for their possible antioxidant activity.



Scheme 2. Synthesis of compounds **9** and **11**.

In recent years many papers reported the potential beneficial effects of different free-radical scavenger antioxidant polyphenols as preventive agents against human neoplastic diseases at several sites including stomach, duodenum, colon, liver, lung, breast, ovary or skin [18]. A review of several papers reached the conclusion that the proofs of the claimed beneficial effects on humans are inconclusive [19]. However, a very recent review on the impact of antioxidant supplementation on chemotherapy suggests that the concurrent use of antioxidants and chemotherapeutic drugs could diminish the dose-limiting toxicity of these latter [20]. The chemical antioxidant activity of compounds under test (**3a–c**, **9** and **11**) was assessed with two methods: the Briggs–Rauscher (BR) oscillating reaction method that works in acidic conditions [21] and the Trolox Equivalent Antioxidant Activity (TEAC) assay working at pH = 7.4 [22].

4. Results and discussion

Collected results of antioxidant activity with the BR method at acidic pH (ca. 2), and with the TEAC assay at pH = 7.4 are reported in Table 1.

In view of a possible development of these new compounds as chemopreventive drugs in food integrators, it is quite important to test antioxidant activity at acidic pH value near to that of gastric fluids. In fact there are several evidences that stomach acts as

Table 1
Relative antioxidant activity of the examined compounds.

Compound	RAC[a] (μM equivalents resorcinol)	TEAC[b] (mM equivalents Trolox)
3a	2.83 ± 0.05	0.91 ± 0.04
3b	2.74 ± 0.06	0.82 ± 0.07
3c	Negligible	0.97 ± 0.05
9	1.28 ± 0.04	1.40 ± 0.09
11	Negligible	Negligible

[a] RAC (Relative Antioxidant Capacity, standard resorcinol) values are the average of at least three measurements at different concentrations ± SE.
[b] TEAC (Trolox Equivalent Antioxidant Capacity) is given as the ratio of the slopes of the straight lines Abs. vs. conc. of the sample and the standard respectively ±SE. (See Supplementary data).

a bioreactor in which many drugs can interact [23,24]; moreover recent *in vivo* studies demonstrated that some polyphenols are promptly absorbed in the stomach [25,26]. TEAC measurements were conducted at pH 7.4, the physiological pH of the blood.

Inspection of data in Table 1 revealed that the relative antioxidant activity in acidic conditions of compounds **3a**, **3b** is quite high, similar to that found for (−)catechin (2.2) and (−)epicatechin (2.6) from green tea [27] that are among the strongest antioxidants. On the contrary, compound **3c** showed negligible activity under these conditions, probably because it interferes with some of the components of the BR mixture before the phenolic OH reacts with the generated HOO• radicals [28] (see also Supplementary data).

The antioxidant capacity values at pH = 7.4 of compounds **3a** and **3b** are quite good, similar to that of α-tocopherol (0.97) but lower than those of other common antioxidants, as quercetin (3.1), cyanidin (2.48) or β-carotene (2.57) [22]. Both the RAC and TEAC values of compound **3a** are a slight but significantly (*t*-Student test, $p < 0.05$) higher than those of compound **3b**. This can be interpreted in terms of the BDE (Bond Dissociation Enthalpy) theory by Wright et al. [29], and with the proposed empirical additivity rules to calculate the BDE of phenolic OH groups and ΔBDE with respect to phenol ($\Delta BDE = BDE_{comp.} - BDE_{PhOH}$) [29]. From the data reported in ref. 29, it can be seen that the effect of a CH_3 group in *ortho*- position with respect to a phenolic group in a benzene ring at a parity of other substituents, decreases the bond enthalpy of the OH group of 8.4 kJ mol^{-1} indicating that this group acts as a better radical scavenger than that of the same compound with an H atom in the *ortho*- position.

Positive controls are the substances used as standard: resorcinol for the BR method and Trolox for the TEAC assay. Compound **11** showed negligible activity either at pH ca. 2 and 7.4. Surprisingly, compound **9** presents a good relative antioxidant activity with both methods even if it contains four OMe groups that are found to have very poor free radicals scavenger power at least in flavonoid structures [30,31]. No doubt about this activity since the inhibitory phase in the BR method is similar to that produced by OH groups and in the TEAC assay the only species with which OMe groups can react is the radical cation ABTS•$^+$ (see Supplementary data). A mechanistic interpretation of this will be given in the next section.

5. Mechanistic interpretation of inhibition in the Briggs–Rauscher method

In 2002, Furrow et al. [32] reported a 13-step new mechanism (named FCA model) for the BR reaction that takes into account the important role played by HOO• radicals in its oscillatory behavior. To simulate the perturbations by a free-radical scavenger on the oscillations, the following steps 1 and 2 were added to FCA model, where ArOH indicates a generic compounds containing an OH phenolic group, e.g. compound **3a**.

$$\text{IN ArOH} + \text{HOO}\bullet \rightarrow \text{ArO}\bullet + H_2O_2 \quad (1)$$

$$\text{DEG ArOH} \rightarrow \text{Products} \quad (2)$$

The step IN represents the typical way of subtraction of a radical by an antioxidant: an H atom transfer from a phenolic –OH group to the radical [33].

The formed aroxyl radical ArO• is quite stable and can react with another radical or with oxygen to give diamagnetic stable compounds. In the simulations ArO• was considered an end product. The 1st order step DEG represents the possible parallel degradation of the inhibitor to unspecified products. The degradation may be due to the oxidation (by acidic iodate) or iodination (by I_2 or HOI) of ArOH. The kinetics of these reactions was recently studied in detail on some diphenols [28]: the results showed that for simulation purposes they can be summarized by step DEG. The kinetic constants of the FCA step were kept fixed to those reported in ref. 28, while k_{IN} and k_{DEG} were allowed to vary for the best fit to

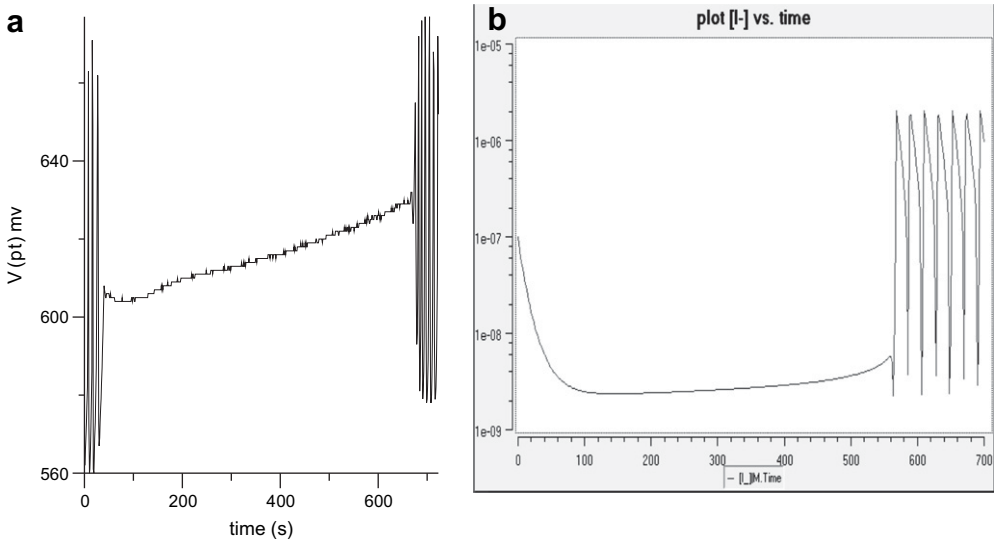


Fig. 1. (a) Experimental behavior of V(I^-)/mV vs. time/s for an inhibited BR mixture (initial conditions: [MA] = 0.050 M, [Mn^{2+}] = 0.0067 M, [IO_3^-] = 0.0667 M, [$HClO_4$] = 0.0266 M, [H_2O_2] = 1.2 M, 1.0 mL of **3a** solution (conc. = 1.01 μM in mixture) added after the third oscillation). (b) Simulated behavior of [I^-] vs. time for a mixture of the same initial composition. The satisfactory agreement between the experimental (626 s) and simulated inhibition time (565 s) can be noted.

Table 2
Experimental and calculated inhibition times (*s*) for compound **3a**.

Conc. (μM)	t_{inhib} (exptl.)	t_{inhib} (calcd.)
5.06	2917	2820
3.54	2073	2268
2.02	1106	1440
1.01	629	565

experimental behaviors. Simulations were performed by using the COPASI numerical integration program [34]. Experimental and simulated behaviors of V(I^-) and [I^-] vs. time for a typical BR mixture perturbed by compound **3a** are reported in Fig. 1(a) and (b) respectively. The satisfactory agreement between the experimental and calculated inhibition times can be noted, although IN and particularly DEG steps represent overall processes for which individual steps and rate constants have not be determined.

The same agreement was obtained with all the explored concentrations of **3a**, Table 2, finding the following unique values for the rate constants: $k_{IN} = 1.6 \times 10^8\ M^{-1}\ s^{-1}$, $k_{DEG} = 6.0 \times 10^{-4}\ s^{-1}$.

The obtained values of k_{IN} and k_{DEG} for the perturbed BR reaction by **3a** are in line with those obtained for ten substituted diphenols [28], ranging from 10^5 to $10^8\ M^{-1}\ s^{-1}$, and from 0 to $10^{-5}\ s^{-1}$. It is to be noted that for the reaction between α-tocopherol and peroxyl radicals (ROO•) a rate constant of about $10^6\ M^{-1}\ s^{-1}$, was experimentally found [33].

To simulate the inhibitory effects by compound **9**, the step IN was modified as follows:

$$\mathrm{IN}\ \mathrm{Ar(OCH_3)_3OCH_3} + \mathrm{HOO^\bullet} \rightarrow \mathrm{Ar(OCH_3)_3O^\bullet} + \mathrm{CH_3OOH} \qquad (1')$$

that hypothesizes a CH_3 group transfer from one OCH_3 group to the hydroperoxyl radical with formation of the methyl hydroperoxide CH_3OOH. This compound was first synthesized in stable form by Rieche and Hitz [35]. In acidic solution (pH = 2) and in the presence of metal ions and oxygen, the corresponding aldehyde is finally formed.

The DEG step was left unchanged with the same meaning as illustrated above.

Typical experimental and simulated behaviors of V(I^-) and [I^-] vs. time for a typical BR mixture perturbed by **9** are reported in Fig. 2(a) and (b) respectively.

The very good agreement between the experimental and calculated inhibition times can be noted, although, as stated above, IN and particularly DEG steps represent overall processes for which individual steps and rate constants have not be determined.

The same agreement was obtained with all the explored concentrations of **9**, Table 3, finding the following unique values for the rate constants: $k_{IN} = 1.7 \times 10^8\ M^{-1}\ s^{-1}$, $k_{DEG} = 1.8 \times 10^{-3}\ s^{-1}$.

These mechanistic calculations are a proof of the possibility of the reaction (1′).

Even though it is not permissible to compare rate constants from different-order rate equations, k_{IN}s are several orders of magnitude higher than k_{DEG}s, so we can conclude that in any case the scavenging action by the present compounds with phenolic OH or OMe groups against HOO• radicals is the source of the observed perturbations on the oscillations of the Briggs–Rauscher reaction.

6. Conclusion

Compounds **3a–c** and **9** showed a good chemical antioxidant activity according to the design of these molecules that include a phenolic OH or OCH_3 group(s) in their structures. The antioxidative mechanism of compound **9** was not directly elucidated. However perturbations of the Briggs–Rauscher oscillating system by this compound together with the decolorization of the $ABTS^{\bullet+}$ radical cation, strongly suggest a mechanism similar to the action of polyphenols. From the bond enthalpies, the O–C(H_3) bond (351 kJ mol^{-1}) seemed to us the best candidate to release a $^\bullet CH_3$ radical by bond homolytic breaking. This hypothesis was confirmed from mechanistic calculations, thus supporting the plausibility of the proposed mechanism.

To confirm whether this action is also explicated in cultured cells, further investigation is needed to test the antioxidant power on these models. In particular, since compounds **3a–b** were selected for further evaluation of their antitumor activity by the Developmental Therapeutics Program (DTP) at the NCI, it will be interesting to consider these results when all the antitumor tests will be completed.

7. Experimental section

7.1. Materials and methods. (for the antioxidant activity see Supplementary data)

The melting points are uncorrected. Elemental analyses were performed with a Fisons Carlo Erba Instrument EA1108 and compounds used for tests were at least 95% pure. Bakerflex plates (silica gel IB2-F) were used for TLC: the eluent was chloroform/

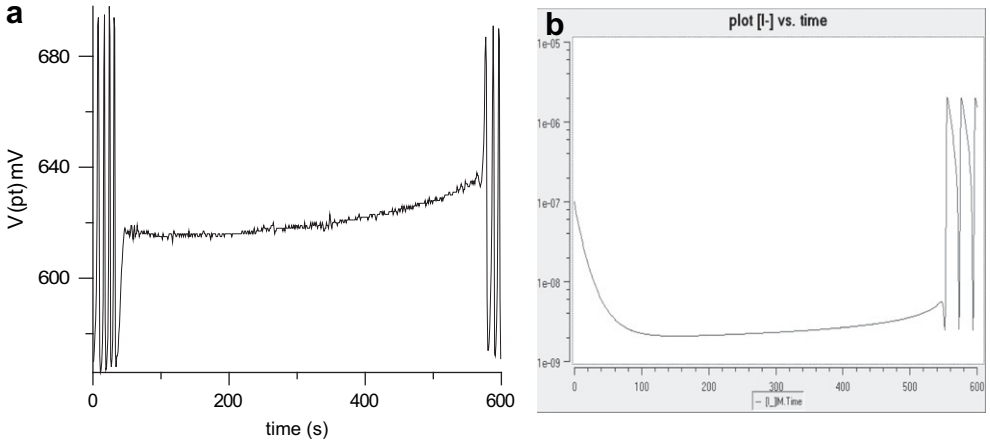


Fig. 2. (a) Experimental behavior of V(I^-)/mV vs. time/s for an inhibited BR mixture (initial conditions: [MA] = 0.050 M, [Mn^{2+}] = 0.0067 M, [IO_3^-] = 0.0667 M, [$HClO_4$] = 0.0266 M, [H_2O_2] = 1.2 M, 1.0 mL of **9** solution (conc. = 1.48 μM in mixture) added after the third oscillation). (b) Simulated behavior of [I^-] vs. time for a mixture of the same initial composition. The very good agreement between the experimental (553 s) and experimental inhibition time (552 s) can be noted.

Table 3
Experimental and calculated inhibition times (*s*) for compound **9**.

Conc. (μM)	t_{inhib} (exptl.)	t_{inhib} (calcd.)
3.71	1066	1051
3.34	967	993
2.97	865	928
2.25	779	776
1.48	553	552

methanol in various proportions. Kieselgel 60 was used for column chromatography; the eluent was a mixture of chloroform/methanol 95/5. The IR spectra were recorded in nujol on a Nicolet Avatar 320 E.S.P.; ν_{max} is expressed in cm^{-1}. The NMR spectra were acquired with a Varian Mercury-plus spectrometer using library sequences; the chemical shift (referenced to solvent signal) is expressed in δ (ppm) and *J* in Hz. MS were recorded on a Thermo Finnigan Mat95XP apparatus.

7.1.1. Synthesis of 3,3-bis(4-amino-2,5-dimethoxyphenyl)-1,3-dihydroindol-2-one ***9***

Isatin (3 mmol) was dissolved in methanol (20 mL) and treated with 2,5-dimethoxyaniline (3 mmol). The reaction mixture was refluxed for 18 h and concentrated under reduced pressure: the resulting solid was purified with column chromatography which gave 15% of unreacted isatin and 70% of compound **9**. Crystallized from methanol, m.p. 235–238 °C dec..

IR: 3400–3260, 1700, 1210, 1040, 740. ^{1}H NMR (400 MHz, $CDCl_3$, 263 K): 3.31 (3H, s, OCH_3 bonded to C_2'), 3.58 (3H, s, OCH_3 bonded to C_2''), 3.57 (3H, s, OCH_3 bonded to C_5'), 3.70 (3H, s, OCH_3 bonded to C_5'' + 4H, broad s, NH_2), 6.31 (1H, s, H_3'), 6.34 (1H, s, H_3''), 6.40 (1H, s, H_6'), 6.86 (1H, s, H_6''), 6.82 (1H, d, H_7, $J = 7.8$), 6.88 (1H, td, H_5, $J = 6.9$, $J = 1.3$), 7.09 (1H, td, H_6, $J = 7.6$, $J = 1.2$), 7.30 (1H, d, H_4, $J = 7.6$), 8.25 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$, 263 K): 55.9 (OCH_3 bonded to C_2''), 56.0 (OCH_3 bonded to C_5'), 56.4 (OCH_3 bonded to C_5''), 56.8 (OCH_3 bonded to C_2'), 59.8 (C_3), 100.7 ($C_3''H$), 101.8 ($C_3'H$), 109.0 (C_7H), 112.7 ($C_6''H$), 113.9 ($C_6'H$), 115.4 (C_1''), 116.5 (C_1'), 122.2 (C_5H), 125.7 (C_4H), 127.3 (C_6H), 136.4 (C_{3a}), 136.5 (C_4' + C_4''), 140.3 (C_5'), 140.7 (C_5''), 141.2 (C_{7a}), 152.0 (C_2''), 152.2 (C_2'), 181.6 (C_2). MS (70 eV): *m*/*z* (%): 435 (100) [M^+], 428 (7), 484 (8), 376 (53), 346 (18), 284 (6), 269 (6), 255 (6), 218 (10). Anal. for $C_{24}H_{25}N_3O_5$ (435.47) calcd (%) C 66.19, H 5.79, N 9.65; found (%) C 66.24, H 5.70, N 9.60.

7.1.2. Synthesis of 2-(2-acetamidophenyl)-N-(2,5-dimethoxyphenyl)-2-oxoacetamide ***11***

Under the experimental conditions described above, by replacing isatin with N-acetyl-isatin, compound **11** was obtained with a yield of 40%. Crystallized from methanol, m.p. 154–155 °C.

IR: 3360–3240, 1680, 1660, 1210, 870. ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C): 2.02 (3H, s, CH_3), 3.72 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.73 (1H, dd, ar, $J = 9$, $J = 3$), 7.06 (1H, d, ar, $J = 9$), 7.27 (1H, m, ar), 7.65 (3H, m, ar), 7.86 (1H, d, ar, $J = 3$), 9.69 (1H, s, NH), 10.59 (1H, s, NH). ^{13}C NMR (300 MHz, [D_6]DMSO, 25 °C): 23.79 (CH_3), 55.52 (CH_3), 56.46 (CH_3), 106.71 (CH), 108.91 (CH), 112.00 (CH), 121.46 (CH), 123.72 (CH), 124.69 (C), 126.86 (C), 130.95 (CH), 133.51 (CH), 137.38 (C), 143.24 (C), 153.18 (C), 160.56 (C), 169.04 (C), 188.85 (C). MS (70 eV): *m*/*z* (%): 342 (16) [M^+], 189 (8), 179 (5), 162 (100), 153 (37), 146 (48), 138 (65), 128 (27), 118 (18), 98 (20), 65 (11); Anal. for $C_{18}H_{18}N_2O_5$ (342.35) calcd (%) C 63.15, H 5.30, N 8.18; found (%) C 63.00, H 5.43, N 8.24.

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Appendix. Supplementary data

Scheme S1 (Mechanism of reaction for the formation of compound **9**). NMR spectra of compound **9**. Experimental section and references related to the antioxidant activity. This material can be found in the online version at doi:10.1016/j.ejmech.2009.12.035.

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