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Preliminary communication

One-pot synthesis and radical scavenging activity of novel polyhydroxylated 3-arylcoumarins

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ABSTRACT

An unexpected domino rearrangement brought about the development of a novel one-pot procedure for synthesis of coumarins. This protocol allowed the gram-scale synthesis of a variety of polyhydroxylated derivatives **3a**–**p**, from readily available starting materials at a low cost. Based on two proven intermediates, a probable mechanism consisting of boron tribromide induced demethylation/lactone ring opening/elimination/isomerization/lactone ring closure reaction sequence of *in situ* formed 3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids was deduced. Compared to the common methods, used for the synthesis of coumarins, the proposed herein possesses great advantages, such as mild conditions, good yields for short reaction time, simple work-up procedure and easy isolation of the final products. The structure of the newly synthesized compounds **3a**–**p** was established by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS and HRMS) and their radical scavenging activity was evaluated *in vitro* against 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH$^\bullet$). The results obtained show that compounds **3g**–**p** posses higher radical scavenging activity ($3.16 \leq SC_{50}$ [μM] ≤ 6.82) than well-known antioxidants such as trolox, protocatechuic acid, caffeic acid and gallic acid (SC_{50} [μM] = 9.34, 8.83, 9.48, 5.33, respectively), which is a precondition for promising antioxidant activity of these compounds to be expected.

1. Introduction

Coumarins are a large class of oxygenated heterocyclic secondary metabolites, that are biosynthesized by plants and fruits *de novo* [1]. They serve as phytoalexins which are directly formed as a defence response to stress (drought and cold), wound, viral infection or invasion by bacterial or fungal pathogens [2,3]. Natural coumarins display a wide range of biological activities [4–7] such as anti-inflammatory, anticoagulant, anticancer, vasorelaxant, and antiviral, to name just a few. In addition, several synthetic coumarin derivatives, particularly 3-aryl substituted ones (see Fig. 1), proved to be efficient antioxidants [8–11], that inhibit variety of enzymes [12–20], possess anti-HIV [21], anticancer [22–24] and vasorelaxant activities [25], and are antagonists of certain receptors [26]. Thus, due to their widespread pharmacological properties, coumarins occupy an important place in the realm of medicinal chemistry. Despite their remarkable medical benefits, it is noteworthy that the coumarins bioavailability is dependent to a large extent on the environmental conditions and seasonal changes, and thus their large scale production from natural sources is unreliable. To overcome this, various synthetic approaches for the synthesis of coumarins have been developed [27–49]. One of the main strategies is based on condensation–cyclization-type transformations employing the well-known Perkin, Pechmann or Knoevenagel reactions [27–35] as a key step for the coumarin backbone formation. An alternative strategy consists in the direct 3-arylation of the coumarin scaffold by metal cross-coupling reactions [36–42] leading to diversely substituted coumarin derivatives. All these methods, however, possess some drawbacks that hinder their benefits from an applied standpoint. In particular, the requirement of strong acids, high temperatures and prolonged reaction times in the classical condensation methods and the expensive, toxic, and sensitive to moisture catalysts in the case of metal cross-coupling reactions. Furthermore, these methods are of limited applicability for the direct synthesis of hydroxylated coumarins, and thus, in order polyhydroxylated derivatives to be synthesized, one should follow multistep approach including sequential protection, condensation, and deprotection steps. This sequence is necessary due to the extreme susceptibility of the hydroxyl function towards oxidation and polymerization, but results in a low overall product yields. Therefore, the need for improved methodologies for the synthesis of coumarin derivatives can be put forward [43–51]. In

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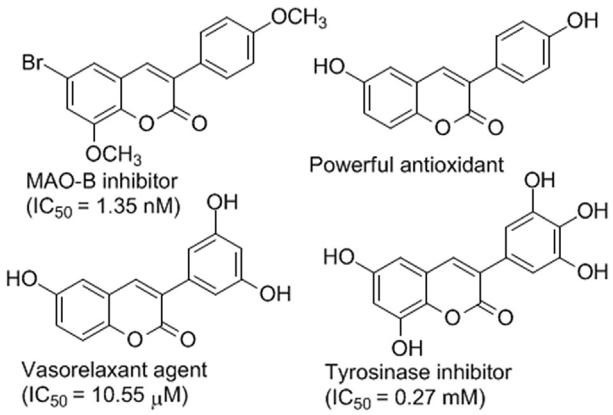


Fig. 1. Structure of some biologically active 3-arylcoumarins.

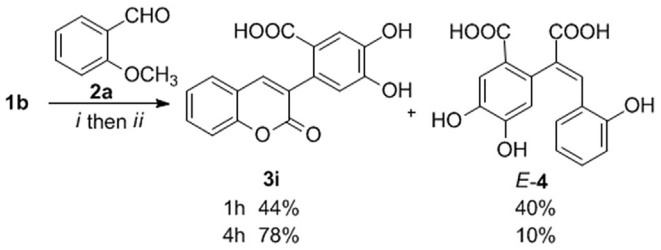
this context, in continuation of an ongoing in our laboratory project on anhydride-based syntheses of biologically active compounds [52–59], herein we report the synthesis of a series of 3-arylcoumarins by means of a novel one-pot procedure, including initial Perkin-like reaction between commercially available homophthalic anhydrides and 2-methoxybenzaldehydes, followed by treatment with BBr_3. This straightforward procedure allows the room-temperature gram-scale production of polyhydroxylated coumarins in good yields for short reaction times, and provides an easy isolation of the final products. Furthermore, in order for the influence of the number and position of the hydroxyl groups in the 3-arylcoumarin scaffold on the radical scavenging activity of the synthesized compounds to be established, an *in vitro* differentiating screening against 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH•) was performed.

2. Results and discussion

2.1. Chemistry

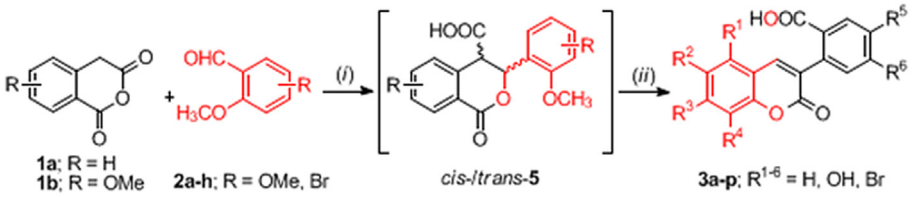
In a recent article of ours [52], we have demonstrated that diastereomeric mixture of methoxylated *cis*- and *trans*-3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids undergoes simultaneous demethylation and lactone-ring opening reaction in presence of BBr_3. This finding resulted in the development of a novel one-pot procedure for the synthesis of polyhydroxylated *cis*-restricted stilbenes possessing a triple biological action as potent antioxidants, antifungal agents and tyrosinase inhibitors. The proposed method consists of sequential reaction between homophthalic anhydrides and aromatic aldehydes to produce diastereomeric mixture of the corresponding 3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids, which, after treatment with BBr_3, give the target polyhydroxylated stilbenes in short reaction times (10–60 min) [52]. In continuation of this study, in order a more complete series of compounds to be synthesized, we were interested to perform reactions between homophthalic anhydrides and a series of 2-methoxybenzaldehydes.

Surprisingly, when 3,4-dimethoxyhomophthalic anhydride (**1b**) and 2-methoxybenzaldehyde (**2a**) were subjected to the reaction conditions depicted in Scheme 1, a by-product, whose structure was latter established as the coumarin **3i**, was isolated in quantity comparable with that of the desired at this stage stilbene *E*-**4a**. This result intrigued us, since, to the best of our knowledge, the synthesis of coumarins according such a protocol is not known. Moreover, a short retrospection of the literature showed that 3-



Scheme 1. Initial synthesis of coumarins. *Reagents and conditions*: (*i*) DMAP/CH_2Cl_2, 10 min, rt, then (*ii*) BBr_3/CH_2Cl_2, rt, 1 or 4 h.

arylcoumarins are normally synthesized under harsh conditions, and that the common methods used for the coumarin scaffold formation are of limited applicability for the direct synthesis of hydroxylated derivatives. So, the above transformation can be considered as attractive for further investigation. We were further delighted to find that the yield of **3i** increases with the time, reaching its maximum in 4 h, and then staying intact even after 12 h. Thus **3i** was obtained in nearly twofold higher yield (78%) compared to the initial conditions (44%). It is noteworthy, that **3i** was isolated as a crystalline product in a high purity, simply by filtration of the worked up reaction mixture, and that some quantities of *E*-**4a** were always present in the filtrate. This shows, on the one hand, that *E*-**4a** could be considered as an intermediate for the synthesis of **3i**, and on the other, that equilibrium between **3i** and *E*-**4a**, in favour of the target coumarin could be assumed. To check this, an isolated *E*-**4a** was reacted at the same conditions and the reaction outcome was monitored by means of TLC. As a result, the expected transformation of *E*-**4a** into **3i** was observed, thus proving the participation of *E*-**4a** as an intermediate in the reaction scheme to **3i** and suggesting some hints regarding the probable reaction mechanism (see below). In addition, when *E*-**4a** was put to crystallize in ethyl acetate, a spontaneous reaction occurs and precipitates of **3i** appear with the time, showing that the lactonization is the thermodynamically favoured process, which proceeds spontaneously to give the more stable product **3i**. In contrary, when **3i** was put under the reaction conditions, no formation of the stilbene *E*-**4a** was observed, thus rejecting the hypothesis for the existing equilibrium between both compounds. The above reasoning, however, suggests the promising potential of the approach under study for the facile synthesis of hydroxylated coumarins in a one-pot manner, from commercially available reagents. Considering this as a great advantage, we were further interested to check the applicability of our methodology by reacting two homophthalic anhydrides with a series of 2-methoxybenzaldehydes. The reaction scheme and conditions are depicted in Scheme 2, and yields and products substitution pattern are given in Table 1. In brief, the obtained by a reaction of the corresponding anhydrides **1a**,**b** and aldehydes **2a**–**h** in presence of DMAP/CH_2Cl_2 diastereomeric mixtures of *cis*- and *trans*-**5** [52–54,59] were further successfully converted without isolation into **3a**–**p** by direct addition of BBr_3/CH_2Cl_2 solution at room temperature. After 4 h, the reaction was terminated by pouring over ice, stirred for additional 30 min for hydrolysis of the boron esters formed, and the target coumarins **3a**–**p** were then isolated simply by filtration. It is noteworthy that the obtained in this way compounds do not need further chromatographic purification, which is a necessary step for isolation of other polyhydroxylated derivatives [12,16,25]. Furthermore, as mentioned above, additional quantities of **3** could be obtained by slow precipitation of the corresponding filtrates, mainly containing stilbenes of type **4**. The structures of **3a**–**p** were elucidated by means of spectral methods. In case of ^1H NMR, ^{13}C NMR and IR methods, the spectra were taken for the



Scheme 2. One-pot synthesis of polyhydroxylated coumarins. *Reagents and conditions*: (*i*) DMAP/CH_2Cl_2, 10–15 min, rt, then (*ii*) BBr_3/CH_2Cl_2, rt, 4 h.

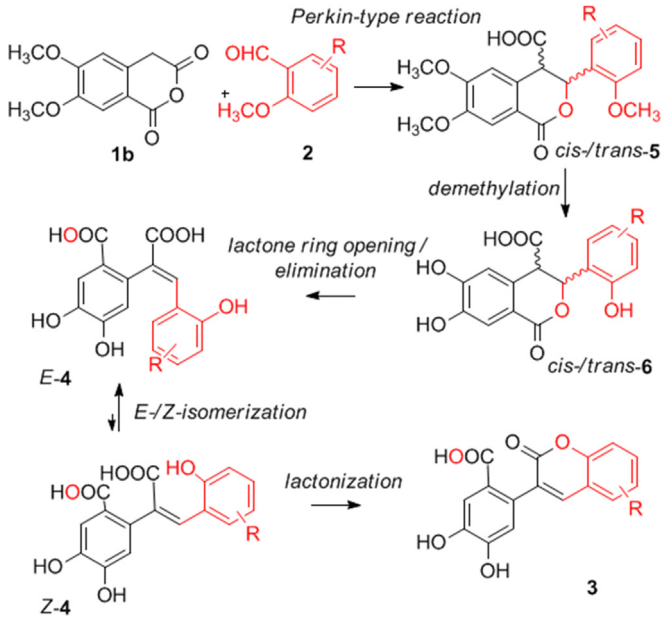
synthesized compounds, while their mass spectra (both MS and HRMS) were obtained after derivatization with diazomethane ethereal solution prior to analysis. However, the data obtained is in agreement with that previously reported for similar compounds [60,61], thus allowing us to assign unequivocally their structures (*cf.* Supporting information). Summarizing, if one follows the one-pot procedure under consideration, polyhydroxylated 3-arylcoumarins are readily available from commercial starting materials in less than 5 h. Compared to the common methods, used for synthesis of coumarins, our method possesses advantages, such as mild conditions, good yields in short reaction time, simple work-up procedure and easy final product isolation. Furthermore, the synthesized herein coumarins bear a carboxylic substituent in their structure, which can be considered as a precondition for increased water solubility of these compounds. On the other hand, it provides the possibility for further modifications to other functional groups, thus broadening the scope of the proposed method.

Let us discuss the mechanistic aspects of the current approach. Considering the particular structure of both starting and target compounds, we studied reaction between 6,7-dimethoxyhomophthalic anhydride (**1b**) and 2,3-dimethoxybenzaldehyde (**2b**) in more details. This reaction was selected because the performed shortly after the BBr_3 addition TLC analysis showed presence of additional compounds in the reaction mixture, which disappear with the time. The latter suggests that they could be considered as intermediates in the reaction scheme. Thus, after flash chromatography of the worked up reaction mixture, we were able to isolate two other compounds beside the coumarin **3l**. The structure of the unknowns was elucidated by means of NMR analysis as *E*-**4b** and mixture of *cis*-/*trans*-**6a** (*cf.* Supporting information). To prove their participation as intermediates, *E*-**4b** and **6a** were further subjected independently to the reaction conditions and the reaction outcome was monitored by means of TLC. As a result, the expected transformation of both compounds into **3l** was observed. It was monitored that *E*-**4b** undergoes direct transformation to **3l**, whereas in case of **6a**, simultaneous formation of both **3l** and *E*-**4b** was detected. It is noteworthy, that in the former case *E*-**4b** also disappeared with the time, which suggests **6a** as an intermediate towards its formation. Consequently, taking into account the above reasoning, and based on previously described by us results [52,53,59], a probable reaction mechanism, whose second part mimics the coumarin biosynthesis [3,62,63] could be proposed (Scheme 3). In brief, in the first part, homophthalic anhydride reacts in a Perkin-like reaction with an aldehyde to give in 10 min a mixture of *cis*- and *trans*-3-aryl substituted 3,4-dihydroisocoumarin-4-carboxylic acids **5** [52,53,59]. Demethylation of **5** in the next step can be considered as a beginning of the second part, which starts a domino process affording the target coumarins **3**. This part consists of four sequential steps, including lactone ring opening, elimination, isomerization and lactone ring closure reactions. In the first step, as was discussed above, the demethylated intermediate **6** undergoes concomitant lactone ring opening and elimination reaction to produce *E*-**4**. Such a reaction was also documented in a recent study of ours [52], where we have shown, that the rate of formation of *E*-**4** from **5** depends on the number of methoxyl groups that have to be demethylated, and that the highly substituted representative (5 groups) reacts quantitatively in 1 h. It is noteworthy that the

Table 1
Yields, substitution patterns, number of hydroxyl groups and DPPH$^{\bullet}$ scavenging activity (SC_{50}) of compounds **3a**–**p** and standard antioxidants.

Compd.	Yield[a] [%]	R^1	R^2	R^3	R^4	R^5	R^6	OH groups (total)	DPPH$^{\bullet}$ EC_{50} [μM][b]
3a	72	H	H	H	H	H	H	0	na[c]
3b	49	H	H	H	OH	H	H	1	na[c]
3c	50	H	H	OH	H	H	H	1	na[c]
3d	63	H	OH	H	H	H	H	1	na[c]
3e	72	OH	H	H	H	H	H	1	na[c]
3f	80	H	Br	H	H	H	H	0	na[c]
3g	72	H	OH	OH	H	H	H	2	5.32 ± 0.05
3h	66	H	H	OH	OH	H	H	2	3.59 ± 0.16
3i	78	H	H	H	H	OH	OH	2	5.14 ± 0.11
3j	77	H	OH	H	H	OH	OH	3	3.17 ± 0.06
3k	44	OH	H	H	H	OH	OH	3	6.86 ± 0.16
3l	70	H	H	H	OH	OH	OH	3	4.09 ± 0.12
3m	65	H	H	OH	H	OH	OH	3	6.02 ± 0.15
3n	44	H	Br	H	H	OH	OH	2	4.02 ± 0.09
3o	55	H	OH	OH	H	OH	OH	4	5.30 ± 0.03
3p	72	H	H	OH	OH	OH	OH	4	3.39 ± 0.05
Trolox								1	9.34 ± 0.07
CA[d]								2	9.48 ± 0.17
PCA[d]								2	8.83 ± 0.62
GA[d]								3	5.34 ± 0.34

[a] Yields refer to isolated crystalline products.
[b] Results are presented as a mean ± SD, $n = 3$.
[c] Not active up to concentration 100 μM.
[d] CA, PCA and GA refer to caffeic acid, protocatechuic acid and gallic acid, respectively.



Scheme 3. Probable reaction pathway for the proposed one-pot synthesis of coumarins.

presence of hydroxyl groups in the 3-aryl substituent in **6**, particularly in *para*-position, accelerates the lactone ring opening reaction by its positive mesomeric effect [52,64], and thus poses difficulties in isolation and structural characterization of these intermediates. The latter also suggests that the formation of *E*-**4** is not the rate limiting step in the synthetic sequence. Further, in order for the coumarin scaffold to be formed, *E*-**4** should isomerise to its *Z*-form, which happens in the next step. This sequence seems to be not illogical, since it mimics the coumarin biosynthetic pathway [63] from *trans*-cinnamic acid, via *ortho*-hydroxylation, *trans-cis* isomerisation of the side chain double bond and further lactonisation. Moreover, some papers [65–67] reported the synthesis of coumarins by cyclisation of obtained in advance *E-ortho*-methoxycinnamates under similar to the reported herein conditions – boron tribromide in dichloromethane. It is noteworthy that these results regard cinnamic acid analogues that always exist as an equilibrium mixture of the corresponding *E*- and *Z*-isomers. In our case, compounds **4** are entirely in their *E*-configuration. This was comprehensively studied and reported in recent studies [52,53], where we have used different NMR techniques and X-ray analysis to show that the incorporated *trans*-cinnamic acid fragment in **4** ensures *cis*-orientation of the phenyl substituents and prevents further isomerization along the carbon–carbon double bond. Nevertheless, despite that the *E*-isomers of **4** are proved to be preferred [52,53], they should isomerize somehow prior to cyclisation to **3**. We believe that the substituents electronic effects are implicated in this process, but in order for the above speculations to be converted into a more conclusive interpretation additional work including detailed reaction progress evaluation by NMR, kinetics measurements and quantum-chemical computations is needed.

2.2. Biological activity

The DPPH• radical is one of the commercially available stable organic nitrogen radicals, which does not have to be generated prior to analysis. The analysis whit it is easy to perform, highly reproducible, comparable with other methods and has been successfully applied for evaluation of the radical scavenging activity of other coumarins [8–11]. Therefore, this method was employed to assess the radical scavenging activity of the synthesized by us compounds **3a**–**p**. The analysis was performed in methanol and the activity was expressed as SC_{50} (μM) – the concentration able to scavenge 50% of DPPH•. For comparison purpose, well-known antioxidants such as Trolox, protocatechuic acid (**PCA**), caffeic acid (**CA**) and gallic acid (**GA**) were used as reference compounds. The results obtained are presented in Table 1 and Fig. 2. In general, the compounds tested can be split into two groups: **3a**–**e** – not active up to concentration 100 μM; and **3g**–**p** – highly active, with $SC_{50} \leq 6.82$ μM. These results suggest that the number of OH groups play an important role in triggering the scavenging activity, since the lack of activity of **3a**–**e** at the concentration measured could be attributed to the absence or presence of only one OH group into the 3-arylcoumarin backbone. The other group (**3g**–**p**) shows comparable, even higher radical scavenging activity than the standards used, as can be seen from the following scavenging activity order: **CA** < Trolox < **PCA** < **3k** < **3m** < **GA** ≈ **3g** ≈ **3i** ≈ **3l** < **3n** < **3h** ≈ **3p** ≈ **3o** ≈ **3j**. Taking into account the substitution pattern, it could be concluded that the main factor for the apparent activity is the presence of a catechol fragment, regardless in which aromatic ring it is. It is noteworthy that **CA** and **PCA** also possess such a fragment, but except **3k** and **3m**, all other compounds are at least twofold more active. This could be attributed to the presence of an extended π-conjugated system providing better delocalization, and thus stabilization, of the radicals formed. Consequently, compounds **3g**–**p** can be considered attractive targets for further detailed studies of their antioxidant activity, since it is well known that one of the main characteristics responsible for the antioxidant activity of phenolic compounds is their ability to scavenge free radicals. Moreover, the observed short range regarding SC_{50} values ($3.16 \leq SC_{50}$ [μM] ≤ 6.82), shows that the activity of **3g**–**p** is nearly independent on the number and position of the hydroxyl groups. The latter suggests that evaluation of other biological activities, in order for double or triple action to be established for these compounds, is worth performing.

3. Conclusions

In summary, we have developed a concise method for the synthesis of coumarins via boron tribromide induced demethylation/lactone ring opening/elimination/isomerization/lactone ring closure reaction sequence of *in situ* formed 3,4-dihydroisocoumarin-4-carboxylic acids. This novel one-pot

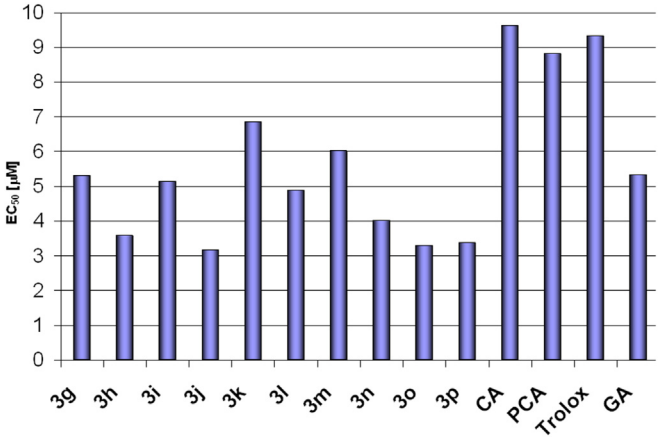


Fig. 2. A comparison of the radical scavenging activity of compounds **3g**–**p** and standard antioxidants.

procedure allows the gram-scale synthesis of a variety of polyhydroxylated coumarin derivatives from readily available starting materials at a low cost. The method proposed provides good yields for short reaction time, which, in combination with both simple work-up procedure and final products isolation in a purity level without the need for any further purification, shows its promising potential for the synthesis of a series of coumarins useful for their biological activity. The performed *in vitro* DPPH• assay show that compounds **3g**–**p** posses both higher and nearly independent on the substitution pattern radical scavenging activity than well-known antioxidants such as Trolox, protocatechuic acid, caffeic acid and gallic acid, which is a precondition for promising antioxidant activity of these compounds to be expected. The latter also suggests that evaluation of other activities of **3g**–**p**, in order for multiple biological actions to be established for these compounds, is worth performing. In this direction, work on the synthesis of particular value added coumarins, as well as work on the biological activity evaluation of the synthesized herein new compounds **3a**–**p** is currently ongoing in our laboratory and the results will be published in due course.

4. Experimental section

4.1. General remarks

All chemicals used in this study were purchased from Sigma–Aldrich (FOT, Bulgaria). Melting points were determined on a Kofler microscope Boetius PHMK 0.5. The reactions were monitored by thin layer chromatography (TLC) on pre-coated polyesters sheets POLIGRAM® SIL G/UV_{254}; spots were visualised with UV light. The IR spectra were acquired in Nujol on a Specord 75 and are reported in reciprocal centimetres. NMR spectra were recorded on a Bruker Avance spectrometer at 600 MHz/150 MHz for ^{1}H and ^{13}C, respectively, using DMSO-d_6 as a solvent. The chemicals shifts (δ) are given in ppm relative to tetramethylsilane as an internal standard and coupling constants (J) values are reported in Hz. The exact mass of compounds **3a**–**p** was determinate by HRMS analyses on DFS High Resolution GC/MS (Thermo), after derivatization with diazomethane. The mass spectra were obtained after preliminary GC separation on Trace GC (Thermo Electron) instrument equipped with a quadruple MS detector DSQ (Thermo Electron). The separation was carried out on DB-5 MS column. The mass spectrometer operates in scan-mode (70 eV ionization potential). The radical scavenging activity was assessed by UV–VIS spectrophotometer Thermo Evolution 60S.

4.2. Chemistry

4.2.1. General procedure for one-pot synthesis of polyhydroxy coumarins *3a*–*p*

An equimolar mixture of the corresponding homophthalic anhydride (**1a**,**b**), an aldehyde **2a**–**h** and DMAP was stirred at room temperature in dry dichloromethane (20 mL). The consumption of the reagents was monitored by TLC. At the end of the reaction (10–15 min), boron tribromide (1.6 M solution in dichloromethane) was slowly added (one equivalent per heteroatom), and after 4 h stirring the reaction mixture was poured over grinded ice (50 g) and stirred for additional 30 min. The crystallized coumarins **3a**–**p** were then filtered off, washed with deionised water and dried at 100 °C under reduced pressure. The obtained in this way coumarins **3a**–**p** were recrystallized from acetic acid/water prior to spectral characterization.

Additional quantities of **3** could be obtained from the filtrates as follows: the corresponding filtrate was saturated with NaCl and extracted with ethyl acetate. The organic phase was washed with brine to a constant pH, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was further dissolved in ethyl acetate. After few days, additional quantities from coumarins **3a**–**p** could be obtained by filtration.

*4.2.1.1. 2-(2-Oxo-2H-chromen-3-yl)benzoic acid (**3a**).* From reaction of homophthalic anhydride (**1a**) (1.08 g, 6.71 mmol), 2-methoxybenzaldehyde (**2a**) (0.91 g, 6.71 mmol), 4-dimethylaminopyridine (0.82 g, 6.71 mmol), boron tribromide (33.5 mL, 53.64 mmol) in 20 mL dichloromethane. Yield: 1.30 g (72%), white solid, mp 259–260 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.90 (bs, 1H, COOH), 8.02 (s, 1H, =CH–), 7.95 (dd, $^{3}J_{H,H}$ = 7.8, $^{4}J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.76 (dd, $^{3}J_{H,H}$ = 7.7, $^{4}J_{H,H}$ = 1.5 Hz, 1H, ArH), 7.69 (dt, $^{3}J_{H,H}$ = 7.5, $^{4}J_{H,H}$ = 1.4 Hz; 1H, ArH), 7.63 (ddd, $^{3}J_{H,H}$ = 8.4, 7.4, $^{4}J_{H,H}$ = 1.6 Hz, 1H, ArH), 7.57 (dt, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.50 (dd, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.0 Hz, 1H, ArH), 7.45 (d, $^{3}J_{H,H}$ = 8.3 Hz, 1H, ArH), 7.39 (dt, $^{3}J_{H,H}$ = 7.5, $^{4}J_{H,H}$ = 1.1 Hz, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.7 (CO_{COOH}), 159.7 ($CO_{lactone}$), 152.8, 138.5, 135.8, 132.1, 131.3, 131.2, 130.8, 130.1, 129.7, 128.7, 128.3, 124.5, 119.4, 115.9; IR (Nujol) ν = 3600–3050 (OH), 1720, 1670 (C=O) cm^{-1}; MS (EI) m/z: 281.1(18), 280.0(100), 254.0(25), 249.0(76), 235.0(13), 221.0(61), 220.0(19), 193(12), 165.0(17), 163.0(12); HRMS (EI): m/z calculate: 280.07356, found: 280.07314 for $C_{17}H_{12}O_4$.

*4.2.1.2. 2-(8-Hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3b**).* From reaction of homophthalic anhydride (**1a**) (0.99 g, 6.09 mmol), 2,3-dimethoxybenzaldehyde (**2b**) (1.01 g, 6.09 mmol), 4-dimethylaminopyridine (0.74 g, 6.09 mmol), boron tribromide (34.3 mL, 54.83 mmol) in 20 mL dichloromethane. Yield: 0.84 g (49%), brown solid, mp 305–306 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.87 (bs, 1H, COOH), 10.24 (bs, 1H, OH), 7.94 (s, 1H, =CH–), 7.93 (dd, $^{3}J_{H,H}$ = 7.9, $^{4}J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.68 (dt, $^{3}J_{H,H}$ = 7.5, $^{4}J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.56 (dt,, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.49 (dd, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.0 Hz, 1H, ArH), 7.19–7.14 (m, 2H, ArH), 7.10 (dd, $^{3}J_{H,H}$ = 6.8, $^{4}J_{H,H}$ = 2.7 Hz, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.9 (CO_{COOH}), 159.8 ($CO_{lactone}$), 144.5, 141.6, 139.0, 136.1, 132.2, 131.4, 131.0, 130.1, 129.8, 128.8, 124.6, 120.5, 118.4, 117.8; IR (Nujol) ν = 3400 (OH), 1705, 1670 (C=O) cm^{-1}; MS (EI) m/z: 311.1(20), 310.1(100), 282.1(19), 279.1(57), 278.1(40), 265.1(13), 251.1(53), 208(16), 207.0(25), 165.0(20), 152.0(25), 151.0(18), 139.0(14), 125.0(15), 76.0(19); HRMS (EI): m/z calculate: 310.08412, found: 310.08392 for $C_{18}H_{14}O_5$.

*4.2.1.3. 2-(7-Hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3c**).* From reaction of homophthalic anhydride (**1a**) (0.99 g, 6.09 mmol), 2,4-dimethoxybenzaldehyde (**2c**) (1.01 g, 6.09 mmol), 4-dimethylaminopyridine (0.74 g, 6.09 mmol), boron tribromide (34.3 mL, 54.83 mmol) in 20 mL dichloromethane. Yield: 0.86 g (50%), beige solid, mp 255–256 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.78 (bs, 1H, COOH), 10.56 (bs, 1H, OH), 7.90 (dd, $^{3}J_{H,H}$ = 7.4, $^{4}J_{H,H}$ = 1.5 Hz, 1H, ArH), 7.89 (s, 1H, =CH–), 7.65 (dt, $^{3}J_{H,H}$ = 7.5, $^{4}J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.57 (d, $^{3}J_{H,H}$ = 8.5, 1H, ArH), 7.52 (dt, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.45 (dd, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.0 Hz, 1H, ArH), 6.83 (dd, $^{3}J_{H,H}$ = 8.5, $^{4}J_{H,H}$ = 2.3 Hz, 1H, ArH), 6.76 (d, $^{4}J_{H,H}$ = 2.3 Hz, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.9 (CO_{COOH}), 160.8 ($CO_{lactone}$), 160.1, 154.7, 139.2, 136.1, 131.9, 131.4, 130.8, 2 × 129.6, 128.3, 125.4, 113.1, 111.8, 101.8; IR (Nujol) ν = 3500–3000 (OH), 1705, 1670 (C=O) cm^{-1}; MS (EI) m/z: 311.1(20), 310.1(100), 282.1(30), 279.0(50), 267.0(22), 251.0(27), 235.0(9), 223.1(7); HRMS (EI): m/z calculate: 310.08412, found: 310.08285 for $C_{18}H_{14}O_5$.

*4.2.1.4. 2-(6-Hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3d**).* From reaction of homophthalic anhydride (**1a**) (0.99 g, 6.09 mmol), 2,5-dimethoxybenzaldehyde (**2d**) (1.01 g, 6.09 mmol), 4-

dimethylaminopyridine (0.74 g, 6.09 mmol), boron tribromide (34.3 mL, 54.83 mmol) in 20 mL dichloromethane. Yield: 1.08 g (63%), white solid, mp 251–252 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.86 (bs, 1H, COOH), 9.76 (bs, 1H, OH), 7.92 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.92 (s, 1H, =CH–), 7.66 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.57 (dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.47 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.0 Hz, 1H, ArH), 7.28 (d, $^3J_{H,H}$ = 8.9, 1H, ArH), 7.07 (d, $^4J_{H,H}$ = 2.9 Hz, 1H, ArH), 7.03 (dd, $^3J_{H,H}$ = 8.9, $^4J_{H,H}$ = 2.9 Hz, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.9 (CO_{COOH}), 160.1 ($CO_{lactone}$), 153.9, 146.3, 138.6, 136.1, 132.2, 131.5, 131.0, 130.2, 129.7, 128.8, 120.1, 119.3, 116.9, 112.5; IR (Nujol) ν = 3500–3000 (OH), 1710, 1680 (C=O) cm^{-1}; MS (EI) *m/z*: 311.2(23), 310.2(100), 279.1(51), 278.1(42), 263.1(15), 251.1(32), 207.1(25), 152.1 (14), 139.0(8), 126.0(10), 76.1(8); HRMS (EI): *m/z* calculate: 310.08412, found: 310.08394 for $C_{18}H_{14}O_5$.

*4.2.1.5. 2-(5-Hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3e**).* From reaction of homophthalic anhydride (**1a**) (0.49 g, 3.01 mmol), 2,6-dimethoxybenzaldehyde (**1e**) (0.50 g, 3.01 mmol), 4-dimethylaminopyridine (0.37 g, 3.01 mmol), boron tribromide (16.9 mL, 27.08 mmol) in 10 mL dichloromethane. Yield: 0.61 g (72%), orange solid, mp 285–286 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.84 (bs, 1H, COOH), 10.80 (bs, 1H, OH), 7.92 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.92 (s, 1H, =CH–), 7.66 (dt, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.54 (dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.48 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.0 Hz, 1H, ArH), 7.45 (t, $^3J_{H,H}$ = 8.3, 1H, ArH), 6.85 (d, $^3J_{H,H}$ = 8.3, 1H, ArH), 6.80 (dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 0.8 Hz, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 168.0 (CO_{COOH}), 160.0 ($CO_{lactone}$), 154.9, 154.2, 136.2, 133.4, 132.2, 132.2, 131.5, 131.0, 129.8, 128.7, 127.8, 110.1, 108.8, 106.5; IR (Nujol) ν = 3500–3000 (OH), 1705, 1680 (C=O) cm^{-1}; MS (EI) *m/z*: 311.2(22), 310.2(100), 282.2(28), 279.1(74), 251.1(48), 236.1(22), 207.1(11), 180.1(7), 152.1(14), 139.1(8); HRMS (EI): *m/z* calculate: 310.08412, found: 310.08382 for $C_{18}H_{14}O_5$.

*4.2.1.6. 2-(6-Bromo-2-oxo-2H-chromen-3-yl)benzoic acid (**3f**).* From reaction of homophthalic anhydride (**1a**) (0.86 g, 5.30 mmol), 5-bromo-2-methoxybenzaldehyde (**2f**) (1.140 g, 5.30 mmol), 4-dimethylaminopyridine (0.60 g, 5.30 mmol), boron tribromide (30.0 mL, 47.72 mmol) in 20 mL dichloromethane. Yield: 1.46 g (80%), white solid, mp 259–260 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.97 (bs, 1H, COOH), 8.00 (d, $^4J_{H,H}$ = 2.4 Hz, 1H, ArH), 7.96 (s, 1H, =CH–), 7.95 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.77 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.4 Hz, 1H, ArH), 7.69 (dt, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.58 (dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.47 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.1 Hz, 1H, ArH), 7.44 (d, $^3J_{H,H}$ = 8.8, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.7 (CO_{COOH}), 159.4 ($CO_{lactone}$), 152.0, 137.2, 135.7, 133.8, 132.4, 131.4, 131.2, 130.9, 130.4, 129.9, 129.1, 121.4, 118.4, 116.2; IR (Nujol) ν = 1730, 1680 (C=O) cm^{-1}; MS (EI) *m/z*: 361.0(18), 360.0(96), 359.0(22), 358.0(100), 330.0(38), 329.0(64), 328.0(34), 327.0(66), 302.0(250), 301.0(63), 300.0(58), 299.0(98), 298.0(44), 220.0(28), 192.0(12), 164.0(14), 163.0(28); HRMS (EI): *m/z* calculate: 357.98407, found: 357.98473 for $C_{17}H_{11}^{79}BrO_4$.

*4.2.1.7. 2-(6,7-Dihydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3g**).* From reaction of homophthalic anhydride (**1a**) (0.91 g, 5.58 mmol), 2,4,5-trimethoxybenzaldehyde (**2g**) (1.09 g, 5.58 mmol), 4-dimethylaminopyridine (0.68 g, 5.58 mmol), boron tribromide (35.0 mL, 55.81 mmol) in 20 mL dichloromethane. Yield: 1.20 g (72%), beige solid, mp 290–291 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.74 (bs, 1H, COOH), 10.19 (bs, 1H, OH), 9.44 (bs, 1H, OH), 7.87 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.83 (s, 1H, =CH–), 7.63 (dt, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.50 (dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.43 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.0 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 6.76 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 168.1 (CO_{COOH}), 160.5 ($CO_{lactone}$), 150.0, 147.9, 143.0, 139.4, 136.4, 132.0, 131.7, 131.0, 129.6, 128.3, 125.6, 112.4, 111.5, 102.4; IR (Nujol) ν = 3550–2500 (OH), 1700, 1660 (C=O) cm^{-1}; MS (EI) *m/z*: 341.2(20), 340.2(100), 309.2(45), 281.1(10), 265.1(14), 237.1(18), 209.1(9), 194.0(10); HRMS (EI): *m/z* calculate: 340.09469, found: 340.09415 for $C_{19}H_{16}O_6$.

*4.2.1.8. 2-(7,8-Dihydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3h**).* From reaction of homophthalic anhydride (**1a**) (0.91 g, 5.58 mmol), 2,3,4-trimethoxybenzaldehyde (**2h**) (1.09 g, 5.58 mmol), 4-dimethylaminopyridine (0.68 g, 5.58 mmol), boron tribromide (35.0 mL, 55.81 mmol) in 20 mL dichloromethane. Yield: 1.10 g (66%), beige solid, mp 285–286 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.64 (bs, 1H, COOH), 10.11 (bs, 1H, OH), 9.41 (bs, 1H, OH), 7.89 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.2 Hz, 1H, ArH), 7.84 (s, 1H, =CH–), 7.64 (dt, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.51 (dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3 Hz, 1H, ArH), 7.45 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.0 Hz, 1H, ArH), 7.06 (d, $^3J_{H,H}$ = 8.5, 1H, ArH), 6.83 (d, $^3J_{H,H}$ = 8.4, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 168.1 (CO_{COOH}), 160.2 ($CO_{lactone}$), 149.3, 143.2, 139.8, 136.4, 132.0, 132.0, 131.6, 131.0, 129.7, 128.4, 125.4, 118.8, 112.7, 112.6; IR (Nujol) ν = 3550–2400 (OH), 1695 (C=O) cm^{-1}; MS (EI) *m/z*: 341.1(22), 340.1(100), 309.1(45), 297.1(22), 281.1(21), 269.1(32), 237.1(14), 223.0(16), 183.0(14), 167.0(12), 139.0(21), 127.0(11); HRMS (EI): *m/z* calculate: 340.09469, found: 340.09421 for $C_{19}H_{16}O_6$.

*4.2.1.9. 4,5-Dihydroxy-2-(2-oxo-2H-chromen-3-yl)benzoic acid (**3i**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.24 g, 5.58 mmol), 2-methoxybenzaldehyde (**2a**) (0.76 g, 5.58 mmol), 4-dimethylaminopyridine (0.68 g, 5.58 mmol), boron tribromide (35.0 mL, 55.81 mmol) in 20 mL dichloromethane. Yield: 1.31 g (78%), beige solid, mp 283–284 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.30 (bs, 1H, COOH), 9.84 (bs, 1H, OH), 9.62 (bs, 1H, OH), 7.82 (s, 1H, =CH–), 7.71 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.4 Hz, 1H, ArH), 7.57 (ddd, $^3J_{H,H}$ = 8.7, 7.5, $^4J_{H,H}$ = 1.6 Hz, 1H, ArH), 7.40 (d, $^3J_{H,H}$ = 8.4, 1H, ArH), 7.39 (s, 1H, ArH), 7.35 (dt, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.0, 1H, ArH), 6.76 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.4 (CO_{COOH}), 160.0 ($CO_{lactone}$), 152.9, 149.0, 145.1, 137.5, 131.1, 130.9, 128.8, 128.2, 124.5, 121.6, 119.7, 118.1, 117.6, 116.0; IR (Nujol) ν = 3550–2400 (OH), 1670 (C=O) cm^{-1}; MS (EI) *m/z*: 341.3(20), 340.2(100), 325.2(5), 312.2 (13), 309.2(50), 281.2(45), 265.2(20), 253.2(8), 237.2(11), 195.1(7), 139.1(10), 69.4(5); HRMS (EI): *m/z* calculate: 340.09469, found: 340.09435 for $C_{19}H_{16}O_6$.

*4.2.1.10. 4,5-Dihydroxy-2-(6-hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3j**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.14 g, 5.15 mmol), 2,5-dimethoxybenzaldehyde (**2d**) (0.86 g, 5.15 mmol), 4-dimethylaminopyridine (0.63 g, 5.15 mmol), boron tribromide (35.4 mL, 56.65 mmol) in 20 mL dichloromethane. Yield: 1.25 g (77%), beige solid, mp 212–213 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.29 (bs, 1H, COOH), 9.81 (bs, 1H, OH), 9.69 (bs, 1H, OH), 9.56 (bs, 1H, OH), 7.73 (s, 1H, =CH–), 7.37 (s, 1H, ArH), 7.23 (d, $^3J_{H,H}$ = 8.9, 1H, ArH), 7.03 (d, $^4J_{H,H}$ = 2.9, 1H, ArH), 6.98 (dd, $^3J_{H,H}$ = 8.9, $^4J_{H,H}$ = 2.9, 1H, ArH), 6.73 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.4 (CO_{COOH}), 160.2 ($CO_{lactone}$), 153.8, 148.9, 146.2, 145.0, 137.4, 130.9, 128.9, 121.6, 120.2, 118.8, 118.1, 117.6, 116.8, 112.3; IR (Nujol) ν = 3550–2400 (OH), 1700, 1670 (C=O) cm^{-1}; MS (EI) *m/z*: 371.2(25), 370.2(100), 339.2(40), 338.2(55), 323.1(39), 211.2(35), 295.2(25), 267.1(22), 239.2(7), 225.1(7); HRMS (EI): *m/z* calculate: 370.10525, found: 370.10483 for $C_{20}H_{18}O_7$.

*4.2.1.11. 4,5-Dihydroxy-2-(5-hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3k**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (0.67 g, 3.01 mmol), 2,6-dimethoxybenzaldehyde (**2e**)

(0.50 g, 3.01 mmol), 4-dimethylaminopyridine (0.37 g, 3.01 mmol), boron tribromide (20.7 mL, 33.11 mmol) in 10 mL dichloromethane. Yield: 0.42 g (44%), pink solid, mp 278–279 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.29 (bs, 1H, COOH), 10.70 (bs, 1H, OH), 9.82 (bs, 1H, OH), 9.54 (bs, 1H, OH), 7.74 (s, 1H, =CH–), 7.37 (s, 1H, ArH), 7.36 (t, $^3J_{H,H}$ = 8.2, 1H, ArH), 6.82 (d, $^3J_{H,H}$ = 8.3, 1H, ArH), 6.76 (dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 0.7, 1H, ArH), 6.74 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.4 (CO_{COOH}), 160.0 ($CO_{lactone}$), 154.6, 154.0, 148.9, 145.0, 132.2, 131.7, 129.0, 128.5, 121.6, 118.1, 117.6, 110.0, 108.9, 106.4; IR (Nujol) ν = 3600–2400 (OH), 1695, 1680 (C=O) cm^{-1}; MS (EI) *m/z*: 371.3(20), 370.2(100), 342.2(21), 339.2 (40), 327.2(10), 211.2(40), 295.2(20), 267.1(10), 253.1(10), 225.1(13), 210.1(7). 139.0(7), 126(9), 58.9(8); HRMS (EI): *m/z* calculate: 370.10525, found: 370.10476 for $C_{20}H_{18}O_7$.

*4.2.1.12. 4,5-Dihydroxy-2-(8-hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3l**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.14 g, 5.15 mmol), 2,3-dimethoxybenzaldehyde (**2b**) (0.86 g, 5.15 mmol), 4-dimethylaminopyridine (0.63 g, 5.15 mmol), boron tribromide (35.4 mL, 56.65 mmol) in 20 mL dichloromethane. Yield: 1.14 g (70%), pink solid, mp 313–314 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.25 (bs, 1H, COOH), 10.15 (bs, 1H, OH), 9.81 (bs, 1H, OH), 9.56 (bs, 1H, OH), 7.74 (s, 1H, =CH–), 7.39 (s, 1H, ArH), 7.21–6.98 (m, 3H, ArH), 6.75 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.4 (CO_{COOH}), 159.9($CO_{lactone}$), 149.0, 145.0, 144.4, 141.5, 137.9, 130.7, 128.9, 124.4, 121.6, 120.6, 118.2, 118.1, 117.7, 117.5; IR (Nujol) ν = 3600–2400 (OH), 1680 (C=O) cm^{-1}; MS (EI) *m/z*: 371.2(20), 370.1(100), 338.1(27), 323.1 (25), 311.1(37), 295.1(20), 283.1(10), 267.1(15), 225.1(13), 226.0(10), 58.9(8); HRMS (EI): *m/z* calculate: 370.10525, found: 370.10486 for $C_{20}H_{18}O_7$.

*4.2.1.13. 4,5-Dihydroxy-2-(7-hydroxy-2-oxo-2H-chromen-3-yl)benzoic acid (**3m**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.14 g, 5.15 mmol), 2,4-dimethoxybenzaldehyde (**2c**) (0.86 g, 5.15 mmol), 4-dimethylaminopyridine (0.63 g, 5.15 mmol), boron tribromide (35.4 mL, 56.65 mmol) in 20 mL dichloromethane. Yield: 1.05 g (65%), pink solid, mp 266–268 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.22 (bs, 1H, COOH), 10.44 (bs, 1H, OH), 9.75 (bs, 1H, OH), 9.49 (bs, 1H, OH), 7.70 (s, 1H, =CH–), 7.52 (d, $^3J_{H,H}$ = 8.5, 1H, ArH), 7.39 (s, 1H, ArH), 6.79 (dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 2.2, 1H, ArH), 6.74 (s, 2H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.6 (CO_{COOH}), 160.6 ($CO_{lactone}$), 160.5, 154.7, 148.9, 144.8, 138.2, 129.4, 129.2, 126.4, 121.8, 118.2, 117.7, 113.1, 112.1, 102.0; IR (Nujol) ν = 3550–2400 (OH), 1680 (C=O) cm^{-1}; MS (EI) *m/z*: 371.2(20), 370.1(100), 342.1(13), 339.1(35), 327.1(13), 311.2(35), 311.1(20), 295.1(15); HRMS (EI): *m/z* calculate: 370.10525, found: 370.10473 for $C_{20}H_{18}O_7$.

*4.2.1.14. 2-(6-Bromo-2-oxo-2H-chromen-3-yl)-4,5-dihydroxybenzoic acid (**3n**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.02 g, 4.57 mmol), 5-bromo-2-methoxybenzaldehyde (**2f**) (0.98 g, 4.57 mmol), 4-dimethylaminopyridine (0.56 g, 4.57 mmol), boron tribromide (28.6 mL, 4.57 mmol) in 20 mL dichloromethane. Yield: 0.75 g (44%), white solid, mp 269–270 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.38 (bs, 1H, COOH), 9.89 (bs, 1H, OH), 9.63 (bs, 1H, OH), 7.97 (d, $^4J_{H,H}$ = 2.4, 1H, ArH), 7.78 (s, 1H, =CH–), 7.72 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.4, 1H, ArH), 7.04 (s, 1H, ArH), 7.39 (d, $^3J_{H,H}$ = 8.8, 1H, ArH), 6.75 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.3 (CO_{COOH}), 159.5 ($CO_{lactone}$), 151.9, 149.0, 145.3, 136.1, 133.4, 132.0, 130.2, 128.4, 121.6, 121.5, 118.3, 118.0, 117.7, 116.1; IR (Nujol) ν = 3550–2400 (OH), 1690, 1670 (C=O) cm^{-1}; MS (EI) *m/z*: 421.1(23), 420.0(99), 419.0(24), 418.0(100), 390.0(16), 389.0(32), 388.0(21), 387.0(33), 361.0(36), 359(36), 354.0(17), 339.0(17); HRMS (EI): *m/z* calculate: 418.00520, found: 418.00469 for $C_{19}H^{79}_{15}BrO_6$.

*4.2.1.15. 2-(6,7-Dihydroxy-2-oxo-2H-chromen-3-yl)-4,5-dihydroxybenzoic acid (**3o**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.06 g, 4.78 mmol), 2,4,5-trimethoxybenzaldehyde (**2g**) (0.94 g, 4.78 mmol), 4-dimethylaminopyridine (0.58 g, 4.78 mmol), boron tribromide (36.0 mL, 57.36 mmol) in 20 mL dichloromethane. Yield: 0.87 g (55%), yellow solid, mp 290–291 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.20 (bs, 1H, COOH), 10.10 (bs, 1H, OH), 9.75 (bs, 1H, OH), 9.49 (bs, 1H, OH), 9.36 (bs, 1H, OH), 7.67 (s, 1H, =CH–), 7.34 (s, 1H, ArH), 7.00 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.69 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.5 (CO_{COOH}), 160.7 ($CO_{lactone}$), 149.5, 148.8, 147.7, 144.7, 142.9, 138.2, 129.3, 126.4, 121.8, 118.2, 117.6, 112.3, 111.6, 102.4; IR (Nujol) ν = 3550–2400 (OH), 1670 (C=O) cm^{-1}; MS (EI) *m/z*: 401.3(22), 400.3(100), 385.2(12), 369.3(30), 353.2(20), 341.2(15), 325.2(12), 297.2(15); HRMS (EI): *m/z* calculate: 400.11582, found: 400.11526 for $C_{21}H_{20}O_8$.

*4.2.1.16. 2-(7,8-Dihydroxy-2-oxo-2H-chromen-3-yl)-4,5-dihydroxybenzoic acid (**3p**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.06 g, 4.78 mmol), 2,3,4-trimethoxybenzaldehyde (**2h**) (0.94 g, 4.78 mmol), 4-dimethylaminopyridine (0.58 g, 4.78 mmol), boron tribromide (36.0 mL, 57.36 mmol) in 20 mL dichloromethane. Yield: 1.14 g (72%), beige solid, mp 290–291 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.23 (bs, 1H, COOH), 10.01 (bs, 1H, OH), 9.78 (bs, 1H, OH), 9.50 (bs, 1H, OH), 9.35 (bs, 1H, OH), 7.65 (s, 1H, =CH–), 7.36 (s, 1H, ArH), 7.01 (d, $^3J_{H,H}$ = 8.5, 1H, ArH), 6.79 (d, $^3J_{H,H}$ = 8.5, 1H, ArH), 6.71 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 167.5 (CO_{COOH}), 160.3 ($CO_{lactone}$), 148.9, 148.8, 144.7, 143.0, 138.7, 132.0, 129.3, 126.1, 121.7, 118.5, 118.2, 117.6, 112.7, 112.5; IR (Nujol) ν = 3550–2400 (OH), 1685, 1650 (C=O) cm^{-1}; MS (EI) *m/z*: 401.3(22), 400.1(100), 369.2(30), 357.2(17), 341.2(20), 325.1(13), 309.1(10); HRMS (EI): *m/z* calculate: 400.11582, found: 400.11538 for $C_{21}H_{20}O_8$.

*4.2.1.17. (E)-2-(1-carboxy-2-(2-hydroxyphenyl)vinyl)-4,5-dihydroxybenzoic acid (E-**4a**).* From reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.24 g, 5.58 mmol), 2-methoxybenzaldehyde (**2a**) (0.76 g, 5.58 mmol), 4-dimethylaminopyridine (0.68 g, 5.58 mmol), boron tribromide (35.0 mL, 55.81 mmol) in 20 mL dichloromethane. Yield: 0.71 g (40%), yellow solid, mp 214–216 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 11.69 (bs, 2H, COOH), 9.70 (bs, 1H, OH), 9.38 (bs, 1H, OH), 9.09 (bs, 1H, OH), 7.80 (s, 1H, =CH–), 7.43 (s, 1H, ArH), 7.03–6.98 (m, 1H, ArH), 6.82 (d, $^3J_{H,H}$ = 7.7, 1H, ArH), 6.54 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.4, 1H, ArH), 6.46 (q, $^3J_{H,H}$ = 7.5, 1H, ArH), 6.31 (s, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 168.2 (CO_{COOH}), 167.1 (CO_{COOH}), 156.3, 148.9, 144.0, 133.4, 131.1, 130.3, 129.4, 129.3, 123.1, 121.6, 118.3, 117.9, 117.7, 115.4; IR (Nujol) ν = 3550–2400 (OH), 1670 (C=O) cm^{-1}; HRMS (EI): *m/z* calculate: 386,13655, found: 386,13592 for $C_{21}H_{22}O_7$.

4.2.2. Isolation of intermediates E-**4b** and cis-/trans-**6**

Compounds *E*-**4b** and *cis*-/*trans*-**6** were isolated from reaction of 6,7-dimetoxihomophthalic anhydride (**1b**) (1.14 g, 5.15 mmol), 2,3-dimethoxybenzaldehyde (**2b**) (0.86 g, 5.15 mmol), 4-dimethylaminopyridine (0.63 g, 5.15 mmol) and boron tribromide (35 mL, 56.65 mmol) in 20 mL dichloromethane, stirred for 30 min and worked up as described in 4.2.1. After isolation of the corresponding coumarin **3l**, the residue was immediately subjected to separation by means of column chromatography (Mobile phase: 49% acetone/50% cyclohexane/1% HCOOH). Compound **6** was isolated as yellow foam (yield: 0.53 g (17%)), and as diastereomeric mixture of the corresponding *cis*-/*trans*- isomers in a ratio 15/85 (^{1}H NMR) [56,57].

*4.2.2.1. (E)-2-(1-carboxy-2-(2,3-dihydroxyphenyl)vinyl)-4,5-dihydroxybenzoic acid (E-**4b**).* Yield: 0.53 g (31%), beige solid, mp 228–230 °C; ^{1}H NMR (600.13 MHz, DMSO-d_6), δ = 12.07 (bs, 2H, COOH), 9.55 (bs, 1H, OH), 9.43 (bs, 1H, OH), 9.25 (bs, 1H, OH), 8.75 (bs, 1H, OH), 7.80 (s, 1H, =CH–), 7.41 (s, 1H, ArH), 6.61 (d, 1H, $^3J_{H,H}$ = 7.4, ArH), 6.32 (s, 1H, ArH), 6.29 (t, $^3J_{H,H}$ = 7.9, 1H, ArH), 5.98 (d, $^3J_{H,H}$ = 7.8, 1H, ArH); ^{13}C NMR (150.92 MHz, DMSO-d_6) δ = 168.6 (CO_{COOH}), 167.3 (CO_{COOH}), 149.1, 145.2, 145.0, 144.2, 133.4, 131.5, 130.8, 122.9, 121.5, 120.1, 118.3, 118.0, 117.9, 115.2; IR (Nujol) ν = 3550–2400 (OH), 1670 (C=O) cm^{-1}.

*4.2.2.2. Cis-/trans-3-(2,3-Dihydroxyphenyl)-6,7-dihydroxy-1-oxoisochroman-4-carboxylic acid (**6**). For cis-isomer*: ^{1}H NMR (250.13 MHz, DMSO-d_6), δ = 7.38 (s, 1H, H-8), 6.86 (d, 1H, $^3J_{H,H}$ = 6.2, ArH), 5.85 (d, $^3J_{H,H}$ = 3.3, 1H, H-3), 3.95 (d, $^3J_{H,H}$ = 3.3, 1H, H-4); *for trans-isomer*: ^{1}H NMR (250.13 MHz, DMSO-d_6), δ = 7.32 (s, 1H, H-8), 6.03 (d, $^3J_{H,H}$ = 5.5, 1H, H-3), 4.25 (d, $^3J_{H,H}$ = 5.5, 1H, H-4), *other signals for both diastereomers*: 12.77 (bs, 1H, COOH), 10.09 (bs, 1H, OH), 9.54 (bs, 2H, OH), 8.80 (bs, 1H, OH), 6.73 (d, 1H, $^3J_{H,H}$ = 7.5, ArH), 6.65 (s, 1H, H-5), 6.55 (t, 1H, $^3J_{H,H}$ = 7.8, ArH), 6.45 (d, $^3J_{H,H}$ = 6.9, 1H, ArH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ = 171.9 (CO_{COOH}), 163.9 ($CO_{lactone}$), 151.4, 145.4, 145.2, 142.8, 129.2, 124.7, 118.7, 117.4, 115.5, 115.2 (×2), 114.3, 75.7 (C-3), 46.4 (C-4); IR (Nujol) ν = 3550–2400 (OH), 1695 (C=O) cm^{-1}.

4.3. Biological activity

4.3.1. DPPH• scavenging assay

A methanolic solution (100 μM) of the DPPH• was prepared daily and protected from light. Absorbance was recorded to check the stability of the radical throughout the time of analysis. Five DPPH• solutions of different concentrations (10, 25, 50, 75 and 100 μM) were also prepared every day and a linear relationship between the radical concentration and absorbance was established. The effect of compounds **3a**–**p** on the DPPH• absorbance was estimated by using the procedure described in Ref. [68]. 0.5 mL of different concentrations of compounds **3a**–**p** (4–25 μM), dissolved in methanol were added to 0.5 mL (100 μM) of DPPH• methanolic solution. The molar ratio between DPPH• and analytes was in the range from 4:1 to 25:1 in favour of DPPH•. The absorbance at 518 nm was recorded at different time intervals until the reaction reached equilibrium. The initial absorbance was close to 0.560 in all cases. The blank reference cuvette contained methanol. All measurements were performed in triplicate. Five different concentrations of each analyte have been assayed in order to check the linearity of the response and to establish the antioxidant activity values in the adequate linear range. The percentage of DPPH• remaining at the steady state (DPPH•$_{rem}$) was determined as:

$$\%DPPH^{\cdot}_{rem} = \left(A_f / A_0\right) * 100,$$

were A_0 and A_f correspond to the absorbance at 518 nm of the radical at the beginning and at steady state, respectively. Concentrations of the compounds **3a**–**p** in the reaction medium were plotted against the percentages of the remanent DPPH• radical at the end of the reaction in order to obtain the EC_{50} index, defined as the amount of antioxidant needed to decrease the initial DPPH• concentration by 50%.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.03.053.

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