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A novel synthesis of 3-aryl coumarins and evaluation of their antioxidant and lipoxygenase inhibitory activity

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ABSTRACT

A series of coumarin analogues bearing a substituted phenyl ring on position 3 were synthesized via a novel methodology, through an intermolecular condensation reaction of 2-hydroxyacetophenones and 2-hydroxybenzaldehyde, with imidazolyl phenylacetic acid active intermediates. The in vitro antioxidant activity of the synthesized compounds was evaluated using two different antioxidant assays (radical scavenging ability of DPPH stable free radical and inhibition of lipid peroxidation induced by the thermal free radical AAPH). Moreover, the ability of the compounds to inhibit soybean lipoxygenase was determined as an indication of potential anti-inflammatory activity.

Coumarins are benzopyrone analogues widely distributed in nature.[1] The fused heterocyclic framework of coumarins has served as the prototype scaffold for the synthesis of a wide variety of analogues in order to investigate their biological activity. In the literature, coumarins are reported to possess a remarkable range of biological properties including antioxidant,[2] anticancer,[3] vasorelaxant,[4] antiviral[5] and anti-inflammatory activities.[6,7] Moreover, several synthetic coumarin derivatives have important pharmacological potential as they proved to be efficient inhibitors of a variety of enzymes such as the human 5-lipoxygenase,[8] aromatase,[9] horseradish peroxidase,[10] hAChE/BACE1[11] and 17β-hydroxysteroid dehydrogenase type 3.[12]

Reactive oxygen species (ROS) are formed by aerobic organisms as an unavoidable consequence of cell metabolism. Although effective natural defense mechanisms against these highly reactive species exist (e.g., natural antioxidants such as vitamins E and C, b-carotene and polyphenolic flavonoids), excessive ROS production which escorts many pathophysiological conditions (oxidative stress) poses the need of further antioxidant protection. As a result, the research for the development of novel, small molecules with antioxidant activity is constantly attracting attention.

Lipoxygenases (LOs) are a family of iron-containing enzymes that catalyse the dioxygenation of polyunsaturated fatty acids in lipids. Lipoxygenases have recently become of interest, as they are considered the key enzymes in the biosynthesis of leukotrienes that have been postulated to play an important role in the pathophysiology of several inflammatory and allergic diseases. Inhibitors of lipoxygenases have attracted attention initially as potential agents for the treatment of inflammatory and allergic diseases, but their therapeutic potential has now been expanded to certain types of cancer and cardiovascular diseases.[13]

This work aims at the development of a novel synthetic approach towards 3-aryl-coumarin derivatives and the evaluation of their antioxidant and lipoxygenase inhibitory activity.

The most widely applied approaches towards the synthesis of coumarin analogues include the Perkin reaction, that uses 2-hydroxyacetophenone and phenylacetic acid as starting materials, and the Pechmann reaction, which involves the condensation of phenols with β-keto-esters in the presence of strong acids. Variations of these methodologies have been developed in an attempt to improve reaction conditions and yields.[14–19]

In order to synthesize the coumarin analogues desired for this study, we developed a smooth, clean and effective procedure toward these heterocyclic compounds, using mild reaction conditions. The major drawbacks of the Perkin and Pechmann procedures include the use of excess acetic anhydride, acyl chlorides, high temperatures and strong acids. In addition, many functional groups cannot stand these harsh conditions. Therefore the scope of the synthesis is limited. Moreover, the availability and safety of acyl chlorides is problematic: certain types of acyl chlorides are unstable, are prepared and isolated with difficulty and give products of hydrolysis in basic or acidic conditions.

We have previously reported extensive studies on the use of 1,1-carbonyldiimidazole (CDI) activated α-amino-acids and phenylacetic acids as acylating agents and in that research, the formation of the

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corresponding imidazolyl intermediates was undoubtedly proven by ^{1}H NMR spectroscopy.[20,21] Therefore, in order to circumvent the aforementioned problems concerning the synthesis of coumarin derivatives, we decided to investigate the potential use of CDI activated phenylacetic acids as acylating agents.

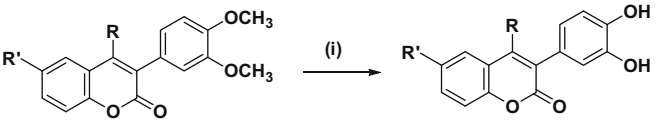
In this work, we found that reaction of a variety of phenylacetic acids with CDI provided sufficient activation and enabled them to smoothly react with 2-hydroxy-acetophenone in the presence of an organic base, DBU, in CH_2Cl_2. The reaction proceeds at room temperature and is completed in 1–2 h (monitoring by TLC is useful). Quenching with aqueous HCl (10%) with vigorous stirring for 10 min, followed by separation of the organic phase and evaporation of the solvent, results to the isolation of the crude product. Purification using flash column chromatography yields the desired coumarin in satisfactory yields (40–60%).[22]

The scope of the reaction was investigated using a variety of substituted phenylacetic acids containing either electron-withdrawing or electron-donating substituents, 2-hydroxy-acetophenone (**1a**), 5-chloro-2-hydroxy-acetophenone (**1b**), 5-bromo-2-hydroxy-acetophenone (**1c**) and 2-hydroxy-benzaldehyde (**2**) (Scheme 1). It is interesting to note that our methodology is applicable even in the case of 5-chloro- and 5-bromo-2-hydroxy-acetophenone, which contain electron-withdrawing substituents.

The presence of a catechol system is well known to improve the antioxidant activity of a compound. Especially in the case of flavonoid analogues as well as in coumarin derivatives, it has been shown that the *ortho*-dihydroxy system forms a resonance stabilized radical which enhances the radical scavenging ability of the compound.[4,10,23] In order to examine the influence of this structural feature on the biological activity of the new coumarin analogues **4** and **5**, the methyl group was removed, using BBr_3 in CH_2Cl_2, providing coumarins **14** and **15**, respectively (Scheme 2).[24]

The structure of all the synthesized coumarin analogues was elucidated using spectroscopic techniques (^{1}H and ^{13}C NMR, ESI/MS).[25]

The in vitro antioxidant activity of the new compounds was evaluated using two antioxidant assays: the radical scavenging ability of the compounds was tested against the 1,1-diphenyl-2-picryl-hydrazyl (DPPH) stable free radical and their ability to inhibit lipid peroxidation induced by the thermal free radical producer 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) was evaluated. Moreover, the ability of the synthesized coumarins to inhibit soybean lipoxygenase was determined. The results are presented in Table 1.



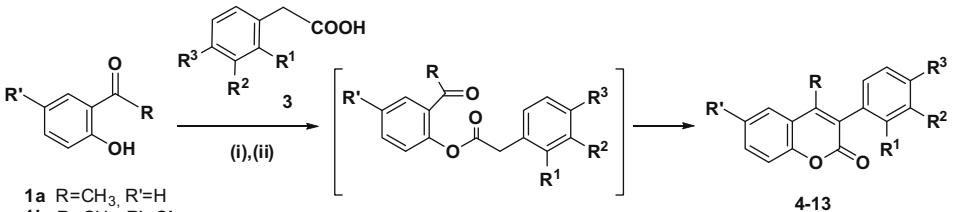
4 R=R'=H
5 R=CH_3, R'=Cl

14 R=R'=H
15 R=CH_3, R'=Cl

Scheme 2. Reagents and conditions: (i) BBr_3, CH_2Cl_2, 0 °C (1 h), rt (3 h).

The scavenging effect of the synthesized compounds on the DPPH radical was evaluated according to the methods of Hadjipavlou-Litina and co-worker.[30] The interaction of the synthesized compounds with the stable free radical DPPH indicates their radical scavenging ability in an iron-free system. The majority of the tested coumarins presented low interaction with the DPPH radical at 50 μM concentration. However, compounds **14** and **15**, which possess the catechol structural feature are potent DPPH radical scavengers, showing high activity comparable to the reference compound NDGA. It is evident that, for this series of compounds, the presence of the catechol system is crucial for this type of activity: the corresponding methoxylated analogues **4** and **5** have very low activity which is remarkably enhanced when the methyl groups are removed (compounds **14** and **15**). In addition, the presence of only one free phenolic hydroxyl group (as in the case of compound **9**), does not favour activity. The observation that the catechol structural feature favours radical scavenging and antioxidant ability of coumarin derivatives is in accordance with previous findings of other research groups studying analogous systems.[10,23]

AAPH induced linoleic acid oxidation is based on the inhibition of lipid peroxidation (LP), and provides a measure of how efficiently antioxidants protect against lipid peroxidation in vitro. Oxidation of exogenous linoleic acid by a thermal free radical producer



1a R=CH_3, R'=H
1b R=CH_3, R'=Cl
1c R=CH_3, R'=Br
2 R=R'=H

4-13

	R	R'	R^1	R^2	R^3
4	H	H	H	OCH_3	OCH_3
5	CH_3	Cl	H	OCH_3	OCH_3
6	CH_3	H	H	OCH_3	OCH_3
7	CH_3	H	H	H	OCH_3
8	CH_3	H	H	H	NO_2
9	CH_3	H	H	H	OH
10	CH_3	H	H	H	Br
11	CH_3	H	OCH_3	H	H
12	CH_3	H	Br	H	H
13	CH_3	Br	H	OCH_3	OCH_3

Scheme 1. Reagents and conditions: (i) CDI, CH_2Cl_2, rt; (ii) DBU, CH_2Cl_2, rt.

Table 1
Interaction % with DPPH, % inhibition of LP induced by AAPH and inhibition of soybean lipoxygenase (LO) at 100 μM for coumarins **4**–**15**

Compound	DPPH (%)		% inhibition of LP induced by AAPH % at 100 μM	% inhibition of LO % at 100 μM
	50 μM			
	20 min	60 min		
4	4	7	47	No
5	4	5	100	12
6	8	10	36	31
7	5	2	24	62
8	5	4	36	No
9	5	9	20	No
10	3	4	70	No
11	3	3	12	No
12	4	3	20	6
13	3	6	90	86
14	85	85	68	9
15	84	83	48	No
NDGA[a]	84	83		40
Trolox			63	

Each in vitro experiment was performed at least in triplicate and the standard deviation of absorbance was less than 10% of the mean.
[a] NDGA—nordihydroguaiaretic acid; No—no activity under the reported experimental conditions.

(AAPH) is followed by UV spectrophotometry in a highly diluted sample.[31]

Amongst the 12 tested coumarins, five exhibited significant LP inhibition, higher than the reference compound trolox. The most efficient LP inhibitor compared to trolox is compound **5**, followed by the coumarins **13**, **10** and **14**. For the compounds which do not have a substituent on the aromatic ring of the benzopyranone moiety, the presence of electron-donating groups on the phenyl ring of position 3 does not favour activity: compounds **6**, **7**, **9**, **11**, which contain methoxy or hydroxy-groups, present low to moderate inhibition potency (12.3–36%). The number and the position of substituents do not significantly increase activity as can be deduced by comparing compounds **6** and **7** as well as **7** and **11**. Substitution of the methoxy-group with bromine dramatically enhances activity as can be seen by comparison of compound **7** with compound **10**. In this case, the position of the substituent plays a major role: a bromine substituent on the *para*-position (compound **10**) gives an active compound (70%) whereas a bromine substituent on the *ortho*-position (compound **12**) leads to a compound with moderate activity (20%). Thus, the lipophilic contribution π of the substituent affects significantly in a positive way the LP inhibition (π value for CH_3O-group = −0.02 whereas π value for Br-group = 0.86). The nature of the electron-withdrawing group is also important, as coumarin derivative **8**, which bears a nitro-group on the *para*-position exhibits only 36% inhibition of LP. The most important structural feature that affects the LP inhibition potency of this series of compounds seems to be the presence of a halogen on the aromatic ring of the benzopyranone fused ring system: compound **6**, without a halogen substituent on the aromatic ring, is a moderate inhibitor (36%) whereas the analogous compounds **5** and **13** (bearing a Cl and a Br substituent, respectively) are very potent inhibitors of LP.

The majority of LO inhibitors are antioxidants or free radical scavengers,[32] since lipoxygenation occurs via a carbon centred radical. LOs contain a 'non-heme' iron per molecule in the enzyme active site as high-spin Fe^{2+} in the native state and the high-spin in the activated state Fe^{3+}. Some studies suggest a relationship between LO inhibition and the ability of the inhibitors to reduce the Fe^{3+} at the active site to the catalytically inactive Fe^{2+}.[33,34]

The synthesized coumarins were tested for their ability to inhibit soybean lipoxygenase using the UV absorbance based enzyme assay.[30] Although the results of this assay cannot be extrapolated to the inhibition of mammalian 5-LO, it has been shown that inhibition of plant LO activity by non-steroidal anti-inflammatory agents is qualitatively similar to the inhibition they cause to the rat mast cell LO. Therefore, the soybean inhibition assay can be used as a simple qualitative assay for such activity. Amongst the tested coumarin analogues, compound **13** (86%) was the most efficient soybean LO inhibitor, as compared to the reference compounds NDGA. This highly active LO inhibitor, may not be a good DPPH radical scavenger but possesses also the best LP inhibitory activity amongst the tested compounds. Moreover, coumarin derivative **7** showed satisfactory LO inhibition (62%), although it is neither a good DPPH scavenger nor a good LP inhibitor.

In conclusion, this study presents the development of an efficient one-step approach towards the synthesis of new coumarin analogues, using commercially available and affordable starting materials which leads to structurally diverse compounds. This new method is straightforward, simple, involves mild reaction conditions easy work-up and isolation procedure of the compounds. The new molecules have been further evaluated for their antioxidant and soybean LO inhibitory activity. The catechol moiety has been identified as the structural requirement for efficient DPPH radical scavenging and lipid peroxidation activity, however it does not favour LO inhibitory ability. The best combined pharmacological profile is exhibited by compound **13**, which is a potent LO inhibitor and efficiently inhibits lipid peroxidation. Synthesis of analogues of **13** in order to perform more detailed structure–activity relationship studies are currently underway.

Acknowledgement

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22. *General procedure for the synthesis of coumarin analogues **4**–**13***: A solution of phenylacetic acid (1 equiv) in CH_2Cl_2 (5 mL) and 1,1-carbonyldiimidazole (CDI) (1.2 equiv) was stirred at room temperature for 30 min. That solution was added dropwise to a mixture of the appropriate 2-hydroxyacetophenone (**1a**, **1b** or **1c**) or 2-hydroxybenzaldehyde (**2**) (1 equiv) in CH_2Cl_2 (5 mL) and DBU (1 equiv). The reaction mixture was stirred for 1–2 h at room temperature. The mixture was acidified with HCl 10%, stirred vigorously for 10 min. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude product. Purification by flash column chromatography (petroleum ether/ethyl acetate 9:1) affords the pure coumarin.
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24. *Demethylation of compounds **4** and **5***: To a stirred solution of the appropriate coumarin (1 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C was added boron tribromide (BBr_3, 1 M solution in hexane) (16 equiv). After 1 h, the resulting mixture was stirred for 3 more hours at room temperature. The yellow mixture was poured into ice water and dissolved in MeOH. The mixture was then extracted with CH_2Cl_2 and the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give the final product.
25. *Structural characterization data for the synthesized compounds:* 3-(3,4-Dimethoxyphenyl)-2H-chromen-2-one (**4**): Yield 59%. Mp 132–136 °C.[26] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 1H), 3.94 (s, 1H), 6.92 (d, J = 8.4 Hz, 1H), 7.36–7.26 (m, 3H), 7.54–7.47 (m, 2H), 7.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 56.0, 111.0, 111.8, 116.3, 119.7, 121.2, 124.4, 127.4, 127.7, 127.8, 131.0, 138.6, 148.7, 149.7, 153.2, 160.6; 6-chloro-3-(3,4-dimethoxyphenyl)-4-methyl-2H-chromen-2-one (**5**): Yield 47%. Mp 179–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.90 (d, J = 11.4 Hz, 6H), 6.82–6.86 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.46–7.50 (m, 1H), 7.63 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 55.9, 111.1, 113.1, 118.2, 122.6, 124.7, 126.4, 128.1, 129.6, 131.1, 146.4, 148.9, 149.2, 151.0, 153.7, 160.5. ESI-HRMS Calcd for $C_{18}H_{16}ClO_4$+H: m/z: 331.0732, found: 331.0720; 3-(3,4-dimethoxyphenyl)-4-methyl-2H-chromen-2-one (**6**): Yield 45%. Mp 156–160 °C.[16] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (dd, $J_{5,6}$ = 8.1 Hz, $J_{5,7}$ = 1.5 Hz, 1H), 7.54 (pseudotriplet, 1H), 7.38–7.29 (m,2H), 6.95 (d, J = 8.1 Hz, 1H), 6.87–6.82 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 55.9, 111.0, 113.1, 116.8, 120.6, 122.6, 124.2, 125.0, 126.8, 127.0, 131.2, 147.7, 148.7, 148.9, 152.6, 161.2; 3-(4-methoxyphenyl)-4-methyl-2H-chromen-2-one (**7**): Yield 44%. Mp 190–193 °C.[14] ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.85 (s, 3H), 6.99 (d, J = 8.4 Hz, 2H), 7.23 (br s, 1H), 7.38–7.29 (m, 3H), 7.53 (pseudotriplet, 1H), 7.67 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCL_3$): δ 16.6, 55.3, 113.9, 116.8, 120.7, 124.2, 125.0, 126.6, 127.0, 131.1, 131.3, 147.3, 152.6, 153.7, 159.4, 161.2; 4-methyl-3-(4-nitrophenyl)-2H-chromen-2-one (**8**): Yield 51%. Mp 200–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.35–7.42 (m, 2H), 7.51 (s, 1H), 7.54 (s, 1H), 7.61 (pseudotriplet, 1H), 7.72 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 8.33 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 117.1, 120.0, 123.6, 124.6, 125.2, 125.3, 131.4, 132.2, 141.3, 147.6, 148.7, 152.8, 153.7, 160.1. ESI-HRMS Calcd for $C_{16}H_{12}NO_4$+H: m/z: 282.0761, found: 282.0758; 3-(4-hydroxyphenyl)-4-methyl-2H-chromen-2-one (**9**): Yield 54%. Mp 243–246 °C.[27] ^{1}H NMR (300 MHz, $CDCl_3$–MeOH): δ 2.29 (s, 3H), 6.86 (dd, J = 6.6 Hz, J = 1.8 Hz, 2H), 7.09 (dd, J = 8.7 Hz, J = 2.1 Hz, 2H), 7.28–7.33 (m, 2H), 7.49 (pseudotriplet, 1H), 7.64 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–MeOH): δ 16.5, 115.3, 116.6, 120.6, 124.2, 125.0, 125.3, 126.9, 131.1, 131.2, 147.7, 152.3, 153.7, 156.7, 161.7; 3-(4-bromophenyl)-4-methyl-2H-chromen-2-one (**10**) Yield 46%. Mp 156–159 °C.[14] ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 7.20 (d, J = 8.4 Hz, 2H), 7.39–7.27 (m, 2H), 7.61–7.54 (m, 3H), 7.69 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 116.9, 120.4, 122.5, 124.4, 125.1, 126.2, 131.6, 131.7, 131.8, 133.3, 147.9, 152.7, 160.6; 3-(2-methoxyphenyl)-4-methyl-2H-chromen-2-one (**11**)[28]: Yield 42%. Mp 160–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.78 (s, 3H), 6.99–7.07 (m, 2H), 7.19 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.29–7.42 (m, 3H), 7.53 (pseudotriplet, 1H), 7.68 (dd, J = 8.1 Hz, J = 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 55.6, 111.2, 116.8, 120.5, 120.6, 123.4, 124.0, 124.3, 124.9, 129.9, 131.0, 131.2, 148.5, 152.8, 157.2, 160.5; 3-(2-bromophenyl)-4-methyl-2H-chromen-2-one (**12**): Yield 43%. Mp 119–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H), 7.44–7.25 (m, 5H), 7.60–7.55 (m, 1H), 7.70 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 117.0, 120.1, 124.3, 125.2, 126.9, 127.7, 129.9, 131.3, 131.7, 132.9, 135.6, 149.1, 152.9, 159.8. ESI-HRMS Calcd for $C_{16}H_{12}{}^{79}BrO_2$+H: m/z: 315.0015, found: 314.9998; 6-bromo-3-(3,4-dimethoxyphenyl)-4-methyl-2H-chromen-2-one (**13**): Yield 44%. Mp 185–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.84 (d, J = 10.2 Hz, 2H), 6.96 (d, J = 8.1 Hz, 1H), 7.24–7.27 (m, 1H), 7.62 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 7.78 (s, 1H); MS (ESI) m/z = 375/377 $[M+H]^+$/$[M+2+H]^+$. ESI-HRMS Calcd for $C_{18}H_{15}{}^{79}BrO_4$+H: m/z: 375.0226, found: 375.0221; 3-(3,4-dihydroxyphenyl)-2H-chromen-2-one (**14**)[29]: Yield 89%. Mp 176–178 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 6.83 (d, J = 8.1 Hz, 1H), 7.09 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.51–7.55 (m, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 116.2, 116.8, 116.9, 121.3, 121.5, 125.7, 127.7, 128.9, 129.2, 132.1, 140.0, 146.0, 147.4, 154.4, 162.6; MS (ESI) m/z = 255 $[M+H]^+$. ESI-HRMS Calcd for $C_{15}H_{10}O_4$+H: m/z: 255.0652, found: 255.0640; 6-chloro-3-(3,4-dihydroxyphenyl)-4-methyl-2H-chromen-2-one (**15**): Yield 88%. Mp 297–299 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 2.34 (s, 3H), 6.62 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 6.74 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.58 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), MS (ESI) m/z = 303/305 $[M+H]^+$/$[M+2+H]^+$. ESI-HRMS Calcd for $C_{16}H_{11}ClO_4$+H: m/z: 303.0419, found: 303.0403.
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