Electrochemically induced tandem Knoevenagel-Michael assembling of aldehydes with kojic acid: direct and efficient arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes formation

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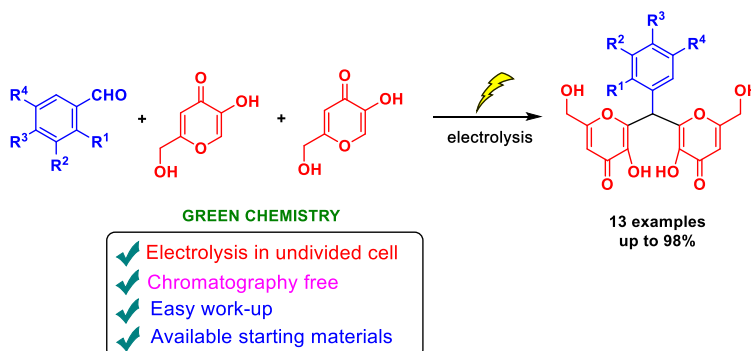**Dedicated to Prof. Jan Bergman on the occasion of his 80th anniversary**

Abstract

The electrochemically induced tandem reaction of aldehydes and two equivalents of kojic acid has been carried out in alcohols in an undivided cell in the presence of sodium halides. It led to the selective formation of substituted arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes in 71-98% yields and with 240-330% current efficiency. This new electrocatalytic process provides green, useful and efficient way to two kojic acid fragments separated by C-aryl-substituted spacer, which are promising compounds for different biomedical applications.

Introduction

Continuously growing interest in convenient and green reaction techniques encourages organic chemists to elaborate new synthetic methodologies.[1]

Tandem reaction is the combination of two or more reactions, which take place in a specific order.[2] These reactions are also one-pot processes and hence, they are very powerful method for the efficient construction of complex organic molecules.[2] These reactions are a part of green chemistry methods, as the stages of isolation and purification of intermediates are omitted, which leads to diminished pollution of the environment. In addition to the intrinsic atom economy and selectivity, the tandem reaction strategy offers significant advantages over conventional linear-type synthesis due to its flexible and convergent nature.[3]

Tandem Knoevenagel–Michael reaction is known in classical organic chemistry,[2] and until now the investigations in this area are under in progress.[4-7]

The main aim of the modern tandem and cascade strategy is to provide high efficiency and operation simplicity accompanying with low waste formation. This new methodology is based on the pot economy principle and unites it with the atom and step economy strategies.[8]

The organic electrochemistry in the last decades became a new useful method with the important synthetic and ecological advantages.[9-12] But, the practical usage of electrochemical procedures is often limited with its technical complexity, and usually long processing times. In the course of our study on the electrochemical transformations of organic compounds, we have found the new type of electrochemical transformation, namely the electrocatalytic chain transformation of organic reagents, induced by the catalytic amount of an electrogenerated base in an undivided cell.[13] We have already successfully applied this electrocatalytic procedure for the synthesis of medicinally relevant 2-amino-4*H*-chromene derivatives.[14-16] This unique electrochemical method utilizes a simple undivided cell and are valuable for the large-scale processes, because of their catalytic nature and the use of a cheap and environmentally responsible chemical reagent — electricity. The employment of this electrocatalytic methodology for the initiation of base-activated cascade reactions is very promising, because it provides the combination of the synthetic virtues of the important cascade strategy with the ecological benefits and convenience of the electrocatalytic procedure.[17, 18]

In the course of our studies on the tandem, cascade and multicomponent electrochemical transformations of organic compounds[19-23] we have found a new type of the electrocatalytic process carrying out in undivided cell and have already successfully applied it for some types of the electrochemicaly induced tandem Knoevenagel-Michael reactions of carbonyl compounds and C-H acids[24-26].

The creation of easy and convenient methodology for the selective assembly of biologically active scaffolds in the electrocatalytic multicomponent processes becomes one of the principal goals of the modern electroorganic and green chemistry.[27-29]

Among the different strategies of the drug discovery search, the identification and use of "privileged structures" or scaffolds gained a special attention in the last decades.[30] Usually, these privileged scaffolds are constructed from heterocyclic ring with specially determined positions of functional groups for target recognition of specified biological receptors.[31]

Heterocycles are the key structural compounds in medicinal chemistry.[32] They are found in many biologically important molecules such as enzyme, vitamins, natural products and pharmacologically active compounds with antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, anti-allergic, anti-HIV, and anticancer activity.[33]

Among the oxygen containing heterocycles, kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one) represents a type of a privileged medicinal scaffold.[34] Usually, these privileged scaffolds are constructed from

heterocyclic ring with specially determined positions of functional groups for target recognition of specified biological receptors.[35] Kojic acid is a known fungal metabolite, which is widely applies in different areas. It was extracted from *Aspergillus oryzae*, nearly one century ago.[36] Kojic acid is often used for averting an enzymatic browning in food production and as skin-lightening agent in the cosmetic field.[37] It showed the potential inhibition of cellular NF-κB activity in human keratinocytes; NF-κB activation is also involved in kojic acid induced anti-melanogenic effect.[38] It has been also found that kojic acid derivatives show antibacterial,[39] anti-inflammatory,[40] antiviral,[41] anti-HIV[42] and antitumor activity[43] as well as inhibitors of oxidases,[44] and tyrosinases.[45]

The introduction of two pharmacology active fragments of kojic acid medicinally privileged scaffold in one molecule, separated by C-aryl-substituted spacer could enhance their pharmacology activity.

We have already implemented some electrochemically induced multicomponent transformations of carbonyl compounds and different C-H acids.[46, 47]

In continuation of our study we report now the data on the new selective and efficient electrocatalytic multicomponent assembling of aldehydes, and two equivalents of kojic acid into arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes (Scheme 1).
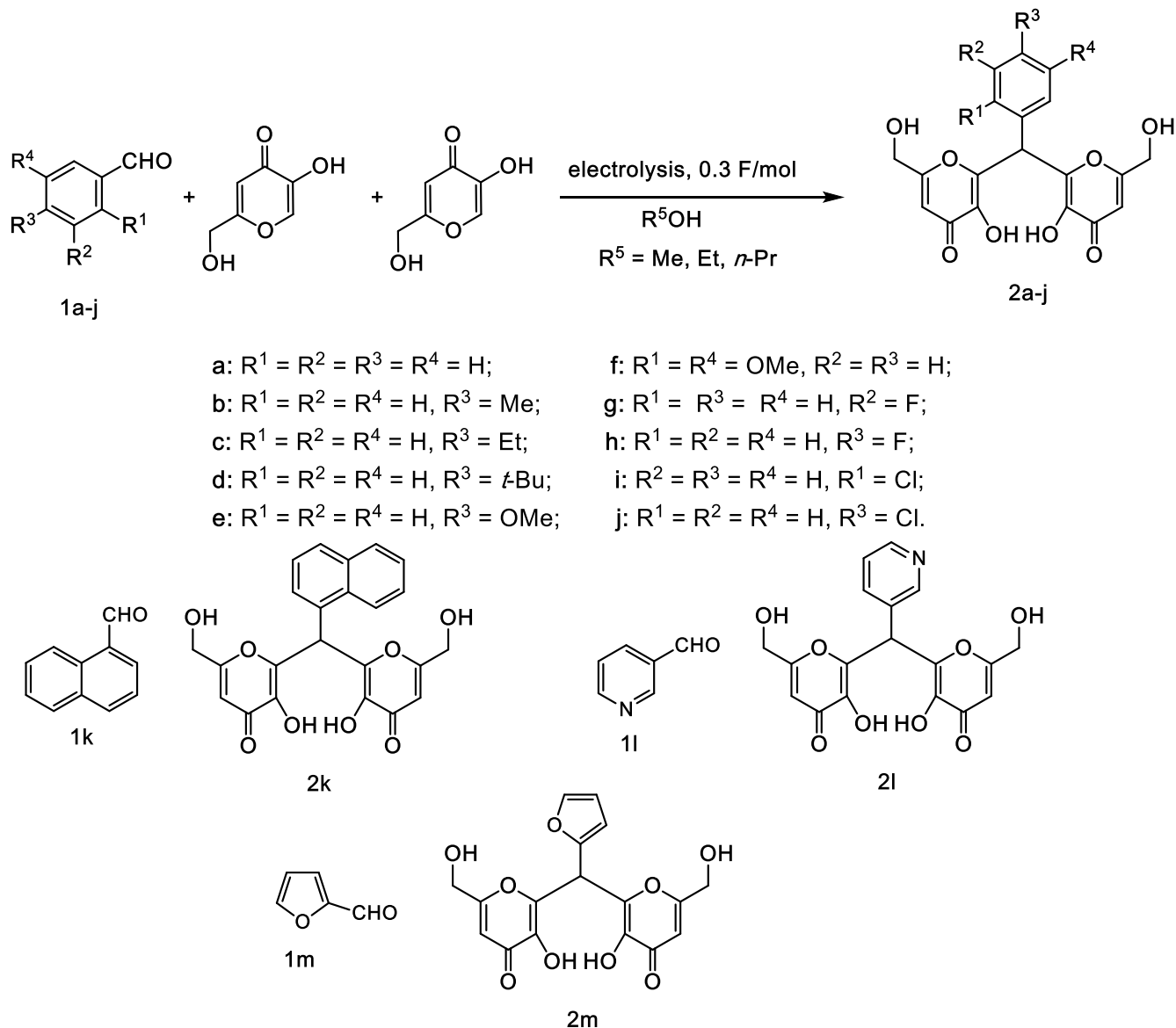
Results and Discussion

Electrocatalytic and electrochemically induced cascade reactions are one of the most useful approaches to 'ideal synthesis'.[48, 49]

Our present study is dealing with the facile and selective electrochemically induced cascade assembling of aldehydes **1a-m** and two equivalents of kojic acid into arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes **2a-m** in alcohols in an undivided cell (Scheme 1, Tables 1, 2).

In the first part of our study, to evaluate the synthetic utility of the electrocatalytic procedure and to investigate the electrolysis conditions, the electrochemically induced cascade assembling of benzaldehyde **1a** with two equivalents of kojic acid was carefully studied under conditions of electrolysis in alcohols in an undivided cell (Table 1).

To start this electrochemical research, the electrochemically induced multicomponent reaction of benzaldehyde **1a**, and two equivalents of kojic acid in methanol in an undivided cell under constant current conditions was studied (Table 1, entries 1, 2). In this case, when 0.1 F/mol of electricity was passed the best yield of 2,2'-[(phenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] **2a** - 43% - was obtained under conditions with heating up to 63 °C. Under the similar conditions in ethanol and *n*-propanol, **2a** was received in 49 and 54% yields (entries 3 and 4, Table 1). As it was found in subsequent experiments, the current density 5 mA/cm^2 (*I* = 25 mA, electrodes surface 5 cm^2) in an undivided cell, sodium bromide as electrolyte, *n*-propanol as solvent, the temperature near to the boiling point of *n*-propanol and 0.3 F/mol of electricity passed, were the optimal conditions for this electrocatalytic chain process of the multicomponent assembling benzaldehyde **1a,** and two equivalents of kojic acid. Under these conditions, **2a** was obtained with the highest substance yield 93% and the current efficiency 310% (Table 1, entry 7). An increase in the current density up to 10 mA/cm^2 (*I* = 50 mA) resulted in the decrease of both the substance and the current reaction yields (entry 9, Table 1). A decrease of the current density to 2 mA/cm^2 (*I* = 10 mA) also led to the decrease of both the current and the substance reaction yields (entry 10, Table 1), more likely due to the insufficient initiation of the electrochemically induced chain reaction in the last case. Thus, the current density 5 mA/cm^2 (*I* = 25 mA, electrodes surface 5 cm^2) in an undivided cell, sodium bromide as electrolyte, *n*-propanol as

solvent, the temperature near to the boiling point of *n*-propanol and 0.3 F/mol of electricity passed, were the optimal conditions for the electrochemically induced chain process of the multicomponent assembling benzaldehyde **1a,** and two equivalents of kojic acid. Under these conditions, 2,2'-[(phenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] **2a** was obtained with the highest substance yield 93% and the current efficiency 310% (Table 1, entry 7).

a: $R^1 = R^2 = R^3 = R^4 = H$;　　　　f: $R^1 = R^4 = OMe$, $R^2 = R^3 = H$;
b: $R^1 = R^2 = R^4 = H$, $R^3 = Me$;　　g: $R^1 = R^3 = R^4 = H$, $R^2 = F$;
c: $R^1 = R^2 = R^4 = H$, $R^3 = Et$;　　h: $R^1 = R^2 = R^4 = H$, $R^3 = F$;
d: $R^1 = R^2 = R^4 = H$, $R^3 = t\text{-}Bu$;　　i: $R^2 = R^3 = R^4 = H$, $R^1 = Cl$;
e: $R^1 = R^2 = R^4 = H$, $R^3 = OMe$;　　j: $R^1 = R^2 = R^4 = H$, $R^3 = Cl$.

Scheme 1. Electrocatalytic assembling of aldehydes with two equivalents of kojic acid.

Under the optimal conditions of the electrolysis, aldehydes **1a–m** and two equivalents of kojic acid in an undivided cell in *n*-propanol were transformed into the arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes **2a-m** in 71-98% yields (current efficiency 237-327%) (Table 2).

In all these electrochemically induced processes, after the electrolysis was finished, the reaction mixture was concentrated to one fifth of its initial volume and cooled to 0° C (*ca.* 4 mL) to crystallize the solid product, which was then filtered out, twice rinsed with an ice-cold ethanol/water solution (4:1, 4 mL), and dried under reduced pressure.

Table 1. Electrocatalytic assembling of benzaldehyde **1a** and two equivalents of kojic acid [a]

Entry	Solvent	Temp, °C	I (mA)	Current density, (mA/cm²)	Time, (min)	Electricity passed (F/mol)	Yield of 2a (%) [a]
1	MeOH	25	25	5	32	0.1	17 [b] (170)
2	MeOH	63	25	5	32	0.1	43 (430)
3	EtOH	78	25	5	32	0.1	49 (490)
4	*n*-PrOH	97	25	5	32	0.1	54 (540)
5	EtOH	78	25	5	64	0.2	63 (315)
6	*n*-PrOH	97	25	5	64	0.2	72 (360)
7	*n*-PrOH	97	25	5	96	0.3	93 (310)
8	*n*-PrOH	97	50	5	128	0.4	88 (220)
9	*n*-PrOH	97	50	10	48	0.3	78 (260)
10	*n*-PrOH	97	10	2	240	0.3	84 (280)
11 [c]	*n*-PrOH	97	25	5	96	0.3	82 (273)
12 [d]	*n*-PrOH	97	25	5	96	0.3	85 (283)

Reaction conditions: Benzaldehyde **1a** (5 mmol), kojic acid (10 mmol), NaBr (1 mmol), alcohol (20 mL), iron cathode (5 cm²), graphite anode (5 cm²), undivided cell.
[a] Yield of isolated **2a** (in parentheses, current efficiency, %). [b] ^{1}H NMR data. [c] NaI as electrolyte. [d] KBr as electrolyte.

The structure of all new compounds **2c,d,f-m** was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy as well as mass spectrometry and high-resolution mass spectrometry data.
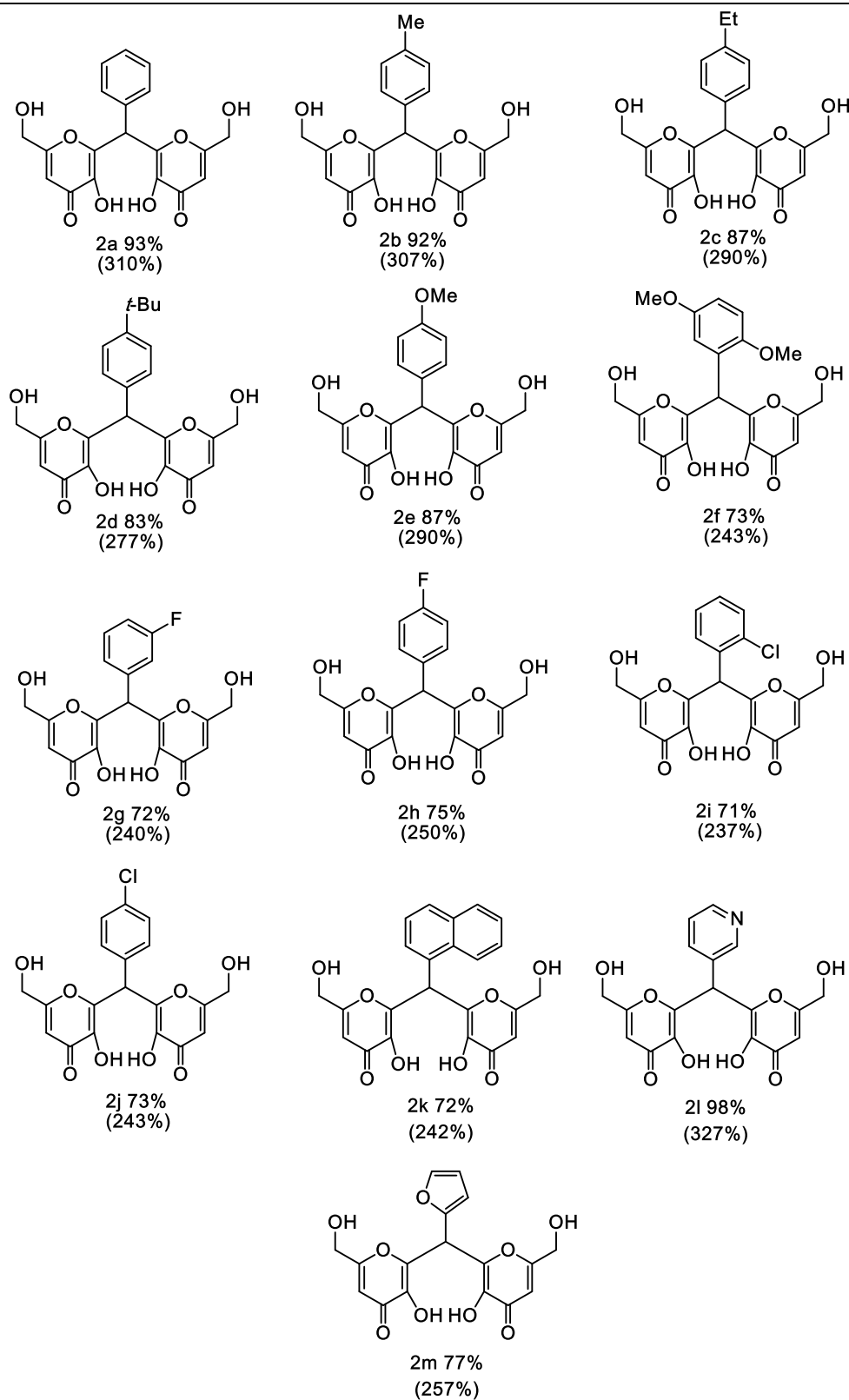
Earlier **2a**, **2b**, **2j** were obtained in 80-88% yields by the reaction of 3 equivalents of aldehydes **1a**, **1b**, **1e** (three fold excess of aldehyde) with 2 equivalents of kojic acid in water-methanol mixture in the presence of 1 equivalent of Na_2CO_3 as catalyst under microwave irradiation with 400 W power at 70 °C.[50]

With the above mentioned results and taking into consideration the mechanistic data on tandem Knoevenagel-Michael reaction,[51] the following mechanism for the electrocatalytic assembling aldehydes **1a-m** with two equivalents of kojic acid with the formation of arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes **2a-m** was proposed (Scheme 2).

The first step of this electrochemically induced process is the deprotonation of propanol at the cathode, which leads to the formation of an alkoxide anion. Then, interaction of the alkoxide anion with kojic acid results in the kojic acid anion **A** formation (Scheme 2).

The following process in the solution is reaction of the kojic acid anion **A** and benzaldehyde **1** with the elimination of a hydroxide anion and formation of Knoevenagel adduct **3**.[52]

The hydroxide-anion promoted Michael addition of the next molecule of kojic acid to the electron deficient Knoevenagel adduct **3** affords the end product of the electrocatalytic chain process, **2** with the regeneration of the alkoxide anion as the last step of the catalytic cycle. Thus, the catalytic chain process continues by the interaction of the alkoxide anion with the next molecule of the kojic acid (Scheme 2).

Table 2. Electrocatalytic assembling of aldehydes **1 a-m** and two equivalents of kojic acid [a]

2a 93%
(310%)

2b 92%
(307%)

2c 87%
(290%)

2d 83%
(277%)

2e 87%
(290%)

2f 73%
(243%)

2g 72%
(240%)

2h 75%
(250%)

2i 71%
(237%)

2j 73%
(243%)

2k 72%
(242%)

2l 98%
(327%)

2m 77%
(257%)

Reaction conditions: Aldehydes **1a-k** (5 mmol), kojic acid (10 mmol), NaBr (1 mmol), *n*-propanol (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), undivided cell, 97° C, 0.3 F/mol of electricity passed.

[a] Yields of isolated **2a-m** (in parentheses, current efficiency).
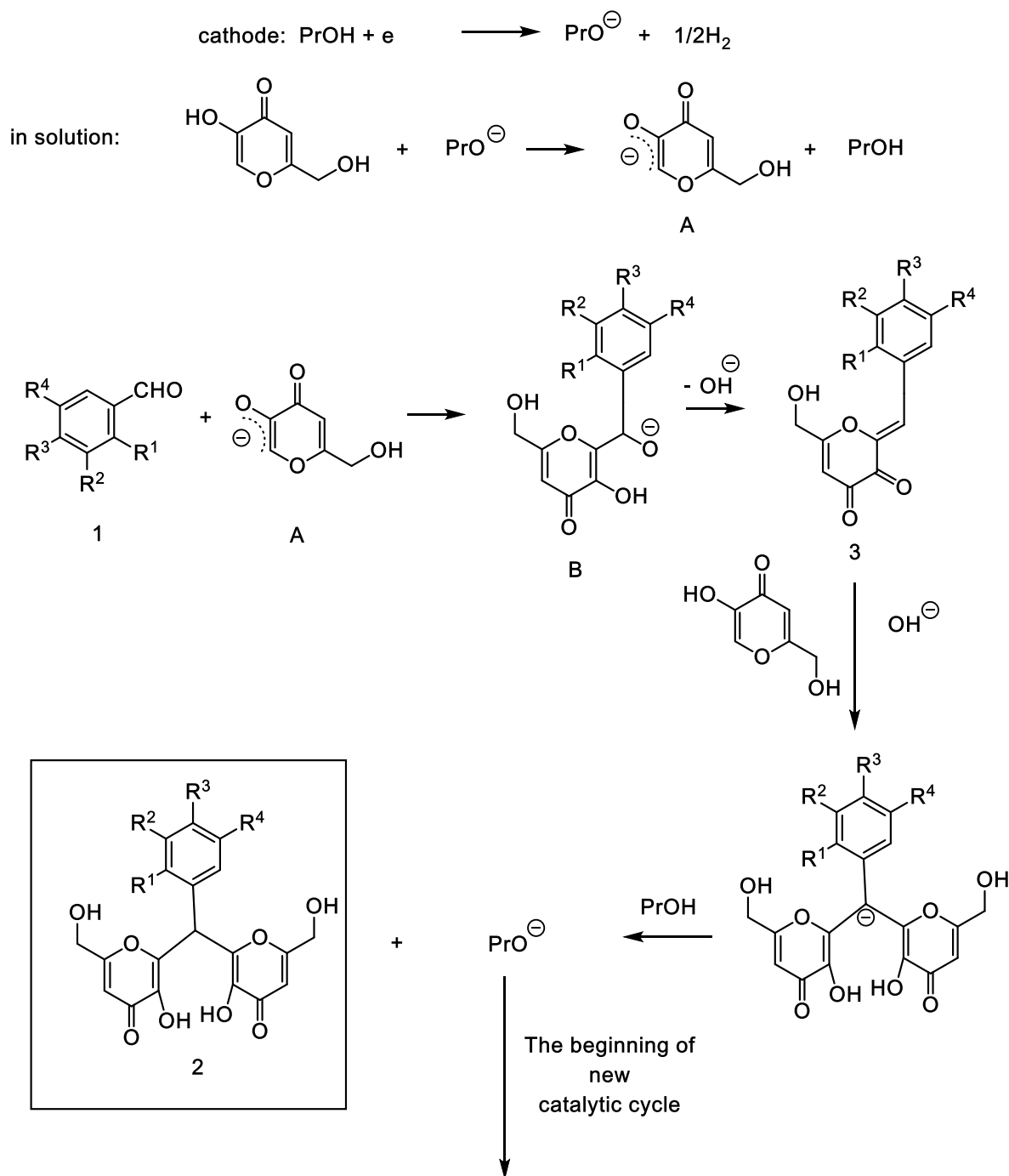
Scheme 2. The mechanism of electrocatalytic transformation of aldehydes with two equivalents of kojic acid.

Conclusions

The new electrochemically induced fast and highly efficient assembling of aldehydes **1a-m** with two equivalents of kojic acid in alcohols in the undivided cell results in the formation of the arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes **2a-m** in high 71-98% yields and with current efficiency 237-327%.

This new one-pot electrochemically induced tandem Knoevenagel-Michael process is simple and efficient way to the arylbis[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methanes containing two kojic acid fragments separated by C-aryl-substituted spacer, which are promising compounds for different biomedical applications, among them anticonvulsant, anti-AIDS agents and anti-inflammatory remedies.

This electrocatalytic efficient procedure utilizes simple equipment, an undivided cell; available starting compounds, it is easily carried out and the isolation procedure is not complicated. Thus, this new method is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes.

Experimental Section

General. All melting points were measured with a Gallenkamp melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with Bruker Avance II 300 spectrometer at ambient temperature. Chemical shift values are relative to Me$_4$Si. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra (EI = 70 eV) were obtained directly with a Kratos MS-30 spectrometer. High-resolution mass spectra (HRMS) (electrospray ionization, ESI) were measured on a BrukermicroTOF II instrument.

General procedure. A solution of aldehyde **1** (5 mmol), kojic acid (1.42 g, 10 mmol), and sodium bromide (0.1 g, 1 mmol) in *n*-propanol (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 97 °C under a constant current density of 5 mA/cm^2 (I = 25 mA, electrodes square 5 cm^2) until the catalytic quantity of 0.3 F/mol of electricity was passed. After the electrolysis was finished, the reaction mixture was concentrated to one fifth of its initial volume (*ca.* 4 mL) and cooled to 0° C to crystallize the solid compound **2**, which was then filtered out, twice rinsed with an ice-cold ethanol/water solution (4:1, 4 mL), and dried under reduced pressure.

2,2'-[(Phenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2a). White powder; yield 1.73 g, (93%); mp: 243–245 °C (decomp.), lit.[52] mp: 244–245.3 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.24 (d, ^2J 16.3 Hz, 2H, CH$_2$), 4.29 (d, ^2J 16.3 Hz, 2H, CH$_2$), 5.63 (br s, 2H, 2 OH), 6.07 (s, 1H, CH), 6.34 (s, 2H, 2 CH), 7.29-7.39 (m, 5H, Ph), 9.33 (br s, 2H, 2 OH) ppm.

2,2'-[(4-Methylphenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2b). Yellowish powder; yield 1.78 g, (92%); mp: 222–223 °C, lit.[52] mp: 223–223.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH$_3$), 4.22 (d, ^2J 16.2 Hz, 2H, CH$_2$), 4.28 (d, ^2J 16.2 Hz, 2H, CH$_2$), 5.29-5.90 (br s, 2H, 2 OH, exchange with D$_2$O), 6.01 (s, 1H, CH), 6.33 (s, 2H, 2 CH), 7.15 (d, ^3J 9.0 Hz, 2H, 2 CH Ar), 7.18 (d, ^3J 9.0 Hz, 2H, 2 CH Ar), 9.06-9.47 (br s, 2H, 2 OH) ppm.

2,2'-[(4-Ethylphenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2c). Yellowish powder; yield 1.74 g, (87%); mp: 190-191 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (t, ^3J 7.6 Hz, 3H, CH$_3$), 2.56 (q, ^3J 7.6 Hz, 2H, CH$_2$), 4.23 (d, ^2J 16.2 Hz, 2H, CH$_2$), 4.28 (d, ^2J 16.2 Hz, 2H, CH$_2$), 6.00 (s, 1H, CH), 6.32 (s, 2H, 2 CH), 7.18 (d, ^3J 8.6 Hz, 2H, 2 CH Ar), 7.21 (d, ^3J 8.6 Hz, 2H, 2 CH Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.5, 27.8, 40.6, 59.5 (2C), 109.1, 110.0, 128.3 (4C), 133.6 (2C), 139.3, 142.3, 143.1, 147.0, 167.6, 168.2, 173.7, 174.0 ppm; IR (KBr): v 3272, 3190, 2927, 1656, 1620, 1578, 1448, 1223, 1082, 764 cm^{-1}; MS (*m/z*, relative intensity %): 400 [M$^+$] (14), 258 (100), 243 (13), 159 (33), 142 (99), 113 (28), 69 (34), 29 (24). MS (ESI): *m/z* 401.1242[M + H]$^+$, calcd for C$_{21}$H$_{20}$O$_8$: 401.1236 [M + H]$^+$.

2,2'-[(4-*Tert*-butylphenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2d). Pale gray powder; yield 1.78 g, (83%); mp: 211-212 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (s, 9H, 3 CH$_3$), 4.24 (d, ^2J

16.4 Hz, 2H, CH$_2$), 4.29 (d, ^2J 16.4 Hz, 2H, CH$_2$), 6.01 (s, 1H, CH), 6.32 (s, 2H, 2 CH), 7.24 (d, ^3J 8.3 Hz, 2H, 2 CH Ar), 7.36 (d, ^3J 8.3 Hz, 2H, 2 CH Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.1 (3C), 34.3, 40.3, 59.6 (2C), 109.1, 110.0, 125.7 (2C), 128.1 (2C), 133.4 (2C), 139.4, 142.2, 147.0, 150.0, 167.7 (2C), 173.7 (2C) ppm; IR (KBr): v 3305, 3092, 2961, 1626, 1572, 1445, 1315, 1222, 1076, 763 cm^{-1}; MS (*m/z*, relative intensity %): 428 [M$^+$] (16), 369 (1), 286 (100), 271 (71), 230 (9), 187 (1), 142 (64), 113 (16), 57 (25), 29 (19). MS (ESI): *m/z* 429.1551 [M + H]$^+$, calcd for C$_{23}$H$_{24}$O$_8$: 429.1549 [M + H]$^+$.

2,2'-[(4-Methoxyphenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2e). Yellowish powder; yield 1.75 g, (87%); mp: 235–237 °C, lit.[52] mp: 235.8–236.7 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.73 (s, 3H, OCH$_3$), 4.17-4.36 (m, 4H, 2 CH$_2$), 5.62 (t, ^3J 5.8 Hz, 2H, 2 OH), 6.00 (s, 1H, CH), 6.32 (s, 2H, 2 CH), 6.91 (d, ^3J 8.5 Hz, 2H, 2 CH Ar), 7.23 (d, ^3J 8.5 Hz, 2H, 2 CH Ar), 9.28 (s, 2H, 2 OH) ppm.

2,2'-[(2,5-Dimethoxyphenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2f). Yellowish powder; yield 1.58 g, (73%); mp: 221-222 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.67 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 4.18 (d, ^2J 16.1 Hz, 2H, CH$_2$), 4.23 (d, ^2J 16.1 Hz, 2H, CH$_2$), 6.23 (s, 1H, CH), 6.31 (s, 2H, 2 CH), 6.76 (d, ^4J 2.2 Hz, 1H, CH Ar), 6.85 (dd, ^3J 8.9 Hz, ^4J 2.2 Hz, 1H, CH Ar), 6.94 (d, ^3J 8.9 Hz, 1H, CH Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.2, 55.4, 56.6, 59.5 (2C), 109.2 (2C), 112.5, 112.8, 116.0, 125.4, 142.5, 147.0 (2C), 151.0, 153.1 (2C), 167.3 (2C), 173.9 (2C) ppm; IR (KBr): v 3283, 3169, 2834, 1617, 1575, 1500, 1452, 1232, 1040, 762 cm^{-1}; MS (*m/z*, relative intensity %): 432 [M$^+$] (32), 401 (2), 292 (60), 290 (100), 259 (25), 191 (24), 142 (98), 137 (34), 69 (41), 29 (51). MS (ESI): *m/z* 433.1131 [M + H]$^+$, calcd for C$_{21}$H$_{20}$O$_{10}$: 433.1135 [M + H]$^+$.

2,2'-[(3-Fluorophenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2g). Yellowish powder; yield 1.41 g, (72%); mp: 241-242 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.23 (d, ^2J 15.7 Hz, 2H, CH$_2$), 4.29 (d, ^2J 15.7 Hz, 2H, CH$_2$), 5.62 (br s, 2H, 2 OH), 6.07 (s, 1H, CH), 6.34 (s, 2H, 2 CH), 7.07-7.22 (m, 3H, 3 CH Ar), 7.35-7.47 (m, 1H, CH Ar), 9.40 (br s, 2H, 2 OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 40.7, 59.5 (2C), 109.2 (2C), 114.7 (d, $^2J_{C-F}$ 22 Hz), 115.2 (d, $^2J_{C-F}$ 22 Hz), 124.6 (d, $^4J_{C-F}$ 2 Hz), 130.9 (d, $^3J_{C-F}$ 8 Hz), 138.9 (d, $^3J_{C-F}$ 8 Hz), 142.4 (2C), 146.2 (2C), 162.3 (d, $^1J_{C-F}$ 224 Hz), 167.8 (2C), 173.6 (2C) ppm; IR (KBr): v 3412, 3225, 2941, 1624, 1582, 1449, 1234, 1208, 1084, 769 cm^{-1}; MS (*m/z*, relative intensity %): 390 [M$^+$] (100), 372 (7), 331 (48), 303 (33), 261 (46), 250 (36), 142 (26), 109 (7), 69 (58), 29 (48). MS (ESI): *m/z* 391.0822 [M + H]$^+$, calcd for C$_{19}$H$_{15}$FO$_8$: 391.0824[M + H]$^+$.

2,2'-[(4-Fluorophenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2h). Yellowish powder; yield 1.46 g, (75%); mp: 230-231 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.23 (d, ^2J 15.8 Hz, 2H, CH$_2$), 4.28 (d, ^2J 15.8 Hz, 2H, CH$_2$), 5.94 (s, 1H, CH), 6.29 (s, 2H, 2 CH), 7.16 (dd, ^3J 8.7 Hz, $^3J_{H-F}$ 9.9 Hz, 2H, 2 CH Ar), 7.35 (dd, ^3J 8.7 Hz, $^4J_{H-F}$ 5.1 Hz, 2H, 2 CH Ar), 8.10-9.25 (br s, 2H, 2 OH, exchange with D$_2$O) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.1, 59.5 (2C), 109.2 (2C), 115.6 (d, $^2J_{C-F}$ 21 Hz, 2C), 130.4 (d, $^3J_{C-F}$ 8 Hz, 2C), 132.6 (d, $^4J_{C-F}$ 2 Hz), 139.4, 143.1, 146.9 (2C), 161.5 (d, $^1J_{C-F}$ 224 Hz), 167.3 (2C), 174.3 (2C) ppm; IR (KBr): v 3308, 2902, 1625, 1572, 1512, 1450, 1331, 1222, 1095, 767 cm^{-1}; MS (*m/z*, relative intensity %): 390 [M$^+$] (2), 261 (2), 248 (34), 191 (1), 149 (44), 142 (16), 109 (71), 69 (40), 29 (100), 18 (50). MS (ESI): *m/z* 391.0825 [M + H]$^+$, calcd for C$_{19}$H$_{15}$FO$_8$: 391.0824[M + H]$^+$.

2,2'-[(2-Chlorophenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2i). Yellowish powder; yield 1.44 g, (71%); mp: 259-260 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.18 (d, ^2J 16.0 Hz, 2H, CH$_2$), 4.23 (d, ^2J 16.0 Hz, 2H, CH$_2$), 5.61 (br s, 2H, 2 OH), 6.30 (s, 1H, CH), 6.32 (s, 2H, 2 CH), 7.30-7.41 (m, 3H, 3 CH Ar), 7.44-7.52 (m, 1H, CH Ar), 9.35 (br s, 2H, 2 OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.4, 59.4 (2C), 109.2 (2C), 127.7, 129.6 (2C), 130.4, 132.9, 134.0 (2C), 142.5, 145.7 (2C), 167.7 (2C), 173.6 (2C) ppm; IR (KBr): v 3244, 2964, 1626, 1575, 1445, 1314, 1214, 1090, 977, 752 cm^{-1}; MS (*m/z*, relative intensity %): 408 [M$^+$] (^{37}Cl, 1), 406 [M$^+$] (^{35}Cl, 8), 319 (4), 279 (^{37}Cl, 10), 277 (^{35}Cl, 21), 231 (^{37}Cl, 44), 229 (^{35}Cl, 68), 201 (8), 142 (14), 101 (26), 69

(75), 55 (100), 29 (53). MS (ESI): *m/z* 409.0506 (^{37}Cl), 407.0532 (^{35}Cl) [M + H]$^+$, calcd for $C_{19}H_{15}ClO_8$: 409.0501 (^{37}Cl), 407.0528 (^{35}Cl) [M + H]$^+$.

2,2'-[(4-Chlorophenyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2j). Yellowish powder; yield 1.48 g, (73%); mp: 242-243 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.23 (d, ^2J 14.8 Hz, 2H, CH$_2$), 4.28 (d, ^2J 14.8 Hz, 2H, CH$_2$), 5.96 (s, 1H, CH), 6.31 (s, 2H, 2 CH), 7.32 (d, ^3J 8.4 Hz, 2H, 2 CH Ar), 7.40 (d, ^3J 8.4 Hz, 2H, 2 CH Ar), 8.07-9.49 (br s, 2H, 2 OH, exchange with D$_2$O) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.8, 59.5 (2C), 109.2 (2C), 128.7 (2C), 130.3 (2C), 132.2 (2C), 135.4, 143.5, 146.7 (2C), 167.2 (2C), 174.5 (2C) ppm; IR (KBr): ν 3330, 3086, 2939, 1620, 1572, 1451, 1332, 1214, 1093, 768 cm^{-1}; MS (*m/z*, relative intensity %): 268 [M - C$_6$H$_5$O$_4$ + H]$^+$ (^{37}Cl, 2), 266 [M - C$_6$H$_5$O$_4$ + H]$^+$ (^{35}Cl, 8), 167 (^{37}Cl, 4), 165 (^{35}Cl, 15),142 (7), 127 (^{37}Cl, 3), 125 (^{35}Cl, 5), 115 (^{37}Cl, 2), 113 (^{35}Cl, 6), 101 (6), 69 (43), 55 (29), 29 (100). MS (ESI): *m/z* 409.0509 (^{37}Cl), 407.0535 (^{35}Cl) [M + H]$^+$, calcd for $C_{19}H_{15}ClO_8$: 409.0501 (^{37}Cl), 407.0528 (^{35}Cl) [M + H]$^+$.

2,2'-[(Pyridin-3-yl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2k). Orange powder; yield 1.96 g, (98%); mp: 157-158 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.18-4.36 (m, 4H, 2 CH$_2$), 6.04 (s, 1H, CH), 6.33 (s, 2H, 2 CH), 7.40 (t, ^3J 7.7 Hz, 1H, CH Ar), 7.79 (d, ^3J 7.7 Hz, 1H, CH Ar), 8.43-8.63 (m, 2H, 2 CH Ar), 8.69-10.14 (br s, 2H, 2 OH, exchange with D$_2$O) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.8, 59.4 (2C), 79.2, 109.2 (2C), 124.0, 132.2, 136.3, 142.4, 145.9, 148.8, 149.2 (2C), 167.7 (2C), 173.6 (2C) ppm; IR (KBr): ν 3425, 3234, 1664, 1631, 1617, 1566, 1448, 1226, 1081, 756 cm^{-1}; MS (ESI): *m/z* 374.0871 [M + H]$^+$, calcd for $C_{18}H_{15}NO_8$: 374.0876 [M + H]$^+$.

2,2'-[(1-Naphthyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2l). Yellowish powder; yield 1.52 g, (72%); mp: 262-263 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.17 (d, ^2J 15.5 Hz, 2H, CH$_2$), 4.25 (d, ^2J 15.5 Hz, 2H, CH$_2$), 5.10-6.18 (br s, 2H, 2 OH), 6.33 (s, 2H, 2 CH), 6.71 (s, 1H, CH), 7.38-7.67 (m, 4H, 4 CH Ar), 7.84-8.12 (m, 3H, 3 CH Ar), 9.49 (br s, 2H, 2 OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.8, 59.5 (2C), 109.2 (2C), 122.2, 125.8, 126.1, 126.3, 127.0, 128.4, 129.1, 130.9, 132.7, 133.5, 139.3, 142.1, 146.9 (2C), 167.8 (2C), 173.6 (2C) ppm; IR (KBr): ν 3454, 3246, 1653, 1632, 1595, 1444, 1245, 1217, 1075, 780 cm^{-1}; MS (ESI): *m/z* 423.1083 [M + H]$^+$, calcd for $C_{23}H_{18}O_8$: 423.1080 [M + H]$^+$.

2,2'-[(2-Furyl)methylene]bis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one] (2m). Pale brown powder; yield 1.39 g, (77%); mp: 210-211 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.19-4,33 (m, 4H, 2 CH$_2$), 4.94-5.92 (br s, 2H, 2 OH, exchange with D$_2$O), 6.11 (s, 2H, 2 CH), 6.28-6.39 (m, 3H, 2 CH + CH Ar), 6.45 (t, ^3J 2.4 Hz, 1H, CH Ar), 7.62 (d, ^3J 2.4 Hz, 1H, CH Ar), 9.14-9.78 (br s, 2H, 2 OH, exchange with D$_2$O) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.5, 59.5 (2C), 108.6, 109.2 (2C), 109.9, 110.9, 139.3, 142.2, 142.9, 144.7, 148.4, 167.9 (2C), 173.6 (2C) ppm; IR (KBr): ν 3364, 3231, 2924, 1647, 1617, 1577, 1450, 1228, 1039, 749 cm^{-1}; MS (ESI): *m/z* 363.0712 [M + H]$^+$, calcd for $C_{17}H_{14}O_9$: 363.0716 [M + H]$^+$.

Acknowledgements

Supplementary Material

^{1}H and ^{13}C NMR spectra of all new compounds **2c,d,f-m** are given in the Supplementary Material associated with this paper.

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