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NATURAL TETRAHYDROCURCUMIN IN MULTI-COMPONENT SYNTHESIS OF 1,4-DIHYDROPYRIDINE DERIVATIVES

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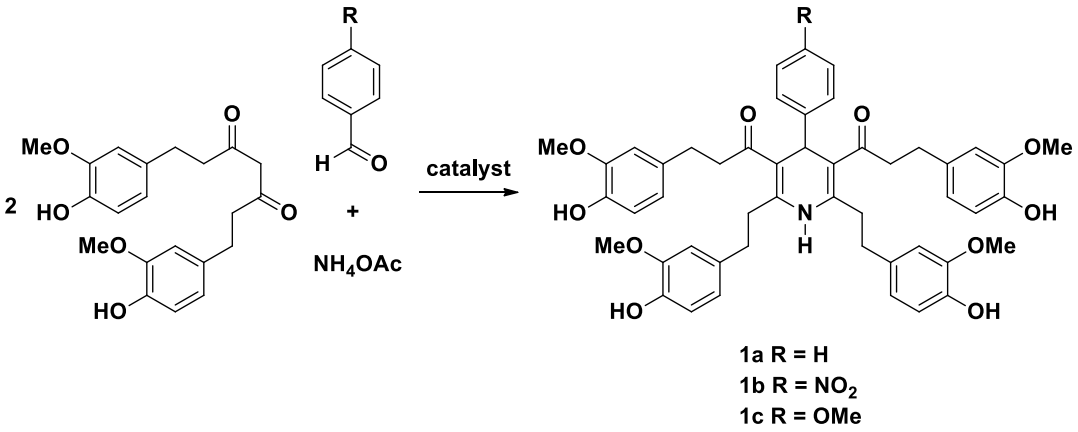
Abstract – The mild condition synthesis of tetrahydrocurcumin- (THC-) dihydropyridine (DHP) was achieved by using the multi-component Hantzsch reaction in the presence of the catalytic amount of *p*-toluenesulfonic acid and 4 Å molecular sieves as a dehydrating agent. The successfully isolated intermediate, enaminone-THC, was the key component to reveal the reaction mechanism of this modified Hantzsch reaction. Due to containing the phenolic diarylheptanoid moiety, these novel heterocycles, THC-DHPs, are expected to exhibit interesting therapeutic properties.

The natural product curcumin, the principal curcuminoid component isolated from the rhizome of Tumeric, *Curcuma longa* L. (Zingiberaceae), exhibits diverse pharmacological effects including anti-inflammatory, antioxidant, anticancer, and anti-HIV activities.[1-5] However, the use of curcumin is not usually as effective as a conventional commercial medicine. To bring the curcumin unit, a diarylheptanoid, into the potential drug structure presents a challenge, but one that would lead to the great benefit. Knowledge of the curcumin structure has been used to design a variety of bioactive analogues.[6] The modification of natural curcumin, in order to build curcumin analogues with expectation of finding new and improved biological properties, has been widely reported.[7-12] The 1,3-dicarbonyl functionality is one of the reasons why synthetic chemists increased their attentions towards curcumin. The utilization of a diketone unit in the skeleton of curcumin in multi-component reactions has always been the focus of our interest.

Tetrahydrocurcumin (THC), derived from the hydrogenation of curcumin, is one of the major metabolites of curcumin with many bioactivities. Literature searching revealed that there are not many reports pertaining to THC analogues.[13] We have recently reported the related multi-component synthesis of dihydropyrimidinones (DHPMs) using THC as the 1,3-dicarbonyl component.[14] The THC precursor was deliberately used as the replacement of curcumin, as the conjugate double bond adjacent to the diketone moiety may cause the unwanted Michael type reaction[15,16] and also stabilize the 1,3-dicarbonyl unit into the corresponding enol tautomer interrupting the desired condensation process.[17] In this work, the Hantzsch reaction, known as one of the most classic multi-component reaction that use 1,3-dicarbonyl unit as a component, was chosen for THC precursor to construct the corresponding 1,4-DHP derivatives. With regard to the biological activities of DHP and their derivatives exhibiting anticancer, antimutagenic, antihypertensive activities and as a calcium channel blocker drug,[18-22] the introduction of two units of pharmacological active THC into the DHP structure would be of particular importance, given the potential pharmacological application of the novel heterocyclic compounds. We, therefore, decided to explore the construction of a THC-DHP model anticipating novel type of hybrid biological activities.

The synthesis of the DHP derivatives were performed by using the Hantzsch condensation of three components, including aldehydes, ammonium salts and THC. The synthetic work commenced by the hydrogenation of curcumin to produce the THC in a good yield. As an initial model of this study, benzaldehyde as the aromatic aldehyde and ammonium acetate as the nitrogen source were exposed to the reaction conditions (Scheme 1).[23-25] There are many types of catalysts that can be used in these multi-component reactions, particularly Lewis acid and Brønsted acid catalysis.[26-28] Based on our experimental experience, Lewis acid catalysts were initially tried as they had been shown to be successful with the DHPM synthesis.[14] However, the reaction gave many by-products leading to impossible isolation. We therefore chose to investigate *p*-TSA as the catalyst, according to the successful use of it as Brønsted acid catalyst in DHP synthesis,[28] due to its toleration to functional groups such as the hydroxyl and methoxy groups in THC.



Scheme 1

Table 1. Optimization of multi-component THC-DHP reaction conditions

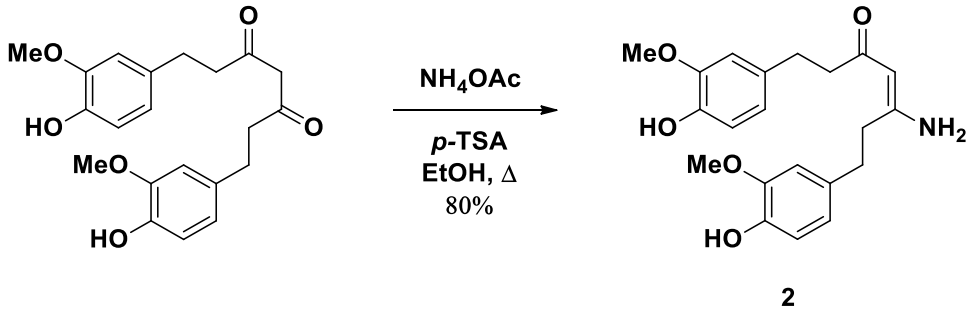
Entry	Benzaldehyde (eq)	Ammonium acetate (eq)	*p*-TSA (mol%)	4 Å MS (mg)	Enaminone-THC (%)	Recovered THC (%)	THC-DHP (yield%)
1	1.0	1.0	10	-	-	82	0
2	1.0	1.5	10	-	-	63	7
3	1.0	2.0	20	-	36	44	6
4	1.0	2.0	40	-	53	26	12
5	1.5	2.0	40	-	29	33	20
6	1.5	2.0	40	30	26	40	25
7	1.5	2.0	40	72	trace	37	30
8	1.5[a]	2.0	40	72	35	58	6
9	1.5[b]	2.0	40	72	54	16	10

[a] 4-Nitrobenzaldehyde was used instead of benzadehyde.
[b] 4-Methoxybenzaldehyde was used instead of benzadehyde.

The condensation using two equivalents of THC and benzaldehyde with ammonium acetate in the presence of 10 mol% of *p*-TSA under refluxing temperature in EtOH, however, did not meet with any success, only giving the recovery of starting materials (Table 1, Entry 1). The reaction conditions were then optimized by increasing the amount of ammonium acetate from 1.0 to 1.5 and then to 2.0 equivalents leading to the expected formation of the desired THP-DHP **1a** in both cases, but disappointingly only in low yields (Entries 2 and 3). A two-fold better yield was obtained under the same conditions except now in the presence of 40 mol% of *p*-TSA (Entry 4). Since the starting materials still remained in the reaction mixture, in order to push the reaction forward to completely produce the Knoevenagel adduct, the amount of benzaldehyde was increased to 1.5 equivalents resulting in a better yield of **1a** (Entry 5). 4 Å Molecular sieves were used as a dehydrating agent to give a better formation of THP-DHP **1a**, due to this being previously reported in the literature.[29] Expectedly, in the cases of the addition of 30 mg and 72 mg of 4 Å molecular sieves, the yields improved to 25% and 30%, respectively (Entries 6 and 7). In order to investigate the versatility of the reaction, a series of THC-DHP derivatives (**1b, 1c**) were also synthesized by using 4-nitrobenzaldehyde or 4-methoxybenzaldehyde instead of benzadehyde (Entries 8 and 9).

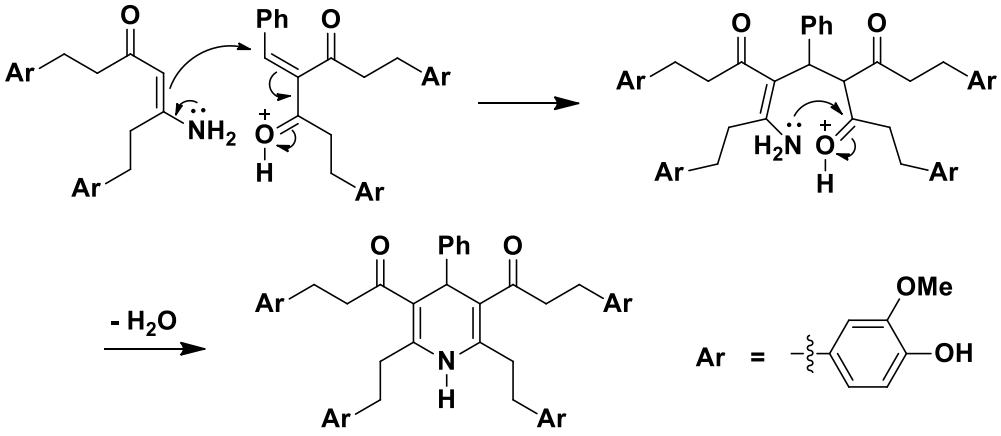
Remarkably, when the amount of ammonium acetate was increased to 2.0 equivalents, an interesting intermediate appeared in all the reactions, which was shown to be the enaminone-THC (**2**) due to its successful isolation by column chromatography. Trace amount of the Knoevenagel adduct, which was inseparable to THC, could also be observed by TLC monitoring. Compound **2** and the desired THC-DHP products (**1a-c**) were fully characterized by ^{1}H-, ^{13}C-, 2D-NMR spectroscopy and HRMS. We therefore deliberately attempted to synthesize this enaminone-THC (**2**) by using THC, and ammonium acetate as

starting materials in the presence of 40 mol% of *p*-TSA refluxing in ethanol for 2 hours. The result confirmed that enaminone-THC (**2**) was generated in excellent yield of 80% (Scheme 2).



Scheme 2

The mechanism conceivably involves the condensation of two principle adducts enaminone-THC (**2**) and the Knoevenagel adduct (**3**). Initially, THC reacts with NH_3 generated by the reaction of ammonium acetate and *p*-TSA to construct the enaminone-THC (**2**). The second equivalent of THC reacts with the aldehyde forming **3**, which is a reversible process due to the low stability of this intermediate. A cycloaddition can then proceed, leading to the desired symmetrical THC-DHP product. It is noteworthy that the removal of water in the reaction condition is important to improve the product yield. This is the first report ever showing the use of THC as a precursor in a cyclocondensation Hantzsch reaction.



Scheme 3

In conclusion, we have successfully utilized a natural hydrogenated curcumin, THC, for the modified multi-component Hantzsch reaction to cleanly form novel THC-DHP compounds. The optimization of the reaction conditions was investigated by varying the equivalents of the starting materials, reagents, and by adding activated molecular sieves as the dehydrating agent. Also the mechanism was proposed based on the evidence of the isolation of a plausible intermediate, enaminone-THC. The evaluation of bioactivities and other applications of these new compounds are under investigation and will be reported in due course.

EXPERIMENTAL

All chemicals and solvents were used as received from standard suppliers unless otherwise state. Reactions were monitored by thin layer chromatography (TLC) using Merck aluminum sheets coated with silica gel F254. Detection was achieved by UV light with wavelength 254 nm, iodine and/or potassium permanganate. Anhydrous Na_2SO_4 was used to dry organic solutions during workups, and the removal of solvents was carried out under vacuum with a rotary evaporator. Column chromatography was performed using silica gel 60. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. IR spectra were obtained in ATR or as neat on a Perkin-Elmer FT-IR Spectrum 400 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AVANCE 400 MHz spectrometer. Chemical shift (δ) are in ppm and coupling constants (J) are in Hertz (Hz). Mass spectra were recorded on Finnigan LC-Q mass spectrometer with an ESI mass selective detector. High resolution mass spectra (HRMS) were measured on an electrospray ionization Bruker Daltomics micrOTOF-QII mass spectrometer.

Procedure for the synthesis of tetrahydrocurcumin- (THC-) dihydropyridines (DHPs)

1,1'-(2,6-Bis(4-hydroxy-3-methoxyphenethyl)-4-phenyl-1,4-dihydropyridine-3,5-diyl)bis(3-(4-hydroxy-3-methoxyphenyl)propan-1-one) (1a). To a solution of tetrahydrocurcumin (0.134 mmol, 50 mg), *p*-TsOH•H_2O (0.027 mmol, 5.11 mg), and 4 Å molecular sieves (72 mg) in EtOH (0.34 mL) was added benzaldehyde (0.10 mmol, 10.69 mL). The mixture was stirred at 80 °C for 20 min before ammonium acetate (0.134 mmol, 10.33 mg) was added. The reaction mixture was stirred at 80 °C for 24 h before being quenched with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product as a yellow oil. Purification was accomplished by column chromatography eluting with 60% EtOAc/Hexane to give **1a** as a yellow waxy solid. Yield: 30%; IR (ν_{max}, cm^{-1}): 3336, 2924, 1601, 1513, 1428, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20-7.10 (3H, m, Ar**H**), 7.00 (2H, d, *J*= 5.8 Hz, Ar**H**), 6.79 (2H, d, *J* = 7.7 Hz, Ar**H**), 6.76 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.65-6.50 (8H, m, Ar**H**), 5.52 (2H, br s, 2×ArO**H**), 5.48 (2H, br s, 2×ArO**H**), 5.20 (1H, br s, N**H**), 4.99 (1H, s, C**H**), 3.77 (6H, s, 2×OC**H**$_3$), 3.76 (6H, s, 2×OC**H**$_3$), 3.75 (6H, s, 2×OC**H**$_3$), 2.85-2.71 (8H, m, 2× C**H**$_2$C**H**$_2$CO), 2.65 (4H, t, *J* = 6.5 Hz, 2×CH_2C**H**$_2$Ar), 2.60-2.49 (4H, m, 2×C**H**$_2$$CH_2$Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.8 (2×**C**O), 146.7 (2×**C**$_{Ar}$OCH$_3$), 146.5 (2×**C**CO), 146.2 (2×**C**$_{Ar}$OCH$_3$), 146.0 (**C**$_{Ar}$CH), 144.4 (2×**C**$_{Ar}$OH), 144.0 (2×**C**$_{Ar}$OH), 133.5 (2×**C**$_{Ar}$$CH_2$), 132.6 (2×**C**$_{Ar}$$CH_2$), 128.8 (**C**H$_{Ar}$), 127.2 (2×**C**H$_{Ar}$), 127.0 (2×**C**H$_{Ar}$), 121.1 (2×**C**H$_{Ar}$), 121.0 (2×**C**H$_{Ar}$), 114.6 (2×**C**H$_{Ar}$), 114.4 (2×**C**H$_{Ar}$), 112.6 (2×**C**NH), 111.3 (4×**C**H$_{Ar}$), 56.0 (4×O**C**H$_3$), 43.1 (2×**C**H_2CO), 40.1 (**C**H), 35.1 (2×**C**H_2CNH), 34.1 (2×**C**H_2Ar), 30.4 (2×**C**H_2Ar). ESMS *m/z*: 812.0 [M-H]$^-$ (85); HRMS: Calcd. for $C_{49}H_{50}NO_{10}$: 812.3440, found 812.3443.

1,1'-(2,6-Bis(4-hydroxy-3-methoxyphenethyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-diyl)bis(3-(4-hydroxy-3-methoxyphenyl)propan-1-one) (1b): To a solution of tetrahydrocurcumin (0.134 mmol, 50 mg), *p*-TsOH•H_2O (0.027 mmol, 5.11 mg), and 4 Å molecular sieves (72 mg) in EtOH (0.34 mL) was added *p*-nitrobenzaldehyde (0.10 mmol, 15.22 mg). The mixture was stirred at 80 °C for 20 min before ammonium acetate (0.134 mmol, 10.33 mg) was added. The reaction mixture was stirred at 80 °C for 24 h before being quenched with water (5 mL) and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product as a yellow oil. Purification was accomplished by column chromatography eluting with 75% EtOAc/Hexane to give **1b** as a yellow waxy solid. Yield: 6%; IR (ν_{max}, cm^{-1}): 3328, 2928, 1600, 1513, 1428, 1344, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.07 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.80 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.75 (2H, d, *J* = 7.7 Hz, Ar**H**), 6.60-6.50 (8H, m, Ar**H**), 5.33 (4H, br s, 4×ArO**H**), 5.27 (1H, br s, N**H**), 5.14 (1H, s, C**H**), 3.76 (6H, s, 2×OC$\mathbf{H}_3$), 3.75 (6H, s, 2×OC$\mathbf{H}_3$), 2.90-2.55 (16H, m, 8×C$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.9 (2×**C**O), 157.9 (**C**$_{Ar}$$NO_2$), 146.9 (2×**C**$_{Ar}$$OCH_3$), 146.9 (2×**C**CO), 146.6 (2×**C**$_{Ar}$$OCH_3$), 146.5 (**C**$_{Ar}$CH), 144.6 (2×**C**$_{Ar}$OH), 144.2 (2×**C**$_{Ar}$OH), 133.2 (2×**C**$_{Ar}$$CH_2$), 132.0 (2×**C**$_{Ar}$$CH_2$), 128.0 (2×**C**H$_{Ar}$), 123.9 (2×**C**H$_{Ar}$), 121.0 (4×**C**H$_{Ar}$), 114.7 (2×**C**H$_{Ar}$), 114.5 (2×**C**H$_{Ar}$), 112.1 (2×**C**NH), 111.3 (4×**C**H$_{Ar}$), 56.1 (2×O**C**H_3), 56.0 (2×O**C**H_3), 43.3 (2×**C**H_2), 39.8 (**C**H), 34.7 (2×**C**H_2), 34.1 (2×**C**H_2), 30.5 (2×**C**H_2). ESMS *m/z*: 857.8 $[M-H]^-$ (100); HRMS: Calcd. for $C_{49}H_{49}N_2O_{12}$: 857.3290, found 857.3255.

1,1'-(2,6-Bis(4-hydroxy-3-methoxyphenethyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-diyl)bis-(3-(4-hydroxy-3-methoxyphenyl)propan-1-one) (1c): To a solution of tetrahydrocurcumin (0.134 mmol, 50 mg), *p*-TsOH•H_2O (0.027 mmol, 5.11 mg), and 4 Å molecular sieves (72 mg) in EtOH (0.34 mL) was added *p*-methoxybenzaldehyde (0.10 mmol, 13.71 mg). The mixture was stirred at 80 °C for 20 min before ammonium acetate (0.134 mmol, 10.33 mg) was added. The reaction mixture was stirred at 80 °C for 24 h before being quenched with water (5 mL) and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product as a yellow oil. Purification was accomplished by column chromatography eluting with 75% EtOAc/Hexane to give the THC-DHP **1c** as a yellow waxy solid. Yield: 10%; IR (ν_{max}, cm^{-1}): 3388, 2930, 1601, 1512, 1428, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.89 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.80 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.75 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.68 (2H, d, *J* = 8.5Hz, Ar**H**), 6.60-6.55 (8H, m, Ar**H**), 5.49 (2H, br s, 2×ArO**H**), 5.42 (2H, br s, 2×ArO**H**), 5.16 (1H, br s, N**H**), 4.90 (1H, s, C**H**), 3.77 (6H, s, 2×OC$\mathbf{H}_3$), 3.76 (6H, s, 2×OC$\mathbf{H}_3$), 3.75 (3H, s, OC$\mathbf{H}_3$), 2.80-2.72 (8H, m, 2×C$\mathbf{H}_2$C$\mathbf{H}_2$CO), 2.64 (4H, t, *J* = 6.4 Hz, 2×CH_2C$\mathbf{H}_2$Ar), 2.60-2.50 (4H, m, 2×C$\mathbf{H}_2$$CH_2$Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.9 (2×**C**O), 158.5 (**C**$_{Ar}$$OCH_3$), 146.8 (2×**C**$_{Ar}$$OCH_3$), 146.5 (2×**C**CO), 145.8 (2×**C**$_{Ar}$$OCH_3$), 144.5 (**C**$_{Ar}$CH), 144.4 (2×**C**$_{Ar}$OH), 144.0 (2×**C**$_{Ar}$OH), 133.6 (2×**C**$_{Ar}$$CH_2$), 132.6 (2×**C**$_{Ar}$$CH_2$), 128.3 (2×**C**H$_{Ar}$), 121.1 (2×**C**H$_{Ar}$),

121.0 (2×**C**H_{Ar}), 114.6 (2×**C**H_{Ar}), 114.4 (2×**C**H_{Ar}), 114.1 (2×**C**H_{Ar}), 113.0 (2×**C**NH), 111.4 (2×**C**H_{Ar}), 111.3 (4×**C**H_{Ar}), 56.1 (2×O**C**H_3), 56.0 (2×O**C**H_3), 55.4 (O**C**H_3), 43.0 (2×**C**H_2CO), 35.0 (**C**H), 34.2 (2×**C**H_2CNH), 30.4 (2×**C**H_2Ar), 29.9 (2×**C**H_2Ar). ESMS *m/z*: 844.5 $[M+H]^+$ (100); HRMS: Calcd. for $C_{50}H_{52}NO_{11}$: 842.3546, found 842.3545.

Procedure for synthesis of enaminone-THC

(Z)-5-Amino-1,7-bis(4-hydroxy-3-methoxyphenyl)hept-4-en-3-one (2): To a solution of tetrahydrocurcumin (0.134 mmol, 50 mg), *p*-TsOH·H_2O (0.054 mmol, 10.22 mg) in EtOH (0.34 mL) was added ammonium acetate (0.269 mmol, 20.70 mg) The reaction mixture was stirred for 2 h before being quenched with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product as a yellow oil. Purification was accomplished by column chromatography eluting with 1:1 EtOAc/Hexane to give **2** as a pale yellow viscous oil. Yield: 80%; IR (ν_{max}, cm^{-1}): 3395, 2935, 1606, 1510, 1428, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.74 (1H, br s, N**H**), 6.81 (1H, d, *J* = 8.9 Hz, Ar**H**), 6.79 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.69 (1H, s, Ar**H**), 6.68 (1H, d, *J* = 6.4 Hz, Ar**H**), 6.66 (1H, d, *J* = 6.6 Hz, Ar**H**), 6.64 (1H, s, Ar**H**), 5.60 (2H, br s, ArO**H**), 5.02 (1H, s, C**H**CO), 4.93 (1H, br s, N**H**), 3.83 (6H, br s, 2×OC**H**$_3$), 2.89 (2H, t, *J* = 7.5 Hz, C**H**$_2$CO), 2.77 (2H, t, *J* = 8.0 Hz,C**H**$_2$CH$_2$CNH$_2$), 2.54 (2H, t, *J* = 7.5 Hz, C**H**$_2$CH$_2$CO), 2.36 (2H, t, *J* = 8.0 Hz, C**H**$_2$CNH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.9 (**C**O), 164.6 (**C**NH$_2$), 146.7 (**C**$_{Ar}$OCH$_3$), 145.6 (**C**$_{Ar}$OCH$_3$), 144.4 (**C**$_{Ar}$OH), 143.8 (**C**$_{Ar}$OH), 134.0 (**C**$_{Ar}$CH$_2$), 132.2 (**C**$_{Ar}$CH$_2$), 121.0 (**C**H$_{Ar}$), 120.9 (**C**H$_{Ar}$), 114.6 (**C**H$_{Ar}$), 114.4 (**C**H$_{Ar}$), 111.2 (**C**H$_{Ar}$), 111.1 (**C**H$_{Ar}$), 95.0 (**C**H), 56.0 (2×O**C**H$_3$), 44.5(**C**H$_2$Ar), 38.7 (**C**H$_2$CNH$_2$), 34.2 (**C**H$_2$Ar), 31.7 (**C**H$_2$CO). ESMS *m/z*: 372.7 $[M+H]^+$ (100); HRMS: Calcd. for $C_{21}H_{24}NO_5$: 370.1647, found 370.1659.

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