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Synthesis of 6-Heterocyclically Appended Tri-*O*-methyl Protected 6-Desmethyl Emodin Derivatives

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Summary. A convenient synthesis of several 6-heterocyclically appended tri-*O*-methyl 6-desmethyl emodin derivatives including the tetrazolyl, oxazolyl, oxazolinyl, benzimidazolyl, benzoxazolyl, and benzothiazolyl derivatives of potential biological and medicinal interest was achieved starting from the tri-*O*-methyl protected emodin aldehyde or nitrile. In addition, these derivatives could serve as synthons for heterocyclic hypericin derivatives.

Keywords. 9,10-Anthraquinones; Heterocycles; NMR Structure elucidation; Tri-*O*-methylemodin aldehyde; Tri-*O*-methylemodin nitrile.

Introduction

Hydroxylated 9,10-anthraquinones are abundant in nature and are used in several fields. They display marked pharmacological activities, and are most notably used as anticancer and antimicrobial drugs [1]. They are also known as photosensitizers [2]. Emodin (1,3,8-trihydroxy-6-methyl-9,10-anthraquinone) itself is a naturally occurring trihydroxylated anthraquinone of particular interest as it is used to prepare hypericin, a well known photosensitizer with broad anticancer and antiviral activity [3–5].

In continuation of our quest to synthesize modified hypericin derivatives, which are intended as photodynamic therapy agents [6–9], we have developed an efficient synthesis route to tri-*O*-methylemodin aldehyde and nitrile [10] very recently envisioning their value as synthons for both heterocyclic emodin and hypericin derivatives. Herein, we report our efforts to prepare such novel heterocyclic tri-*O*-methylemodin derivatives including the position 6-appended tetrazolyl, oxazolyl, oxazolinyl, benzimidazolyl, benzoxazolyl, and benzothiazolyl derivatives, which are of potential biological and medicinal interest as well as for gaining

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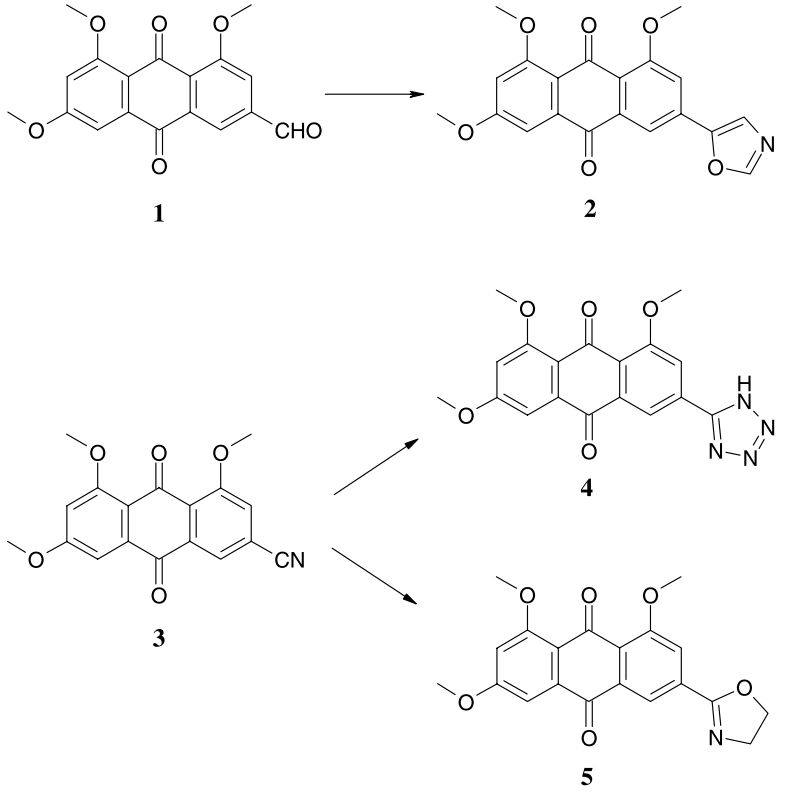
access to heterocyclic synthons for the synthesis of heterocyclic hypericin derivatives as new anticipated photodynamic therapy agents.

Results and Discussion

Starting from tri-*O*-methylemodin aldehyde (**1**) our strategy was to achieve a short synthesis of a heterocyclic ring involving the aldehyde carbon of **1**. This should avoid the envisaged steric effect which might hinder the hypericin formation, and should gain a shift of the long wavelength absorption band of hypericin ($\lambda_{max} \sim 598$ nm) towards the emission wavelength range of medicinal lasers ($\lambda_{max} \sim 650$ nm) as a final target. With this in mind, condensation of the aldehyde with active methylene containing compounds *via* aldol or *Kneovenagel* reaction followed by reaction with nucleophiles was put aside. Instead, a one-step synthesis of heterocycles satisfying partially this aim, such as oxazole, tetrazole, and oxazoline derivatives was achieved from the available protected emodin aldehyde and emodin nitrile [10].

Formation of the oxazole ring of **2** was carried out in the manner described by *Herr et al.* [11]. Thus, a mixture of aldehyde **1**, tosylmethyl isocyanide (*TosMIC*), and potassium carbonate was refluxed in methanol for 14 h to produce the oxazole **2** in 82% yield (Scheme 1).



Scheme 1

Besides its interest to the medicinal chemist [12], we decided to prepare the tetrazole **4** with the intention to gain a notable bathochromic shift of its absorption. It is noteworthy that standard conditions for the formation of tetrazoles from nitriles [13] using ammonium chloride and sodium azide in dimethylformamide at 125–140°C over 22 h led to decomposition of the starting nitrile **3** only. However, starting with emodin nitrile **3**, the tetrazole **4** was prepared *via* its reaction with sodium azide using 1-methylpyrrolidin-2-one (*NMP*) as solvent and triethylammonium chloride as catalyst [14, 15] in 68% yield (Scheme 1).

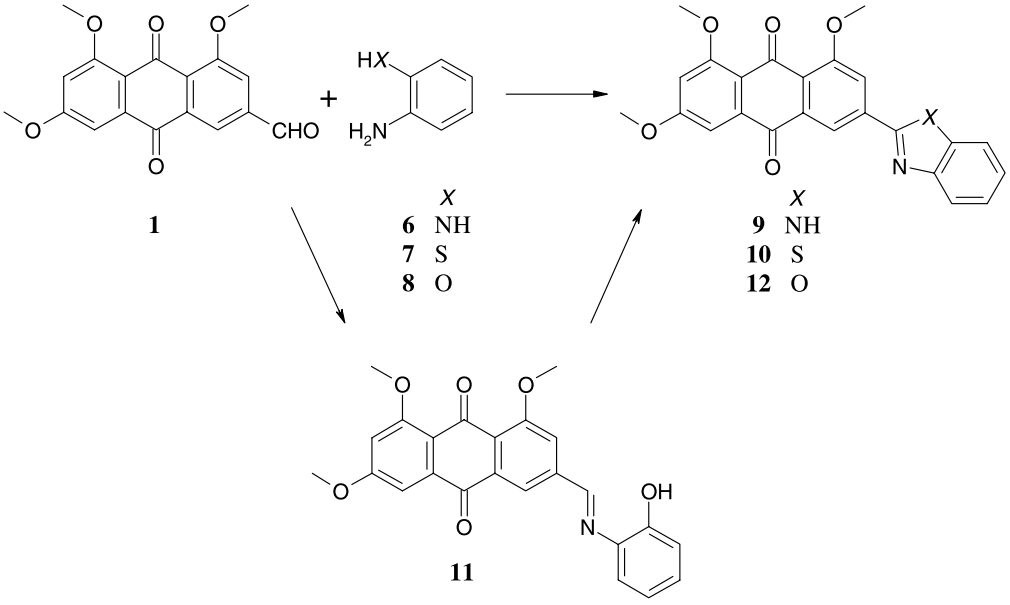
Since the use of oxazoline building blocks in pharmaceutical drug discovery is continually increasing [16], synthesis of the oxazoline ring of **5** was also targeted. The well-known conditions of nitrile-oxazoline conversion failed in our case. Thus, refluxing **3** with ethanolamine in chlorobenzene using zinc chloride as catalyst [17–19] led to decomposition of the starting nitrile, whereas the uncatalyzed reaction in boiling *o*-dichlorobenzene [20] led to recovery of unchanged **3** only. However, synthesis of **5** was achieved by the reaction of the nitrile **3** with aminoethanol in a mixture of glycerol/ethylene glycol using potassium carbonate as the catalyst [21] in 77% yield (Scheme 1).

Compounds **2**, **4**, and **5** were fully characterized on the basis of their IR, UV/Vis, MS, and NMR spectra, particularly by 2D NMR measurements including HSQC, HMBC, and N*O*ESY experiments.

Besides their anticipated medicinal interest, the abovementioned heterocycles did not show a significant bathochromic shift in their absorption spectra ($\Delta\lambda_{max} < 10$ nm in comparison to 1,3,8-trimethoxy-6-methyl-9,10-anthraquinone). Consequently, we pursued with the synthesis of benzo condensed heterocycles, in particular benzimidazole, benzothiazole, and benzoxazole derivatives as convenient substrates from the readily available aldehyde **1**. Thus, benzimidazole **9** and benzothiazole **10** were synthesized according to conventional procedures [22–24] by refluxing **1** with *o*-phenylenediamine (**6**) or *o*-aminothiophenol (**7**) in nitrobenzene in 52% and 70% yield (Scheme 2). However, applying this procedure to prepare the benzoxazole **12** led exclusively to the intermediate *Schiff* base **11**, which was subsequently oxidized to **12** by means of lead tetraacetate in acetic acid at 80°C [25] (Scheme 2) in 63% overall yield.

Compounds **9** and **11** were fully characterized on the basis of their IR, UV/Vis, MS, and NMR spectra, particularly by 2D NMR measurements inclucing HSQC, HMBC, and N*O*ESY experiments. For compound **9** it is noteworthy that assignment of the benzimidazolyl substituent shifts in particular was not possible due to broad signals originating from dynamic effects. Unfortunately, a full NMR spectroscopic assignment of **10** and **12** could not be achieved due to their poor solubility even in *DMSO* at elevated temperature (55°C). However, they displayed satisfying IR, MS, and ^{1}H NMR spectra.

Regarding the UV absorption of the aforementioned benzo analogs **9**, **10**, and **12**, there was no significant shift towards longer wavelengths observable for **10** and **12** ($\Delta\lambda_{max} < 10$ nm in comparison to 1,3,8-trimethoxy-6-methyl-9,10-anthraquinone). Fortunately however, the benzimidazolyl derivative **9** showed a bathochromic shift of $\Delta\lambda_{max} > 15$ nm in comparison to 1,3,8-trimethoxy-6-methyl-9, 10-anthraquinone, which seems to be promising for pursuing the synthesis of a hypericin derivative with anticipated photodynamic properties.



Scheme 2

Experimental

Solvents were of p.a. quality. Melting points were measured on a *Kofler* melting point microscope (Reichert; Vienna). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX 200 MHz and a Bruker Avance DRX 500 MHz spectrometer using a TXI cryoprobe with z-gradient coil. Standard temperature for NMR experiments in *DMSO* was 30°C and 25°C for $CDCl_3$. 2D NMR experiments were performed on the 500 MHz spectrometer using standard pulse sequences as provided by the manufacturer. Typical 90° hard pulse durations were 8.2 µs (^{1}H) and 16.6 µs (^{13}C), 90° pulses in decoupling experiments were set to 67 µs. HSQC and HMBC experiments were optimized for coupling constants of 145 Hz for single quantum correlations and 10 Hz for multi-bond correlations. N*O*ESY mixing time was set to 400 ms. IR, UV/Vis, and mass spectra were recorded using the Bruker Tensor 27, Varian Cary 100 Bio UV/Vis, Hewlett Packard 59987 quadrupole, and Fisons MD 800 instruments. Tri-*O*-methylemodin aldehyde (**1**) and the corresponding nitrile **2** were prepared according to Ref. [10]. All novel compounds were judged to be pure (>97%) by means of their ^{1}H NMR spectra and chromatography.

1,3,8-Trimethoxy-6-(1,3-oxazol-5-yl)anthraquinone (**2**, $C_{20}H_{15}NO_6$)

To a solution of 0.163 g of **1** (0.5 mmol) in 40 cm^3 of methanol 0.100 g of *TosMIC* (0.5 mmol) and 0.160 g of K_2CO_3 (1.16 mmol) were added and the reaction mixture was stirred at reflux for 16 h. After cooling, the reaction mixture was poured onto 200 cm^3 of cold distilled H_2O, extracted with 2×50 cm^3 of $CHCl_3$, and dried (Na_2SO_4). Vacuum filtration of the extract on silica gel and concentration under reduced pressure provided 0.150 g (82%) of **2**. Mp 254–256°C; TLC: $R_f = 0.17$ ($CHCl_3$:$CH_3COOC_2H_5$ = 2:1), $R_f = 0.83$ ($CHCl_3$:CH_3OH = 5:2); ^{1}H NMR (500 MHz, *DMSO*-d$_6$): $\delta = 8.58$ (s, ar-H2′), 8.07 (s, ar-H4′), 7.96 (d, $J = 1.5$ Hz, ar-H5), 7.76 (d, $J = 1.5$ Hz, ar-H7), 7.20 (d, $J = 2.5$ Hz, ar-H4), 7.00 (d, $J = 2.5$ Hz, ar-H2), 3.99 (s, 8-OCH_3), 3.95 (s, 3-OCH_3), 3.91 (s, 1-OCH_3) ppm; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.10$ (s, ar-H), 8.01 (s, ar-H), 7.61 (s, ar-H), 7.54 (s, ar-H), 7.36 (s, ar-H), 6.80 (s, ar-H), 4.17 (s, OCH_3), 4.04 (s, 2OCH_3) ppm; N*O*ESY (*DMSO*-d$_6$): 1-O*CH*$_3$ ↔ ar-*H*2,

3-OCH_3 ↔ ar-*H*2 and ar-*H*4, 8-OCH_3 ↔ ar-*H*7, ar-*H*7 ↔ ar-*H*4′; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 182.9$ (10-CO), 179.4 (9-CO), 163.5 (C3), 161.2 (C1), 159.6 (C8), 153.0 (C2′), 149.0 (C5′), 135.5 (C4a or C10a), 134.9 (C10a or C4a), 132.0 (C6), 125.2 (C4′), 122.9 (C8a), 117.6 (C9a), 113.5 (C7), 113.2 (C5), 105.2 (C2), 102.5 (C4), 56.65 (8-OCH_3), 56.43 (1-OCH_3), 55.97 (3-OCH_3) ppm; HSQC (*DMSO*-d_6): ar-*H*2 ↔ *C*2, ar-*H*4 ↔ *C*4, ar-*H*5 ↔ *C*5, ar-*H*7 ↔ *C*7, 1-OCH_3 ↔ 1-O*C*H_3, 3-OCH_3 ↔ 3-O*C*H_3, 8-OCH_3 ↔ 8-O*C*H_3, ar-*H*2′ ↔ *C*2′, ar-*H*4′ ↔ *C*4′; HMBC (*DMSO*-d_6): *C*1 → 1-OCH_3 and ar-*H*2, *C*2 → ar-*H*4, *C*3 → 3-OCH_3, ar-*H*2 and ar-*H*4, *C*4 → ar-*H*2, *C*5 → ar-*H*7, *C*6 → ar-*H*7, *C*7 → ar-*H*5, *C*8 → 8-OCH_3 and ar-*H*7, *C*10 → ar-*H*4 and ar-*H*5, *C*8a → ar-*H*5 and ar-*H*7, *C*9a → ar-*H*2 and ar-*H*4, *C*2′ → ar-*H*4′, *C*4′ → ar-*H*2′, *C*5′ → ar-*H*5, ar-*H*7, ar-*H*2′, and ar-*H*4′; NCI-MS (solid probe, CH_4): $m/z = 365$ ([M]$^-$); IR (KBr): $\bar{\nu} = 3119$, 2944, 2843 (OCH_3), 1656 (CO), 1599 (C=C), 1566, 1462, 1416, 1249, 1196, 1167, 1144, 1114, 1070, 1012, 946, 881, 856, 755, 644, 609 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 241$ (100), 289 (86), 408 (28) nm (rel. int.).

1,3,8-Trimethoxy-6-(1H-tetrazol-5-yl)anthraquinone (**4**, $C_{18}H_{14}N_4O_5$)

A mixture of 0.065 g of **3** (0.2 mmol), 0.040 g of NaN_3 (0.6 mmol), 0.080 g of $Et_3N \cdot HCl$ (0.6 mmol), and 10 cm^3 of *NMP* was stirred for 18 h at 110°C under Ar. After cooling and pouring the reaction mixture into 100 cm^3 of ice/H_2O, the resulting solution was acidified to $pH = 1$ with 6 *M* HCl (*caution*: hydrazoic acid), and extracted with 2×50 cm^3 of ethyl acetate. The organic extract was evaporated and the residue was purified by chromatography on silica gel using chloroform:methanol (5:1) as eluent to recover 0.015 g of starting nitrile **3** in the first fraction. Increasing the polarity of eluent to (5:2) afforded 0.050 g (68%) of **4**. Mp 271–273°C; TLC: $R_f = 0.00$ ($CHCl_3$:$CH_3COOC_2H_5$ = 2:1), $R_f = 0.30$ ($CHCl_3$:CH_3OH = 5:2); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 8.32$ (d, $J = 1.2$ Hz, ar-H5), 8.03 (d, $J = 1.2$ Hz, ar-H7), 7.23 (d, $J = 2.5$ Hz, ar-H4), 6.99 (d, $J = 2.5$ Hz, ar-H2), 3.97 (s, 8-OCH_3), 3.95 (s, 3-OCH_3), 3.91 (s, 1-OCH_3) ppm – NH was not observed, presumably due to exchange; N*O*ESY (*DMSO*-d_6): 1-OCH_3 ↔ ar-*H*2, 3-OCH_3 ↔ ar-*H*2 and ar-*H*4, 8-OCH_3 ↔ ar-*H*7; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 183.4$ (10-CO), 179.9 (9-CO), 163.4 (C3), 161.1 (C1), 159.6 (C=N), 159.3 (C8), 137.7 (C6), 135.7 (C4a), 134.4 (C10a), 121.8 (C8a), 117.8 (C9a), 115.5 (C5), 114.8 (C7), 105.1 (C2), 102.3 (C4), 56.39 (1-OCH_3), 56.18 (8-OCH_3), 55.91 (3-OCH_3) ppm; HSQC (*DMSO*-d_6): ar-*H*2 ↔ *C*2, ar-*H*4 ↔ *C*4, ar-*H*5 ↔ *C*5, ar-*H*7 ↔ *C*7, 1-OCH_3 ↔ 1-O*C*H_3, 3-OCH_3 ↔ 3-O*C*H_3, 8-OCH_3 ↔ 8-O*C*H_3; HMBC (*DMSO*-d_6): *C*1 → 1-OCH_3 and ar-*H*2, *C*2 → ar-*H*4, *C*3 → 3-OCH_3, ar-*H*2 and ar-*H*4, *C*4 → ar-*H*2, *C*5 → ar-*H*7, *C*6 → ar-*H*7, *C*7 → ar-*H*5, *C*8 → 8-OCH_3 and ar-*H*7, *C*9 → ar-*H*2 and ar-*H*7, *C*10 → ar-*H*4 and ar-*H*5, *C*4a → ar-*H*4, *C*8a → ar-*H*5 and ar-*H*7, *C*9a → ar-*H*2 and ar-*H*4, *C*5′ → ar-*H*5 and ar-*H*7; NCI-MS (solid probe, CH_4): $m/z = 366$ ([M]$^-$); ESI-MS (*Me*OH:CH_2Cl_2 = 1.2:1 + 1% CF_3COOH, $\gamma = 1.0$ mg/cm^3, positive ion mode): $m/z = 367$ ([M + H]$^+$), 339 ([M + H-N_2]$^+$); IR (KBr): $\bar{\nu} = 3085$ (NH), 2948, 2865 (OCH_3), 1655 (CO), 1599 (C=C), 1562, 1461, 1421, 1324, 1257, 1241, 1153, 1067, 1000, 946, 752 cm^{-1}; UV-Vis (CH_3OH): $\lambda_{max} = 231$ (100), 286 (89), 409 (17) nm (rel. int.).

6-(4,5-Dihydro-1,3-oxazol-2-yl)-1,3,8-trimethoxyanthraquinone (**5**, $C_{20}H_{17}NO_6$)

A suspension of 0.080 g of ethanolamine (1.3 mmol) and 0.020 g of K_2CO_3 (0.14 mmol) in a mixture of 12 cm^3 of ethylene glycol and 6 cm^3 of glycerol was heated to 105°C. After addition of 0.045 g of **3** (0.14 mmol) the mixture was stirred for 18 h at 115°C under Ar. The resultant mixture was cooled, diluted with distilled H_2O, and extracted with 2×50 cm^3 of ethyl acetate. After removal of ethyl acetate, the crude product was purified by column chromatography on silica gel using chloroform:ethyl acetate (1:1) as eluent to give 0.040 g (77%) of **5**. Mp 269–272°C; TLC: $R_f = 0.10$ ($CHCl_3$:$CH_3COOC_2H_5$ = 2:1), $R_f = 0.82$ ($CHCl_3$:CH_3OH = 5:2); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 8.09$ (s, ar-H5), 7.81 (s, ar-H7), 7.19 (d, $J = 2.2$ Hz, ar-H4), 6.99 (d, $J = 2.2$ Hz, ar-H2), 4.49 (t, $J = 9.5$ Hz, 5′-CH_2), 4.03 (t, $J = 9.5$ Hz, 4′-CH_2), 3.96 (s, 8-OCH_3), 3.95 (s,

3-OCH_3), 3.91 (1-OCH_3) ppm; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.35$ (s, ar-H), 7.90 (s, ar-H), 7.36 (s, ar-H), 6.80 (s, ar-H), 4.54 (t, $J = 9.4$ Hz, –CH_2), 4.16 (t, $J = 9.4$ Hz, –CH_2), 4.07 (s, OCH_3), 3.99 (s, 2-OCH_3) ppm; N*O*ESY (*DMSO*-d_6): 1-$OCH_3 \leftrightarrow$ ar-*H*2, 3-$OCH_3 \leftrightarrow$ ar-*H*2 and ar-*H*4, 8-$OCH_3 \leftrightarrow$ ar-*H*7, 4′-$CH_2 \leftrightarrow$ 5′-CH_2; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 182.6$ (10-CO), 179.5 (9-CO), 163.6 (C3), 161.7 (C2′), 161.2 (C1), 158.9 (C8), 135.4 (C4a), 134.3 (C10a), 131.9 (C6), 125.1 (C8a), 117.5 (C9a), 117.1 (C5), 116.8 (C7), 105.1 (C2), 102.4 (C4), 67.96 (C5′), 56.40 (8-OCH_3 or 1-OCH_3), 56.39 (1-OCH_3 or 8-OCH_3), 55.93 (3-OCH_3), 54.59 (C4′) ppm; HSQC (*DMSO*-d_6): ar-*H*2 $\leftrightarrow$ *C*2, ar-*H*4 $\leftrightarrow$ *C*4, ar-*H*5 $\leftrightarrow$ *C*5, ar-*H*7 $\leftrightarrow$ *C*7, 1-$OCH_3 \leftrightarrow$ 1-OCH_3, 3-$OCH_3 \leftrightarrow$ 3-OCH_3, 8-$OCH_3 \leftrightarrow$ 8-OCH_3, 4′-$CH_2 \leftrightarrow$ *C*4′, 5′-$CH_2 \leftrightarrow$ *C*5′; HMBC (*DMSO*-d_6): *C*1 $\rightarrow$ 1-OCH_3 and ar-*H*2, *C*2 $\rightarrow$ ar-*H*4, *C*3 $\rightarrow$ 3-OCH_3, ar-*H*2, and ar-*H*4, *C*4 $\rightarrow$ ar-*H*2, *C*5 $\rightarrow$ ar-*H*7, *C*6 $\rightarrow$ ar-*H*7 and 4′-CH_2, *C*7 $\rightarrow$ ar-*H*5, *C*8 $\rightarrow$ 8-OCH_3 and ar-*H*7, *C*10 $\rightarrow$ ar-*H*4 and ar-*H*5, *C*4a $\rightarrow$ ar-*H*4, *C*8a $\rightarrow$ ar-*H*5 and ar-*H*7, *C*9a $\rightarrow$ ar-*H*2 and ar-*H*4, *C*2′ $\rightarrow$ ar-*H*5, ar-*H*7, 4′-CH_2 and 5′-CH_2, *C*4′ $\rightarrow$ 5′-CH_2, *C*5′ $\rightarrow$ 4′-CH_2; NCI-MS (solid probe, CH_4): $m/z = 367$ ($[M]^-$); IR (KBr): $\bar{\nu} = 2944$ (CH-aliph), 1671 (CO), 1599 (C=C), 1564, 1459, 1416, 1327, 1255, 1167, 1015, 962, 882, 754, 715 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 255$ (100), 280 (96), 405 (29) nm (rel. int.).

6-(1H-Benzimidazol-2-yl)-1,3,8-trimethoxyanthraquinone (**9**, $C_{24}H_{18}N_2O_5$)

A mixture of 0.326 g of **1** (1 mmol) and 0.110 g of *o*-phenylenediamine (1 mmol) was refluxed in 20 cm^3 of nitrobenzene for 4 h. After cooling, the solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel using chloroform:ethyl acetate (2:1) as eluent to afford 0.210 g (51%) of **9**. Mp 285–286°C; TLC: $R_f = 0.15$ ($CHCl_3$:$CH_3COOC_2H_5$ = 2:1), $R_f = 0.90$ ($CHCl_3$:CH_3OH = 5:2); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 13.36$ br. (s, NH), 8.51 (s, ar-H5), 8.24 (s, ar-H7), 7.69–7.67 (m, 2ar-H), 7.30–7.27 (m, 2ar-H), 7.24 (d, $J = 1.7$ Hz, ar-H4), 7.01 (d, $J = 1.7$ Hz, ar-H2), 4.05 (s, 8-OCH_3), 3.96 (s, 3-OCH_3), 3.92 (s, 1-OCH_3) ppm; N*O*ESY (*DMSO*-d_6): 1-$OCH_3 \leftrightarrow$ ar-*H*2, 3-$OCH_3 \leftrightarrow$ ar-*H*2 and ar-*H*4, 8-$OCH_3 \leftrightarrow$ ar-*H*7; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 182.9$ (10-CO), 179.6 (9-CO), 163.5 (C3), 161.2 (C1), 159.3 (C8), 149.3 br. (C = N), 135.6 (C4a), 134.7 (C6 and C10a), 134.5 br. (C3a′ and C7a′), 123.7 (C8a), 122.7 br. (2C′), 117.6 (C9a), 116.0 (C5), 115.7 (C7), 115.6 br. (2C′), 105.2 (C2), 102.4 (C4), 56.56 (8-OCH_3), 56.41 (1-OCH_3), 55.97 (3-OCH_3) ppm; HSQC (*DMSO*-d_6): ar-*H*2 $\leftrightarrow$ *C*2, ar-*H*4 $\leftrightarrow$ *C*4, ar-*H*5 $\leftrightarrow$ *C*5, ar-*H*7 $\leftrightarrow$ *C*7, 1-$OCH_3 \leftrightarrow$ 1-OCH_3, 3-$OCH_3 \leftrightarrow$ 3-OCH_3, 8-$OCH_3 \leftrightarrow$ 8-OCH_3, ar-*H*4′/ar-*H*7′ $\leftrightarrow$ *C*4′/*C*7′, ar-*H*5′/ar-*H*6′ $\leftrightarrow$ *C*5′/*C*6′; HMBC (*DMSO*-d_6): *C*1 $\rightarrow$ 1-OCH_3 and ar-*H*2, *C*2 $\rightarrow$ ar-*H*4, *C*3 $\rightarrow$ 3-OCH_3, ar-*H*2, and ar-*H*4, *C*4 $\rightarrow$ ar-*H*2, *C*5 $\rightarrow$ ar-*H*7, *C*6 $\rightarrow$ ar-*H*7, *C*7 $\rightarrow$ ar-*H*5, *C*8 $\rightarrow$ 8-OCH_3 and ar-*H*7, *C*9 $\rightarrow$ ar-*H*2 and ar-*H*7, *C*10 $\rightarrow$ ar-*H*4 and ar-*H*5, *C*4a $\rightarrow$ ar-*H*4, *C*8a $\rightarrow$ ar-*H*5 and ar-*H*7, *C*9a $\rightarrow$ ar-*H*2 and ar-*H*4, *C*2′ $\rightarrow$ ar-*H*5 and ar-*H*7; NCI-MS (solid probe, CH_4): $m/z = 414$ ($[M]^-$); ESI-MS (*Me*OH:CH_2Cl_2 = 1:1 + 1% CF_3COOH, $\gamma = 1.0$ mg/cm^3, positive ion mode): $m/z = 415$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3261$ (NH), 2942, 2841 (CH-aliph), 1656 (CO), 1597 (C=C), 1562, 1460, 1325, 1260, 1148, 1018, 842, 754 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 309$ (100), 418 (85) nm (rel. int.).

6-(1,3-Benzothiazol-2-yl)-1,3,8-trimethoxyanthraquinone (**10**, $C_{24}H_{17}NO_5S$)

A mixture of 0.163 g of **1** (0.5 mmol) and 0.060 g of *o*-aminothiophenol (0.5 mmol) was refluxed in 20 cm^3 of nitrobenzene for 18 h. After cooling, the solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel using chloroform:ethyl acetate (4:1) as eluent to afford 0.150 g (70%) of **10**. Mp 292–294°C; TLC: $R_f = 0.65$ ($CHCl_3$:$CH_3COOC_2H_5$ = 2:1), $R_f = 0.92$ ($CHCl_3$:CH_3OH = 5:2); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 8.27$ (d, $J = 1.1$ Hz, ar-H5), 8.24 (d, $J = 7.8$ Hz, ar-H4′ or ar-H7′), 8.19 (d, $J = 7.8$ Hz, ar-H7′ or ar-H4′), 8.08 (d, $J = 1.1$ Hz, ar-H7), 7.62 (t, $J = 7.8$ Hz, ar-H5′ or ar-H6′), 7.55 (t, $J = 7.8$ Hz, ar-H6′ or ar-H5′), 7.24 (d, $J = 2.2$ Hz, ar-H4), 7.03 (d, $J = 2.2$ Hz, ar-H2), 4.07 (s, OCH_3), 3.97 (s, OCH_3), 3.93 (s, OCH_3) ppm; the ^{13}C spectrum could not be obtained due to the very poor solubility of this compound; ESI-MS (*Me*OH:CH_2Cl_2 = 1:1 + 1% CF_3COOH, $\gamma = 1.0$ mg/cm^3, positive ion mode): $m/z = 432$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3003$ (=CH),

2945, 2840 (CH-aliph), 1660 (CO), 1601 (C=C), 1565, 1456, 1410, 1352, 1251, 1165, 1069, 1001, 947, 895, 876, 777, 755, 666 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda_{max} = 234$ (100), 305 (76), 408 (24) nm (rel. int.).

6-[[(2-Hydroxyphenyl)imino]methyl]-1,3,8-trimethoxyanthraquinone (**11**, $C_{24}H_{19}NO_6$)

A mixture of 0.326 g of **1** (1 mmol) and 0.110 g of *o*-aminophenol (1 mmol) was refluxed in 20 cm^3 of nitrobenzene for 5 h. After cooling, the resulting precipitate was filtered, washed with ethanol, diethyl ether and dried to give 0.100 g of **11**. The filtrate was concentrated under vacuum, and the residue was purified by chromatography on silica gel using chloroform:ethyl acetate (4:1) as eluent to afford additional 0.220 g; overall yield 0.320 g (77%) of **11**. Mp 262–263°C; TLC: $R_f = 0.58$ ($CHCl_3$:$CH_3COOC_2H_5 = 2{:}1$), $R_f = 0.91$ ($CHCl_3$:$CH_3OH = 5{:}2$); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 9.22$ (s, ar-OH), 8.88 (s, –CH=N), 8.21 (s, ar-H5), 8.18 (s, ar-H7), 7.31 (d, $J = 7.6$ Hz, ar-H6′), 7.19 (d, $J = 2.2$ Hz, ar-H4), 7.14 (t, $J = 7.6$ Hz, ar-H5′), 6.98 (d, $J = 2.2$ Hz, ar-H2), 6.94 (d, $J = 7.6$ Hz, ar-H3′), 6.87 (t, $J = 7.6$ Hz, ar-H4′), 4.01 (s, 8-OCH_3), 3.94 (s, 3-OCH_3), 3.91 (s, 1-OCH_3) ppm; N*O*ESY (*DMSO*-d_6): 1-O*CH*$_3$ ↔ ar-*H*2, 3-O*CH*$_3$ ↔ ar-*H*2 and ar-*H*4, 8-O*CH*$_3$ ↔ ar-*H*7, 2′-O*H* ↔ ar-*H*3′, –C*H*=N ↔ ar-*H*6′, ar-*H*3′ ↔ ar-*H*4′, ar-*H*4′ ↔ ar-*H*5′, ar-*H*5′ ↔ ar-*H*6′; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 182.9$ (10-CO), 179.8 (9-CO), 163.5 (C3), 161.1 (C1), 159.1 (C8), 157.5 (C=N), 151.7 (C2′), 140.8 (C6), 137.0 (C1′), 135.5 (C4a), 134.3 (C10a), 128.3 (C5′), 124.8 (C8a), 119.5 (C4′), 119.2 (C6′ and C5), 117.7 (C9a), 117.2 (C7), 116.3 (C3′), 105.0 (C2), 102.3 (C4), 56.55 (8-OCH_3), 56.37 (1-OCH_3), 55.90 (3-OCH_3) ppm; HSQC (*DMSO*-d_6): ar-*H*2 ↔ *C*2, ar-*H*4 ↔ *C*4, ar-*H*5 ↔ *C*5, ar-*H*7 ↔ *C*7, 1-O*CH*$_3$ ↔ 1-O*C*H$_3$, 3-O*CH*$_3$ ↔ 3-O*C*H$_3$, 8-O*CH*$_3$ ↔ 8-O*C*H$_3$, –C*H*=N ↔ –*C*H = N, ar-*H*3′ ↔ *C*3′, ar-*H*4′ ↔ *C*4′, ar-*H*5′ ↔ *C*5′, ar-*H*6′ ↔ *C*6′; HMBC (*DMSO*-d_6): *C*1 → 1-O*CH*$_3$ and ar-*H*2, *C*2 → ar-*H*4, *C*3 → 3-O*CH*$_3$, ar-*H*2, and ar-*H*4, *C*4 → ar-*H*2, *C*5 → ar-*H*7 and –C*H*=N, *C*6 → ar-*H*7, ar-*H*5, and –C*H*=N, *C*7 → ar-*H*5 and –C*H* = N, *C*8 → 8-O*CH*$_3$ and ar-*H*7, *C*9 → ar-*H*2 and ar-*H*7, *C*10 → ar-*H*4 and ar-*H*5, *C*4a → ar-*H*4, *C*8a → ar-*H*5 and ar-*H*7, *C*9a → ar-*H*2 and ar-*H*4, –*C*H=N → ar-*H*5 and ar-*H*7, *C*1′ → –C*H*=N, 2′-O*H*, ar-*H*3′, ar-*H*4′, ar-*H*5′, and ar-*H*6′, *C*2′ → 2′–O*H*, ar-*H*3′, ar-*H*4′, ar-*H*5′, and ar-*H*6′, *C*3′ → 2′-O*H*, ar-*H*4′, ar-*H*5′, and ar-*H*6′, *C*4′ → ar-*H*3′, ar-*H*5′, and ar-*H*6′, *C*5′ → ar-*H*4′ and ar-*H*6′, *C*6′ → ar-*H*4′ and ar-*H*5′; NCI-MS (solid probe, CH_4): $m/z = 417$ ([M]$^-$); IR (KBr): $\bar{\nu} = 3417$ (OH), 2943, 2840 (CH-aliph), 1667 (CO), 1598 (C=C), 1566, 1460, 1375, 1325, 1254, 1070, 1025, 982, 946, 915, 886, 738, 657, 558 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 248$ (100), 290 (86), 422 (47) nm (rel. int.).

6-(1,3-Benzoxazol-2-yl)-1,3,8-trimethoxyanthraquinone (**12**, $C_{24}H_{17}NO_6$)

A mixture of 0.075 g of **11** (0.18 mmol) and 0.110 g of $(CH_3COO)_4Pb$ (0.25 mmol) was stirred in 15 cm^3 of CH_3COOH at 80°C for 16 h. After cooling, the product was collected by filtration, washed with water, acetone and diethyl ether, and dried under vacuum to yield 0.060 g (82%) of **12**. Mp 291–294°C; TLC: $R_f = 0.61$ ($CHCl_3$:$CH_3COOC_2H_5 = 2{:}1$), $R_f = 0.92$ ($CHCl_3$:$CH_3OH = 5{:}2$); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 8.44$ (s, ar-H5), 8.17 (s, ar-H7), 7.92–7.90 (m, 2ar-H), 7.54–7.47 (m, 2ar-H), 7.25 (d, $J = 2.2$ Hz, ar-H4), 7.04 (d, $J = 2.2$ Hz, ar-H2), 4.07 (s, OCH_3), 3.97 (s, OCH_3), 3.93 (s, OCH_3) ppm; the ^{13}C spectrum could not be obtained due to the very poor solubility of this compound; ESI-MS (*Me*OH:$CH_2Cl_2 = 2{:}3 + 1\%$ CF_3COOH, $\gamma = 1.0$ mg/cm^3, positive ion mode): $m/z = 416$ ([M + H]$^+$); IR (KBr): $\bar{\nu} = 3097$ (=CH), 2948, 2842 (CH-aliph), 1669 (CO), 1601 (C=C), 1566, 1457, 1415, 1353, 1250, 1203, 1167, 1147, 1117, 1066, 949, 885, 851, 786, 757, 657 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda_{max} = 238$ (97), 302 (100), 408 (26) nm (rel. int.).

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