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Streamlined Access to Functionalized Chromenes and Quinolines using Domino Reactions of Salicylic Aldehydes and Methyl 4-Chloro-2-butynoate

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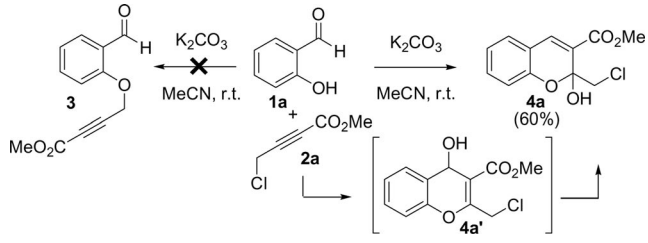
Methyl 4-chloro-2-butynoate was used in a modified Morita–Baylis–Hillman reaction with salicylic aldehydes. The chlorine atom in the alkynoate moiety allows its efficient isomerization to the corresponding allene, and remains in the adduct as a reactive site. Further one-pot derivatization leads to a variety of substituted chromenes and quinolines.

Introduction

Benzopyran and quinoline heterocyclic ring systems are present in a vast number of natural products and bioactive substances, with a wide application range.[1,2] These heterocycles are privileged structures, constituting pivotal drug-like scaffolds in medicinal chemistry, and have received much attention.[3] Therefore, simple and direct access to suitably functionalized precursors that may streamline the preparation of a variety of substituted derivatives is important in organic synthesis, with direct applications in medicinal chemistry. Especially appealing are methodologies leading to diverse scaffolds.[4]

Herein, we present our results in this area, and disclose a straightforward, one-pot protocol based on a domino reaction with salicylic aldehydes and 4-chloro-2-butynoate as initial synthetic inputs (Scheme 1). This reaction leads to functionalized adducts that are further derivatized to yield a diverse set of substituted benzopyrans and quinolines, displaying up to three diversity points. The process displays similarities to the Morita–Baylis–Hillman reaction (MBH), which has become a practical and versatile synthetic tool. Recent developments in the field include enantioselective versions, mechanistic studies, derivatization of the adducts and, interestingly, the application of a new set of reactants.[5] The pioneering work of Shi has paved the way to the inclusion of conjugated allenes in this process, showing the viability of this structural group in the preparation of substituted benzopyrans.[5b,6] However, in spite of reliable synthetic access to allenyl esters,[7] their preparation remains laborious because of the multistep sequences required. Furthermore, the alkynyl isomeric counterparts (i.e, the commercially available tetrolic esters), have proven to be unsuitable substrates, with sluggish reactions and poor conversion yields.[8]



Scheme 1. Preparation of chromene **4a**.

Results and Discussion

In the course of a different research project, we needed access to compound **3**, and envisaged its preparation by treatment of salicylic aldehyde (**1a**) with the readily available methyl 4-chloro-2-butynoate (**2a**).[9] Unexpectedly, the reaction furnished a mixture of 2*H*-chromene **4a** and 4*H*-chromene **4a′** instead (Scheme 1). Moreover, the 4*H*-chromene spontaneously isomerized through a 1,3-hydroxy shift to the 2*H*-isomer **4a** (isolated yield 60%) either upon chromatographic purification (SiO_2) or under slight acid catalysis (adventitious HCl in $CDCl_3$), which presumably reflects its greater thermodynamic stability.[10] It should be noted that on prolonged exposure to K_2CO_3, halohydrin **4a** slowly decomposed to give a complex mixture in which the putative epoxide could be detected (MS evidence).

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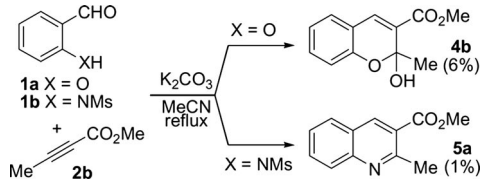
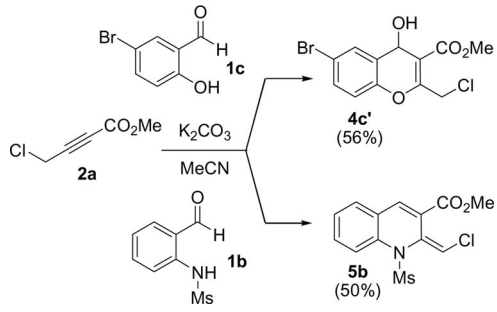
Initially, experiments were carried out by pre-forming the sodium salt of aldehyde **1a** and then slowly adding alkynoate **2a**. We found that comparable results were obtained by changing the order of addition of the reagents or base to the reaction medium. The reaction proceeded smoothly at room temperature in acetone, *N*,*N*-dimethylformamide (DMF) and acetonitrile (with better yields in the latter solvent), but was less productive in dichloromethane or in tetrahydrofuran (THF)/water mixtures. The base of choice was anhydrous K_2CO_3 but although theoretically a catalytic amount should have sufficed, it was determined that a slight molar excess (1.2 equiv.) was required.

The reactivity of methyl 4-bromo-2-butynoate[11] was then studied. Its reaction with salicylic aldehyde (**1a**) afforded the analogous chromene containing a salicyl substituent at the exocyclic methylene moiety (NMR and MS evidence). Interestingly, no reaction took place when methyl 3-phenylpropiolate was exposed to **1a** under the usual conditions. However, methyl 2-butynoate (**2b**) reacted sluggishly at reflux temperature for prolonged times to afford chromene **4b**[12] (6%, Scheme 2); when interacting with protected anthranilic aldehyde (**1b**),[14] the quinoline **5a**[13] was detected in trace amounts, presumably after spontaneous elimination–hydrolysis steps.



Scheme 2. Methyl 2-butynoate reactions.

These results suggest the intermediacy of isomeric allene species as the reactive inputs for this transformation, and highlight the active role of the chloromethyl substituent, which seems to efficiently promote the isomerization under mild conditions. We next attempted the reaction with 5-bromosalicylic aldehyde (**1c**), which successfully gave the corresponding benzopyran **4c′** (56%, Scheme 3). Interestingly, in this case, we isolated the non-isomerized adduct. The reasons for this unexpected behavior are not clear, considering Shi's observations on this isomerization process.[6] However, this material slowly converted into **4c** when exposed to acids, which is in agreement with the greater thermodynamic stability of the latter isomer, and probably means that the isomerization step is kinetically less favored in this series. When aldehyde **1b** was treated with the chloroalkynoate **2a**, the 1,2-dihydroquinoline derivative **5b** was obtained stereoselectively (50%; Scheme 3). The structure of this compound was confirmed by X-ray diffraction analysis (Figure 1). The possibility of accessing functionalized quinolines from 2-aminobenzaldehydes through an MBH-type reaction is noteworthy because previous approaches involved the use of *o*-nitrobenzaldehyde precursors.[5] On the other hand, the distinct reactivity pathways followed by the oxygen- and nitrogen-heterocyclic systems are being investigated, and may reflect subtle differences in the isomerization and elimination reaction rates promoted by the respective heteroatoms.



Scheme 3. Reaction of alkynoate **2a** with aldehydes **1c** and **1b**.

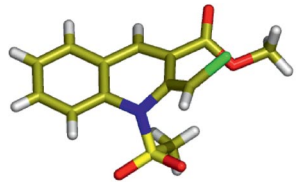
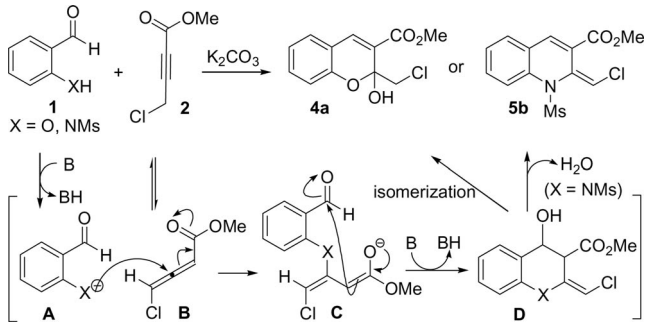


Figure 1. X-ray structure of quinoline derivative **5b**.

A likely mechanistic proposal that may account for the experimental observations is shown in Scheme 4. The alkynoate must isomerize to the allene derivative **B** to react with the anionic species **A**, setting the stage for the conjugate addition to afford enolate **C**. This step may take place with *anti* stereoselectivity, with the incoming nucleophile avoiding the same face as the chlorine atom, thereby exclusively forming the *E* isomer. The enolate then undergoes an intramolecular aldol reaction with the aldehyde, giving rise to the bicyclic intermediate **D**, which either readily isomerizes to **4a** (X = O), or dehydrates (X = NMs), affording 1,2-dihydroquinoline **5b**. The overall domino process comprises the following sequence: allene formation, conjugate addition, aldol cyclization, and a final dehydration or isomerization step.[6,8,15] This mechanistic hypothesis was supported by independent experiments in which, under Et_3N treatment, **B** was generated almost quantitatively at room temp. in one hour, although it began to decompose rapidly; however, when K_2CO_3 was used as the base, the rate of the reaction was slower (50% after 12 h at r.t.), but the stability

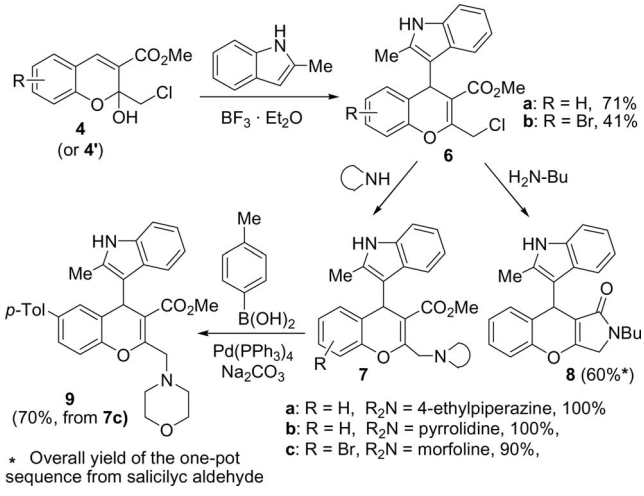


Scheme 4. Mechanistic proposal.

was higher, and subsequent treatment with salicylic aldehyde under the standard conditions afforded **4a** as expected.

The 4-chloro-2-butynoate substrate was the compound of choice for this transformation because use of this substrate balanced the reactivity toward a mild base (to generate the reactive allenoate **B**) at the same time as generating stable adducts that were ready for further derivatization. In sharp contrast, γ-unsubstituted 2-butynoates led to poor conversion under these conditions, presumably because it failed to provide suitable amounts of the allenoate. In this respect, it should be noted that Shi and Cao have documented relevant examples of the direct addition of salicylic aldehydes and imine derivatives to activated (highly electrophilic) alkynoates that take place without the participation of allenoate species.[16]

In this regard, chromenes **4** and **4′** are particularly attractive systems because their polyfunctional character offers the possibility of orthogonal transformations. The formation of stabilized cationic species by hydroxyl group activation through acid catalysis has been recently disclosed, and this has allowed the introduction of silyl enol ethers at the 4-position of activated 2*H*-chromenes.[17] To expand the nucleophile range, we reacted 2-methylindole with chromene **4a** in the presence of $BF_3{\cdot}Et_2O$.[18] Under these conditions, substitution at the 4-position occurred, giving rise to adduct **6a** (71%, Scheme 5). The same result was obtained when the crude mixture of isomers **4a** and **4a′** was employed, indicating that the 4-position in this chromene ring is the most reactive. Analogously, treatment of bromo-derivative **4c′** afforded the corresponding adduct **6b** (41%).



Scheme 5. Reaction of chromene **4** with indole and amines.

Next, the functionalization of compounds **6** was carried out with amines. Rewardingly, the reaction was selective and, whereas secondary amines cleanly afforded derivatives **7** in high yields, primary amines gave rise to the fused tricyclic lactam **8** with almost quantitative conversion at room temperature. The structure of this latter compound was confirmed by X-ray diffraction analysis (Figure 2), which also secured the assignment of the indole substitution in these series. We were also able to introduce an additional diversity element through the Suzuki coupling; thus, the bromo-derivative **7c** was treated with 4-tolylboronic acid under standard Pd-catalysis to conveniently afford adduct **9** (70%, Scheme 5).

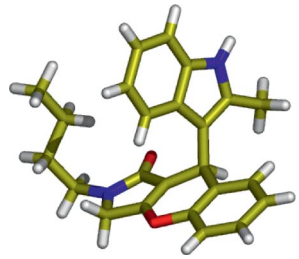
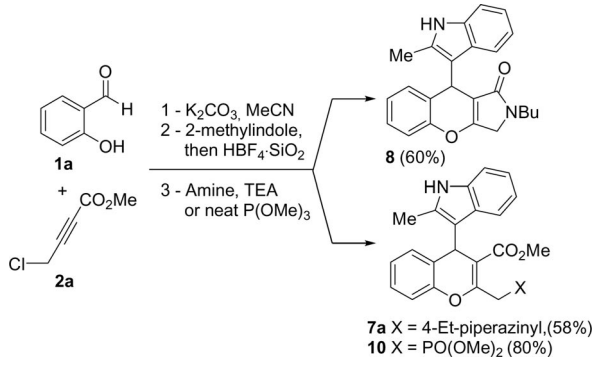


Figure 2. X-ray structure of lactam **8**.

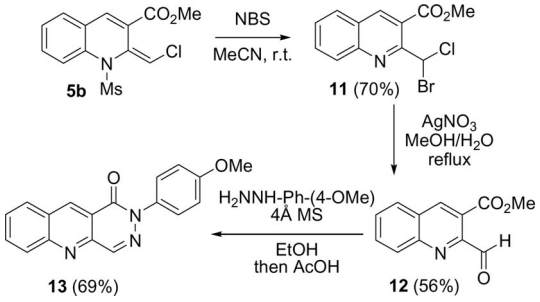
While searching for a robust and efficient route to polysubstituted chromenes **7** and **8**, we attempted a one-pot version of the entire process, starting from the reactants **1a** and **2a**. Recently, the acid catalyst $HBF_4{\cdot}SiO_2$[19] was successfully used in the electrophilic substitution of indoles.[20] We explored the compatibility of this catalyst with the basic MBH reaction system, which would allow both steps to be performed in tandem. Thus, 2-methylindole and an excess of $HBF_4{\cdot}SiO_2$ (to quench the K_2CO_3 and keep an acidic environment) were added to the reaction vessel in which compound **4a** was synthesized. Afterwards, the corresponding amine and the required amount of a neutralizing base were added to the mixture and the three-step sequence leading to substituted chromenes was successfully completed; compounds **7a** and **8** were obtained in 58% and 60% overall yields, respectively (Scheme 6). Similarly, phosphonate **10** (80%) was prepared by addition of neat trimethyl phosphite in the last step. Cyanide addition resulted in the formation of a somewhat unstable adduct that decomposed during attempts at purification.



Scheme 6. Tandem one-pot protocols.

We then explored the derivatization of quinoline derivative **5b**, which proved to be unreactive under a variety of hydrolytic, oxidative, and reductive conditions. Rewardingly, upon treatment with *N*-bromosuccinimide (NBS), we observed a clean conversion into the bromochloro-derivative **11** (70%, Scheme 7).[21] Subsequent $AgNO_3$-mediated hydrolysis[22] afforded the corresponding quinoline aldehyde **12**[23] (56%). Finally, successful reaction of this compound

with 4-methoxyphenyl hydrazine to obtain the pyridazinone adduct **13** (69%) demonstrated the feasibility of this approach to reach this biologically important scaffold.[24]



Scheme 7. Post-condensation reactions of quinoline **5b**.

Conclusions

We have developed a practical and versatile approach to polysubstituted 4*H*-chromenes and quinolines, based on the participation of 4-chloro-2-butynoate in a modified MBH-type reaction.[25] This complex cascade process can be applied in one-pot sequences to streamline the preparation of these derivatives.

Experimental Section

General: Chemicals were purchased and used without further purification. Room temp. refers to a temperature of 25 °C. Analytical thin layer chromatography (TLC) was carried out on pre-coated Merk silica gel 60 F254 plates and visualized under a UV lamp. ^{1}H NMR spectra were recorded with a Varian Mercury 400 (400 MHz) instrument using internal deuterium lock and $CDCl_3$ as a solvent (unless otherwise indicated). The chemical shift (δ) are given in units of parts per million (ppm) relative to tetramethylsilane (TMS; δ = 0.00 ppm). The multiplicity of each signal is indicated by: s (singlet), br. s (broad singlet), d (doublet), t (triplet), td (triplet of doublets), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (multiplet), or br. m (broad multiplet). Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded with a Varian Mercury 400 (101 MHz) instrument using internal deuterium lock and proton decoupling. The chemical shift data for each signal are given as δ in units of ppm relative to TMS (δ = 0.00 ppm). ^{31}P NMR spectra were recorded with a Varian Inova 300 (121.4 MHz) instrument using proton decoupling and internal deuterium lock. The chemical shift data for each signal are given as δ in units of ppm relative to an external standard of 85% H_3PO_4. IR spectra were recorded with a Thermo Nicolet Nexus spectrometer as thin films between KBr discs. Absorption maxima are reported in wavenumbers (cm^{-1}). Intensities of the maxima are quoted as: strong (s), medium (m), or weak (w). High Resolution Mass Spectrometry (HRMS) was performed by the University of Barcelona Mass Spectrometry Service. Flash Column chromatography was carried out on silica gel as indicated, under a positive pressure of compressed air.

General One-Pot Procedure for the Synthesis of 4*H*-Chromene Derivatives 7 and 8: Salicylaldehyde **1** (1.0 equiv.) and methyl 4-chlorobut-2-ynoate (**2a**; 1.1 equiv.) were dissolved in acetonitrile (0.1 M with respect to the aldehyde component), K_2CO_3 (1.2 equiv.) was added and the resulting mixture was stirred at r.t. for 6 h. 2-Methylindole (1.5 equiv.) was then added, followed by HBF_4·SiO_2 (until ca. pH 3),[26] and the resulting mixture was stirred for an additional 5 h. Triethylamine (until ca. pH 11) was then added to the mixture, followed by the corresponding primary or secondary amine (2.0 equiv.), and the resulting mixture was stirred overnight.

Methyl 2-(Chloromethyl)-2-hydroxy-2*H*-chromene-3-carboxylate (4a): Salycylaldehyde (**1a**, 442 mg, 3.62 mmol, 1.0 equiv.) and methyl 4-chlorobut-2-ynoate (**2a**, 528 mg, 3.98 mmol, 1.1 equiv.) were dissolved in acetonitrile (10 mL) and K_2CO_3 (600 mg, 4.34 mmol, 1.2 equiv.) was added. The resulting mixture was stirred at r.t. for 5 h. The solids were removed by filtration and the resulting solution was concentrated under reduced pressure. The residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **4a** as a yellow, waxy solid (552 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.39–7.35 (m, 1 H), 7.28–7.25 (m, 1 H), 7.04–7.00 (m, 2 H), 4.30 (d, J = 11.2 Hz, 1 H, CH_2), 4.07 (d, J = 11.2 Hz, 1 H, CH_2), 3.88 (s, 3 H, OCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.60, 152.58, 137.29, 133.15, 129.24, 122.36, 121.80, 118.20, 116.81, 98.28, 52.57, 49.28 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3032.7 (w), 2949.5 (w), 2847.0 (w), 1706.8 (s), 1629.9 (m), 1578.6 (w), 1489.0 (m), 1431.3 (m), 1278.0 (w), 1220.0 (s), 1104.6 (m), 1053.4 (s) cm^{-1}. HRMS: calcd. for $C_{12}H_{12}ClO_4$ $[M + H]^+$ 255.0419; found 255.0424; calcd. for $C_{12}H_{10}ClO_3$ $[M – OH]^+$ 237.0313; found 237.032; calcd. for $C_{12}H_{11}O_4$ $[M – Cl]^+$ 219.0652; found 219.066.

Methyl 6-Bromo-2-(chloromethyl)-4-hydroxy-4*H*-chromene-3-carboxylate (4c′): 5-Bromo-2-hydroxybenzaldehyde (**1c**; 1.0 g, 4.97 mmol, 1.0 equiv.) and methyl 4-chlorobut-2-ynoate (**2a**; 983 μL, 7.45 mmol, 1.5 equiv.) were dissolved in acetonitrile (10 mL) and K_2CO_3 (690 mg, 4.97 mmol, 1.0 equiv.) was added. The resulting mixture was stirred at r.t. for 6 h. The solids were removed by filtration and the resulting solution was concentrated under reduced pressure. The residue was adsorbed onto silica gel and purified by silica gel flash chromatography (hexane/ethyl acetate) to give **4c′** as a yellow, waxy solid (922 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 2.4 Hz, 1 H), 7.47 (dd, J = 8.7, 2.4 Hz, 1 H), 7.06 (d, J = 8.7 Hz, 1 H), 5.62 (s, 1 H), 4.12 (d, J = 4.0 Hz, 1 H, CH_2), 3.94 (d, J = 4.1 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.16, 155.71, 150.18, 134.04, 132.48, 120.71, 119.44, 115.62, 102.41, 54.43, 51.59 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3429 (w, br), 2951 (m), 2853 (w), 1715 (s), 1634 (m), 1479 (s), 1228 (s), 1056 (m) cm^{-1}. HRMS: calcd. for $C_{12}H_9BrClO_3$ $[M – HO]^+$ 314.9418; found 314.9417.

(*E*)-Methyl 2-(Chloromethylene)-1-(methylsulfonyl)-1,2-dihydroquinoline-3-carboxylate (5b): *N*-Mesyl 2-aminobenzaldehyde (**1b**; 398 mg, 2.0 mmol, 1.0 equiv.) and methyl 4-chlorobut-2-ynoate (292 mg, 2.2 mmol, 1.1 equiv.) were dissolved in acetonitrile (10 mL) and K_2CO_3 (332 mg, 2.4 mmol, 1.2 equiv.) was added. The resulting mixture was heated to reflux with stirring for 16 h. The solids were then removed by filtration, the resulting solution was concentrated under reduced pressure and the residue was adsorbed onto silica and purified by flash chromatography on silica gel (hexane/ethyl acetate), to give **5b** as a colorless solid (310 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.1 Hz, 1 H), 7.45–7.36 (m, 3 H), 7.32 (td, J = 7.5, 1.1 Hz, 1 H), 6.60 (s, 1 H), 3.91 (s, 3 H, OCH_3), 2.75 (s, 3 H, SO_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.84, 137.14, 134.46, 131.01, 129.14, 129.03, 127.33, 126.08, 125.89, 125.53, 124.30, 52.95, 37.73 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3090.4 (w), 3007.1 (w), 2943.1 (w), 1718.7 (s), 1553.0 (w), 1348.0 (s), 1252.0 (m), 1207.1 (m), 1066.2 (m), 950.9 (m) cm^{-1}. HRMS: calcd. for $C_{13}H_{13}ClNO_4S$ $[M + H]^+$ 314.0254; found

314.0248; calcd. for $C_{12}H_{10}ClNO_2$ $[M - SO_2CH_2]^+$ 235.0394; found 235.0393.

Methyl 2-(Chloromethyl)-4-(2-methyl-1*H*-indol-3-yl)-4*H*-chromene-3-carboxylate (6a): Method 1: Compound **4a** (75 mg, 0.29 mmol, 1.0 equiv.) was dissolved in anhydrous dichloromethane (2 mL) under an atmosphere of argon. The mixture was cooled to –78 °C, $BF_3{\cdot}EtO_2$ (40 μL, 0.32 mmol, 1.1 equiv.) was added and the resulting mixture was stirred at –78 °C for 5 min, then 2-methylindole (46.3 mg, 0.35 mmol, 1.2 equiv.) was added and the mixture was warmed to r.t. and stirred overnight. The mixture was washed with satd. aq. sodium hydrogen carbonate (3 times), dried with Na_2SO_4 and concentrated under reduced pressure. The resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **6a** as a pale-brown solid (76 mg, 71%).

Method 2: Compound **4a** (667 mg, 2.6 mmol, 1.0 equiv.) then 2-methylindole (515 mg, 3.9 mmol, 1.5 equiv.) were dissolved in acetonitrile, $HBF_4{\cdot}SiO_2$ (100 mg) was added and the resulting mixture was stirred for 6 h. The mixture was then filtered and the solvent was removed under reduced pressure. The resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **6a** as a pale-brown solid (523 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (br. s, 1 H, NH), 7.42 (d, J = 7.79 Hz, 1 H), 7.20 (d, J = 7.79 Hz, 1 H), 7.14–6.91 (m, 6 H), 5.42 (s, 1 H, 4-H), 4.83 (d, J = 11.3 Hz, 1 H, CH_2), 4.74 (d, J = 11.3 Hz, 1 H, CH_2), 3.60 (s, 3 H, OCH_3), 2.43 (s, 3 H, C-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.86, 155.41, 149.39, 135.16, 132.00, 129.58, 127.83, 127.61, 125.07, 123.73, 121.18, 119.76, 118.38, 116.18, 116.14, 110.44, 108.16, 51.97, 40.91, 31.99, 12.07 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3391.5 (s, br.), 2949.5 (w), 2911.0 (w), 1719.6 (s), 1698.7 (s), 1614.5 (w), 1586.4 (m), 1558.3 (s), 1431.8 (m), 1337.0 (m), 1217.6 (s), 1101.7 (m), 1056.0 (m), 926.5 (w) cm^{-1}. HRMS: calcd. for $C_{21}H_{22}ClN_2O_3$ $[M + NH_4]^+$ 385.1313; found 385.1321.

Methyl 6-Bromo-2-(chloromethyl)-4-(2-methyl-1*H*-indol-3-yl)-4*H*-chromene-3-carboxylate (6b): Compound **4c′** (760 mg, 2.40 mmol, 1.0 equiv.) then 2-methylindole (331 mg, 2.52 mmol, 1.05 equiv.) were dissolved in acetonitrile, $HBF_4{\cdot}SiO_2$ (80 mg) was added and the resulting mixture was stirred for 6 h. The mixture was then filtered and the solvent removed under reduced pressure. The resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **6b** as a yellow solid (413 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 1 H, NH), 7.38 (d, J = 7.8 Hz, 1 H), 7.23 (m, J = 8.7, 2.4 Hz, 2 H), 7.02 (m, 4 H), 5.37 (s, 1 H, 4-H), 4.82 (d, J = 11.4 Hz, 1 H, CH_2), 4.73 (m, 1 H, CH_2), 3.61 (s, 3 H, OCH_3), 2.44 (s, 3 H, C-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.43, 155.14, 148.50, 135.18, 132.19, 132.10, 130.92, 127.35, 125.83, 121.35, 119.88, 118.19, 118.03, 117.33, 115.45, 110.50, 107.99, 52.03, 40.65, 31.94, 12.08 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3400 (s, br.), 3056 (w), 2951 (m), 2917 (m), 2855 (w), 1713 (s), 1649 (s) cm^{-1}. HRMS: calcd. for $C_{21}H_{17}BrClNNaO_3$ $[M + Na]^+$ 467.9978; found 467.9971.

Methyl 2-[(4-Ethylpiperazin-1-yl)methyl]-4-(2-methyl-1*H*-indol-3-yl)-4*H*-chromene-3-carboxylate (7a): Method 1: Compound **6a** (200 mg, 0.54 mmol, 1.0 equiv.) was dissolved in acetonitrile (8 mL), *N*-ethyl piperazine (145 μL, 1.14 mmol, 2.1 equiv.) was added and the resulting mixture was stirred at r.t. for 20 h. The solvent was removed under reduced pressure and the resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (dichloromethane/methanol) to furnish **7a** in quantitative yield (240 mg).

Method 2: Compound **7a** was prepared according to the general one-pot procedure, using salicylaldehyde **1a** (200 mg, 1.64 mmol, 1.0 equiv.), methyl 4-chlorobut-2-ynoate **2a** (239 mg, 1.80 mmol, 1.1 equiv.), 2-methylindole (322 mg, 2.46 mmol, 1.5 equiv.) and *N*-ethyl piperazine (416 μL, 3.28 mmol, 2.0 equiv.). The crude product was purified by flash chromatography on silica gel (dichloromethane/methanol) affording **7a** (426 mg, 58% overall yield with respect to salicylaldehyde **1a**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, NH), 7.36 (d, J = 7.9 Hz, 1 H), 7.19 (d, J = 7.9 Hz, 1 H), 7.12–6.99 (m, 3 H), 6.98–6.86 (m, 3 H), 5.40 (s, 1 H, 4-H), 3.89 (d, J = 13.5 Hz, 1 H, CH_2), 3.70 (d, J = 13.5 Hz, 1 H, CH_2), 3.55 (s, 3 H, OCH_3), 2.88–2.77 (br. m, 4 H), 2.74–2.62 (br. m, 4 H), 2.58 (q, J = 7.3 Hz, 2 H, CH_2-Me), 2.45 (s, 3 H, C-CH_3), 1.17 (t, J = 7.3 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.80, 156.29, 149.53, 135.33, 131.70, 129.53, 127.59, 127.52, 124.70, 124.11, 121.00, 119.43, 118.45, 116.27, 116.06, 110.47, 108.81, 57.25, 52.64, 52.40, 52.32, 51.59, 32.17, 12.01, 11.40 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3391.5 (w, br.), 3173.7 (w), 3045.5 (w), 2936.6 (m), 2802.1 (m), 1706.8 (s), 1649.1 (w), 1585.0 (m), 1489.0 (m), 1328.8 (w), 1213.5 (s), 1047.0 (m) cm^{-1}. HRMS: calcd. for $C_{27}H_{32}N_3O_3$ $[M + H]^+$ 446.2438; found 446.2445.

Methyl 4-(2-Methyl-1*H*-indol-3-yl)-2-(pyrrolidin-1-ylmethyl)-4*H*-chromene-3-carboxylate (7b): Compound **6a** (160 mg, 0.45 mmol, 1.0 equiv.) was dissolved in acetonitrile (7 mL), pyrrolidine (126 μL, 1.36 mmol, 3.0 equiv.) was added and the resulting mixture was stirred at r.t. for 20 h. The solvent was removed under reduced pressure and the resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate) furnishing compound **7b** in quantitative yield (175 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H, NH), 7.42 (d, J = 7.8 Hz, 1 H), 7.17 (d, J = 7.9 Hz, 1 H), 7.10–6.99 (m, 3 H), 6.99–6.94 (m, 2 H), 6.92–6.86 (m, 1 H), 5.42 (s, 1 H, 4-H), 4.07 (d, J = 13.5 Hz, 1 H, CH_2), 3.82 (d, J = 13.5 Hz, 1 H, CH_2), 3.55 (s, 3 H, OCH_3), 2.77 (d, J = 3.9 Hz, 4 H, CH_2-CH_2-N), 2.42 (s, 3 H, C-CH_3), 1.82 (s, 4 H, CH_2-CH_2-N) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.80, 157.61, 149.58, 135.26, 131.60, 129.42, 127.56, 127.46, 124.55, 124.18, 120.91, 119.40, 118.50, 116.28, 116.26, 110.33, 107.73, 54.67, 54.25, 51.46, 32.04, 23.78, 11.94 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3399 (m), 3054 (w), 2951 (m), 1713 (s), 1458 (s), 1217 (s), 1189 (m), 1054 (m) cm^{-1}. HRMS: calcd. for $C_{25}H_{27}N_2O_3$ $[M + H]^+$ 403.2022; found 403.2014.

Methyl 6-Bromo-4-(2-methyl-1*H*-indol-3-yl)-2-(morpholinomethyl)-4*H*-chromene-3-carboxylate (7c): Compound **6b** (410 mg, 0.92 mmol, 1.0 equiv.) was dissolved in acetonitrile (6 mL), K_2CO_3 (140 mg, 1.01 mmol, 1.1 equiv.) followed by morpholine (88 μL, 1.01 mmol, 1.1 equiv.) were added and the resulting mixture was stirred at r.t. for 16 h. The solvent was removed under reduced pressure and the resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **7c** as a yellow solid (410 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, NH), 7.34 (d, J = 7.9 Hz, 1 H), 7.24–7.16 (m, 2 H), 7.09–7.02 (m, 2 H), 7.00–6.92 (m, 2 H), 5.37 (s, 1 H, 4-H), 3.82 (d, J = 13.5 Hz, 1 H, CH_2), 3.73 (m, 5 H), 3.57 (s, 3 H, OCH_3), 2.66 (dd, J = 7.1, 3.7 Hz, 4 H, CH_2-CH_2-N), 2.45 (s, 3 H, C-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.39, 156.10, 148.63, 135.31, 132.11, 131.69, 130.66, 127.21, 126.20, 121.21, 119.57, 118.28, 118.10, 116.91, 115.41, 110.47, 108.65, 67.21, 57.69, 53.79, 51.61, 32.10, 11.94 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3395 (s, br.), 2952 (s), 2855 (s), 1714 (s), 1476 (s) cm^{-1}. HRMS: calcd. for $C_{25}H_{26}BrN_2O_4$ $[M + H]^+$ 497.1076; found 497.1068.

2-Butyl-9-(2-methyl-1*H*-indol-3-yl)-2,3-dihydrochromeno[3,2-*c*]-pyrrol-1(9*H*)-one (8): Compound **8** was prepared according to the

general one-pot procedure, using salicylaldehyde (**1a**; 100 mg, 0.82 mmol, 1.0 equiv.), 4-chlorobut-2-ynoate (**2a**; 120 mg, 0.90 mmol, 1.1 equiv.), 2-methylindole (161 mg, 1.23 mmol, 1.5 equiv.), and *n*-butylamine (162 μL, 1.64 mmol, 2.0 equiv.). The crude product was purified by flash chromatography on silica gel (dichloromethane/methanol) to afford **8** (182 mg, 60% overall yield with respect to salicylaldehyde **1a**). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 10.77 (s, 1 H, NH), 7.23–7.14 (m, 3 H), 7.05–6.96 (m, 2 H), 6.92 (d, J = 7.8 Hz, 1 H), 6.86 (t, J = 7.2 Hz, 1 H), 6.70 (t, J = 7.3 Hz, 1 H), 5.09 (s, 1 H, 9-H), 4.21 (d, J = 18.2 Hz, 1 H, CH_2), 4.14 (d, J = 18.2 Hz, 1 H, CH_2), 3.31 (s, 3 H, C-CH_3), 3.29–3.20 (m, 1 H), 3.20–3.11 (m, 1 H), 1.47–1.31 (m, 2 H), 1.23–1.11 (m, 2 H), 0.81 (t, J = 7.3 Hz, 3 H, -CH_2-CH_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 168.67, 160.52, 150.19, 135.12, 132.18, 130.84, 127.83, 126.78, 124.81, 124.52, 119.65, 118.16, 116.99, 116.41, 112.93, 110.48, 107.77, 47.23, 40.32, 30.02, 28.19, 19.39, 13.55, 11.54 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3269.7 (m, br.), 3052.0 (w), 2955.9 (w), 2917.4 (w), 2859.8 (w), 1696.2 (m), 1668.6 (s), 1650.1 (s), 1557.9 (s), 1456.5 (s), 1392.2 (m), 1251.3 (w), 1078.3 (m) cm^{-1}. HRMS: calcd. for $C_{24}H_{25}N_2O_2$ [M + H]$^+$ 373.1911; found 373.1913.

Methyl 4-(2-Methyl-1*H*-indol-3-yl)-2-(morpholinomethyl)-6-(*p*-tolyl)-4*H*-chromene-3-carboxylate (9): Compound **7c** (110 mg, 0.23 mmol, 1.0 equiv.), 4-methyl boronic acid (88 mg, 0.57 mmol, 2.5 equiv.), and $Pd(PPh_3)_4$ (26 mg, 0.023 mmol, 0.01 equiv.) were placed in a Schlenk tube under an atmosphere of argon. *N*,*N*-Dimethylformamide (3 mL) and aq. Na_2CO_3 (2 M, 912 μL, 1.82 mmol, 8.0 equiv.) were added and the resulting mixture was heated to 150 °C for 24 h. The mixture was then filtered through Celite, the solvent was removed under reduced pressure and the residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (hexane/ethyl acetate), furnishing **9** as a colorless solid (79 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (s, 1 H, NH), 7.35 (d, J = 7.8 Hz, 1 H), 7.25–7.17 (m, 3 H), 7.11 (d, J = 7.9 Hz, 1 H), 7.08–7.03 (m, 4 H), 6.95 (t, J = 7.5 Hz, 1 H), 6.89 (t, J = 7.4 Hz, 1 H), 5.38 (s, 1 H, 4-H), 3.80 (d, J = 13.5 Hz, 1 H, CH_2), 3.70–3.62 (m, 5 H), 3.50 (s, 3 H, OCH_3), 2.64–2.54 (m, 4 H), 2.40 (s, 3 H, C-CH_3), 2.25 (s, 3 H, C-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.78, 156.57, 148.98, 137.80, 137.72, 136.99, 135.34, 131.54, 129.54, 127.89, 127.54, 126.90, 126.31, 124.35, 121.11, 119.54, 118.65, 116.64, 116.18, 110.36, 108.79, 67.35, 57.84, 53.85, 51.59, 32.39, 21.25, 12.12 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3405 (w), 2949 (w), 2855 (w), 1713 (m), 1489 (s), 1212 (s), 1115 (m) cm^{-1}. HRMS: calcd. for $C_{32}H_{33}N_2O_4$ [M + H]$^+$ 509.2440; found 509.2441.

Methyl 2-[(Dimethoxyphosphoryl)methyl]-4-(2-methyl-1*H*-indol-3-yl)-4*H*-chromene-3-carboxylate (10): Compound **10** was prepared using a modified version of the general one-pot procedure. Salicylaldehyde (**1a**; 250 mg, 2.05 mmol, 1.0 equiv.) and methyl 4-chlorobut-2-ynoate (**2a**; 300 mg, 2.25 mmol, 1.1 equiv.) were dissolved in acetonitrile (20 mL), K_2CO_3 (340 mg, 2.46 mmol, 1.2 equiv.) was added and the resulting mixture was stirred at r.t. for 6 h. 2-Methylindole (402 mg, 3.08 mmol, 1.5 equiv.) was then added, followed by HBF_4·SiO_2 (amount required to reach ca. pH 3), and the resulting mixture was stirred for an additional 6 h. The mixture was treated with solid $NaHCO_3$ (500 mg) and the solids were removed by filtration, the mixture was concentrated under reduced pressure and the residue was redissolved in neat $P(OMe)_3$. The resulting solution was heated to reflux overnight, then concentrated under reduced pressure and the resulting residue was adsorbed onto silica gel and purified by flash chromatography on silica gel (dichloromethane/methanol) to afford **10** (722 mg, 80% overall yield with respect to salicylaldehyde **1a**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1 H, NH), 7.41 (d, J = 7.8 Hz, 1 H), 7.19 (d, J = 7.9 Hz, 1 H), 7.12–7.06 (m, 1 H), 7.05–6.99 (m, 2 H), 6.99–6.94 (m, 2 H), 6.93–6.88 (m, 1 H), 5.42 (d, J = 4.5 Hz, 1 H, 4-H), 3.90 (ddd, J = 22.2, 14.7, 0.8 Hz, 1 H, CH_2), 3.78 (d, J = 10.9 Hz, 3 H, P-OCH_3), 3.76 (d, J = 10.9 Hz, 3 H, P-OCH_3), 3.61–3.50 (m, 4 H), 2.42 (s, 3 H, C-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.60 (d, J_{C-P} = 3.2 Hz), 152.52 (d, J_{C-P} = 12.7 Hz), 149.45, 135.31, 132.03, 129.68, 127.62, 127.59, 124.91, 124.23, 120.86, 119.41, 118.36, 116.06 (d, J_{C-P} = 3.2 Hz), 115.88, 110.46, 107.78 (d, J_{C-P} = 9.8 Hz), 53.16 (d, J_{C-P} = 6.6 Hz), 53.15 (d, J_{C-P} = 6.5 Hz), 51.67, 31.91 (d, J_{C-P} = 1.7 Hz), 29.88 (d, J_{C-P} = 136.6 Hz), 11.86 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 26.21 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3256.9 (m, br.), 2994.3 (w), 2049.5 (m), 2853.4 (m), 1693.9 (s), 1655.5 (m), 1450.5 (w), 1335.2 (w), 1213.5 (s), 1104.6 (w), 1047.0 (s) cm^{-1}. HRMS: calcd. for $C_{23}H_{25}NO_6P$ [M + H]$^+$ 442.1414; found 442.1418; calcd. for $C_{23}H_{24}NNaO_6P$ [M + Na]$^+$ 464.1233; found 464.1233.

Methyl 2-(Bromochloromethyl)quinoline-3-carboxylate (11): Compound **5b** (100 mg, 0.33 mmol, 1.0 equiv.) was dissolved in acetonitrile (2 mL), *N*-bromosuccinimide (118 mg, 0.69 mmol, 2.1 equiv.) was added and the resulting mixture was stirred at r.t. for 2 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (hexane/ethyl acetate), affording **11** as a colorless solid (73 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.87 (s, 1 H, 4-H), 8.27 (dd, J = 8.5, 0.7 Hz, 1 H), 8.20 (s, 1 H, -CHClBr), 7.93 (d, J = 8.1 Hz, 1 H), 7.90 (ddd, J = 8.5, 7.0, 1.3 Hz, 1 H), 7.67 (ddd, J = 8.5, 7.0, 1.3 Hz, 1 H), 4.04 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.74, 155.53, 148.88, 141.50, 132.93, 129.91, 128.86, 128.72, 127.04, 119.60, 55.90, 53.26 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3064.8 (m, br.), 2949.5 (m), 1777.2 (w), 1706.7 (s), 1649.1 (w), 1431.3 (w), 1284.0 (w), 1162.3 (s), 1060.0 (w), 848.4 (w) cm^{-1}. HRMS: calcd. for $C_{12}H_{10}BrClNO_2$ [M + H]$^+$ 313.9578; found 313.9577; calcd. for $C_{12}H_9ClNO_2$ [M – Br]$^+$ 234.0316; found 234.0320.

Methyl 2-Formylquinoline-3-carboxylate (12): Compound **11** (180 mg, 0.57 mmol, 1.0 equiv.) was dissolved in a methanol/water mixture (3:1, 4 mL) and silver nitrate (290 mg, 1.7 mmol, 3.0 equiv.) was added. The resulting mixture was heated to reflux for 2 h, then cooled to r.t., concentrated under reduced pressure and a mixture of ethyl acetate and satd. aq. ammonium chloride was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (×3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **12** as a colorless solid (69 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.40 (s, 1 H, CHO), 8.60 (s, 1 H, 4-H), 8.29 (d, J = 8.0 Hz, 1 H), 7.95 (d, J = 7.9 Hz, 1 H), 7.90 (ddd, J = 8.1, 7.0, 1.4 Hz, 1 H), 7.74 (ddd, J = 8.1, 7.0, 1.4 Hz, 1 H), 4.02 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.79, 167.16, 151.47, 148.20, 138.74, 132.40, 130.66, 129.97, 128.61, 128.04, 124.64, 53.30 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3052.0 (w), 2949.5 (m), 2834.2 (w), 1731.6 (m), 1713.2 (s), 1553.0 (m), 1431.3 (m), 1245.6 (s), 1207.1 (m), 1123.8 (w), 1066.2 (s) cm^{-1}. HRMS: calcd. for $C_{12}H_{10}NO_3$ [M + H]$^+$ 216.0655; found 216.0659; calcd. for $C_{12}H_9NNaO_3$ [M + Na]$^+$ 238.0475; found 238.0473.

2-(4-Methoxyphenyl)pyridazino[4,5-*b*]quinolin-1(2*H*)-one (13): Compound **12** (34 mg, 0.16 mmol, 1.0 equiv.) was dissolved in anhydrous ethanol (1 mL) under an atmosphere of argon in the presence of activated 4 Å molecular sieves. 4-Methoxyphenylhydrazine (26 mg, 0.19 mmol, 1.2 equiv.) was added and the resulting mixture was stirred for 3 h at r.t., after which time conversion into the corresponding hydrazone was complete. Fuming acetic acid (45 μL,

0.79 mmol, 5.0 equiv.) was added and the resulting mixture was heated to reflux overnight. The mixture was then filtered, the solvent was removed under reduced pressure and the residue was taken up in ethyl acetate/satd. aq. sodium hydrogen carbonate. The layers were separated and the aqueous layer was extracted with ethyl acetate (×3). The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate) to give **13** (33 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (s, 1 H, 4-H), 8.65 (s, 1 H, 10-H), 8.30 (d, J = 8.7 Hz, 1 H), 8.14 (d, J = 8.3 Hz, 1 H), 7.98 (ddd, J = 8.3, 6.8, 1.3 Hz, 1 H), 7.75 (t, J = 8.3 Hz, 1 H), 7.61 (d, J = 9.0 Hz, 2 H), 7.04 (d, J = 9.0 Hz, 2 H), 3.88 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.43, 159.24, 151.51, 145.42, 140.69, 137.95, 134.75, 133.39, 130.15, 129.65, 128.94, 128.78, 127.09, 121.97, 114.34, 55.80 ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3051.7 (w), 2949.5 (w), 2917.4 (w), 2840.6 (w), 1661.9 (s), 1610. (m), 1501.8 (w), 1495.4 (m), 1091.8 (s) cm^{-1}. HRMS: calcd. for $C_{18}H_{14}N_3O_2$ $[M + H]^+$ 304.1081; found 304.1082; calcd. for $C_{18}H_{13}N_3NaO_2$ $[M + Na]^+$ 326.0900; found 326.0901.

CCDC-788117 (for **5b**) and -788116 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds.

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