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# Synthesis of Two Unnatural Oxygenated Aaptaminoids

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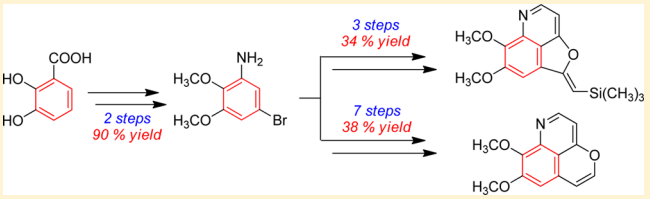
Supporting Information

**ABSTRACT:** Two unprecedented oxygenated aaptaminoids have been synthesized starting from cheap and easily available 2,3-dihydroxybenzoic acid with the satisfactory overall yields of 31% and 34%. The key step of the procedure is the divergent thermic 5-*exodig* vs base-promoted 6-*endodig* cyclization of a 5-alkynylquinolinone derivative.




Aaptamine[1] **I** is the ancestor of a series of natural alkaloids known as "aaptamines" and characterized by the presence of a benzo[*de*][1,6]naphthyridine ring in their framework (Figure 1). All aaptamines have been isolated from marine

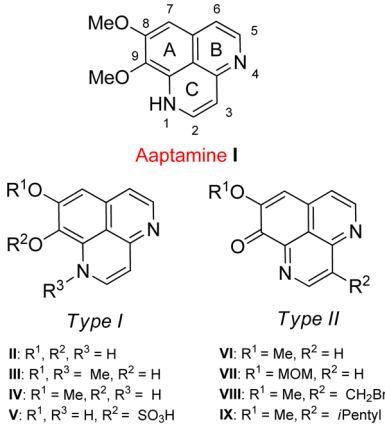



**Figure 1.** Main members of the family of tricyclic aaptamines.

sponges of the class *Demospongiae* (also called "horny sponges" or "siliceous sponges"), the largest class in the phylum *Porifera*. In particular, sponges of genus *Aaptos* are the most important producers of aaptamines.

Aaptamine **I** was isolated for the first time in 1981 by the Nakamura group[2] from the sponge *Aaptos aaptos* (Schmidt, 1864) collected off the Okinawa island coast. Five years later, the same group isolated from the same kind of sponge (*A. aaptos*) two congeners, the 9-demethylaaptamine **IV** and the demethyloxyaaptamine **VI**[3] (Figure 1). Over the following years aaptamine **I** and its congeners have been found in many other horny sponges collected from the Indian Ocean and the Red Sea, off the coasts of Australia, Indonesia, and Malaysia, from the Caribbean Sea, and off the Brazilian coast.

Aaptamines show a broad range of pharmacological activities such as antioxidant and scavenger of free radicals, enzymatic inhibitor, antiviral, antimicrobial, and antifungal agents, cytotoxic agent, and antagonist of some receptors. In particular, the ancestor aaptamine **I** shows in vitro a significant antioxidant activity[4] (albeit slightly lower than those of isoaaptamine **III** and demethylaaptamine **IV**, Figure 1), a moderate antifungal activity toward *Candida tropicalis*,[5] and an interesting cytotoxic activity toward cancer cells.[1,6] It is an especially effective competitive $\alpha$-adrenoceptor antagonist endowed with potential cardiotonic effects.[7]

A number of total syntheses of aaptamine have been reported,[1,8] involving two conceptually different approaches for the construction of the benzo[*de*][1,6]naphthyridine ring (Figure 2): the synthesis of a new pyridine ring fused with a preformed isoquinoline scaffold (AB)[9] or fused with a quinoline skeleton (AC).[10]

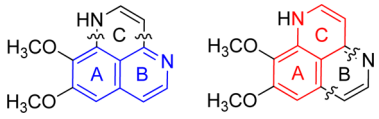



**Figure 2.** Disconnections in reported total synthesis of aaptamine **I**.

For several years, we have been interested in the development of domino strategies[11] for the synthesis of nitrogen-containing heterocycles[12] starting from alkynes.[13] Many efforts have been devoted to the synthesis of nitrogen-containing rings by tandem imination/annulation of $\gamma$- or $\delta$-ketoalkynes in the presence of ammonia.[14,15] In particular, a series of substituted isoquinolines have been recently obtained by microwave-enhanced domino reactions of *o*-alkynylbenzaldehydes[16] and *o*-alkynylacetophenones[17] (the latter, with the aid of silver

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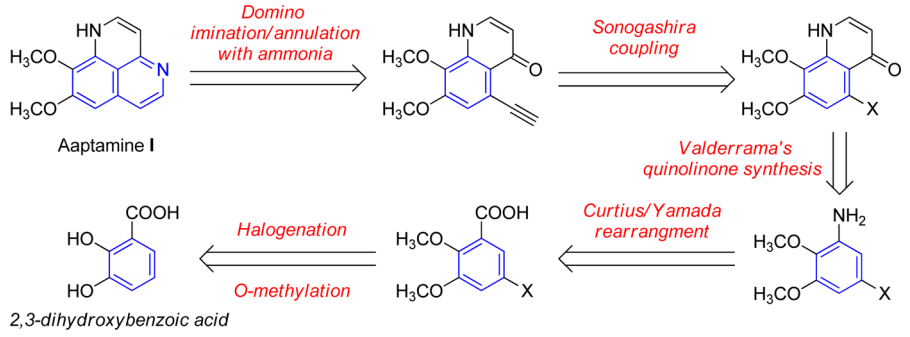
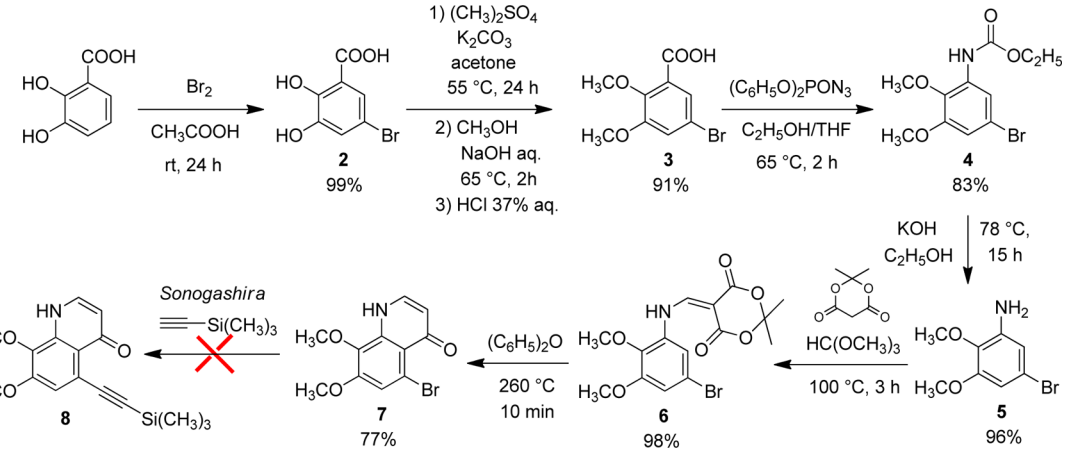
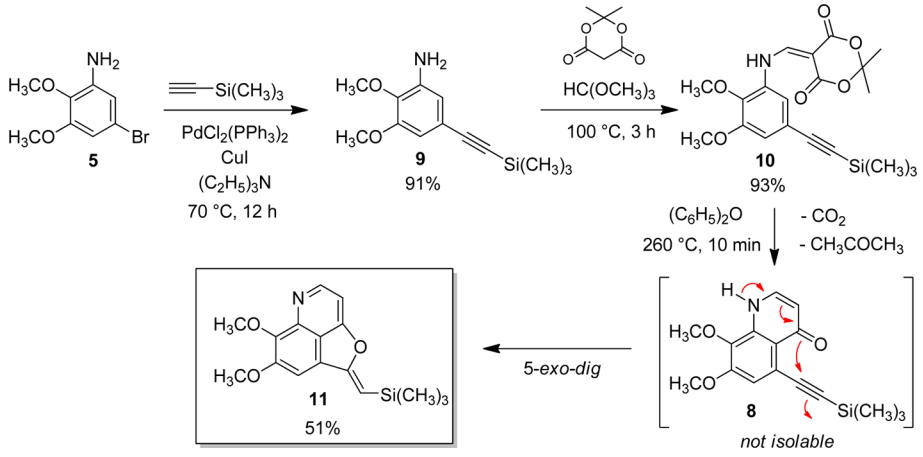
**Scheme 1. Retrosynthetic Analysis**




**Scheme 2. Synthesis of Quinolinone 7 and the First Attempt to Key Intermediate 8**




**Scheme 3. Synthesis of Oxygenated Aaptaminoid 11**




catalysis). The approach was also successfully transformed into a multicomponent process starting from simple *o*-bromobenzaldehyde, terminal alkynes, and ammonia.[18] Bearing in mind the strategies reported in the literature, we were intrigued to verify the possibility to apply our domino approach to the isoquinoline nucleus as a key step for a new total synthesis of aaptamine **I**. Thus, we planned a retrosynthetic analysis (Scheme 1) that involves our imination/cyclization sequence on a properly substituted 5-ethynylquinolin-4(1*H*)-one as final key-step. The 5-ethynylquinolin-4(1*H*)-one seemed to be easily obtainable by a classical Sonogashira coupling between the corresponding 5-haloquinolin-4(1*H*)-one and a terminal alkyne. Substituted quinolinone could be prepared by the Valderrama's synthesis starting from properly functionalized aniline, in turn obtainable through a Curtius–Yamada rearrangement starting from the suitable substituted benzoic acid synthesized from cheap and available 2,3-dihydroxybenzoic acid by a simple aromatic halogenation and O-methylation reactions (Scheme 1).

Once the key intermediates were identified, we performed the synthesis (Scheme 2). By treating 2,3-dihydroxybenzoic acid with bromine in acetic acid at room temperature for 24 h, the 5-bromo-2,3-dihydroxybenzoic acid, **2**, was selectively obtained in almost quantitative yield.[19] The hydroxyl groups of **2** were efficiently methylated by reaction with dimethyl sulfate in acetone and potassium carbonate followed by basic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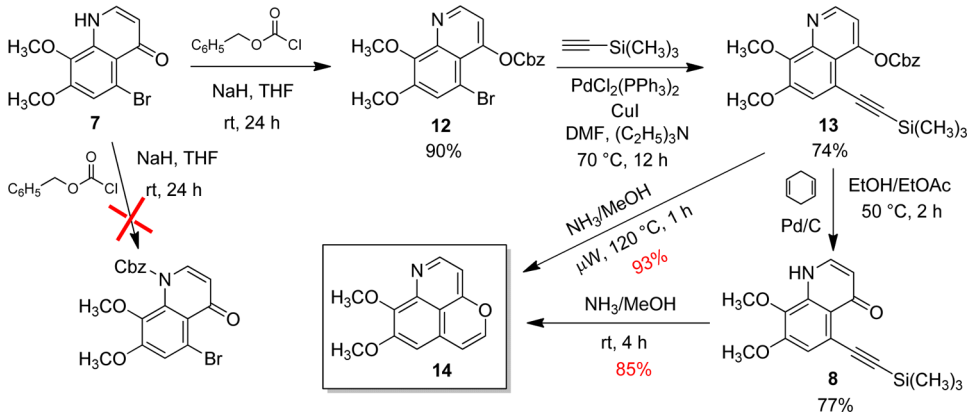
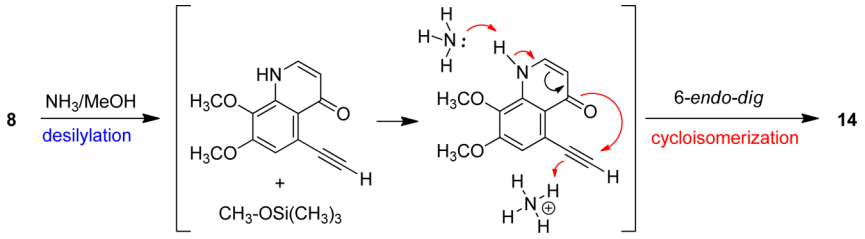
**Scheme 4. Synthesis of Oxygenated Aaptaminoid 14**




**Scheme 5. Proposed Mechanism for the Formation of Aaptaminoid 14**




hydrolysis of methyl ester and acidification to give the 5-bromo-2,3-dimethoxybenzoic acid, **3**.[19] The synthesis of **3** through this double step was necessary because the direct bromination of the simple and readily available 2,3-dimethoxybenzoic acid led to the formation of a mixture of 4- and 5-bromo-derivatives. The acid **3** was transformed into the amine **5** via a Curtius–Yamada reaction[20] in two steps; the treatment of **3** with diphenylphosphoryl azide in a mixture of ethanol and THF at 65 °C for 2 h gave the carbamate **4** which was immediately hydrolyzed by treatment with KOH in ethanol at reflux to give the amine **5** in excellent yield.[21]

The 5-bromoquinolinone **7** was obtained in two steps following the Valderrama's protocol.[22] The bromoaniline **5** was reacted with trimethyl orthoformate and Meldrum's acid to give the intermediate **6** in quantitative yield; next, the 5-bromoquinolinone **7** was obtained by brief heating of **6** in diphenylether at 260 °C with good yield. Unexpectedly, despite a number of different reaction conditions having been tested, any attempt to obtain the key intermediate **8** by a Sonogashira cross-coupling reaction failed (Scheme 2).

To overcome this drawback, we decided to introduce the triple bond in an earlier step of the synthesis (Scheme 3). Hence, bromoaniline **5** was reacted with trimethylsilylacetylene under classical Sonogashira[23] conditions to quickly give alkynylaniline **9** in very good yield. The treatment of **9** with trimethyl orthoformate and Meldrum's acid at 100 °C for 3 h gave the intermediate **10** in 93% yield.[19] Surprisingly, the heating of **10** at 260 °C for 10 min did not provide the expected 5-alkynylquinolinone **8** but gave directly the tricyclic compound **11**, via a sequential double cyclization, namely the synthesis of quinolinone **8** as a non-isolable intermediate, followed by the thermally promoted 5-*exodig* cycloisomerization (Scheme 3). The structure[24] of the new oxygenated aaptaminoid **11** was assigned on the basis of NMR and MS data, and confirmed by X-ray diffractometric analysis.

These results prompted us to try an alternative approach to alkynylquinolinone **8**. We were persuaded that the failure of the alkynylation of 5-bromoquinolinone, **7**, was somewhat related to the presence of a secondary enaminone system, inside the bicyclic ring, that behaves like an interfering amide vinylog. Consequently, we tried to protect the nitrogen of the quinolinone (Scheme 4). Nevertheless, all attempts to protect the nitrogen with di-*tert*-butyl dicarbonate[25] and *p*-toluenesulfonyl chloride inexplicably failed, whereas the treatment of **7** with sodium hydride and benzyl chloroformate[26] in THF gave, unexpectedly, the O-protected 5-bromo-4-hydroxyquinoline derivative, **12**, in good yield.[27] As hypothesized, after the deactivation of the enaminone system, the Sonogashira reaction between compound **12** and trimethylsilylacetylene took place and gave the alkynylated product **13** in good yield. The latter was easily deprotected by hydrogenolysis with 1,4-cyclohexadiene and Pd/C[28] to give the key intermediate **8** in good yield. However, the reaction of **8** with ammonia in methanol, already at rt, gave the new oxygenated aaptaminoid **14** in 85% yield. Furthermore, the direct reaction of **13** with ammonia in methanol at 120 °C under microwave heating for 1 h gave the aaptaminoid **14** in even better yield (Scheme 4). The structure[29] of **14** was assigned on the basis of NMR and MS data and confirmed by the X-ray diffractometric analysis.

The straightforward formation of pyrano[2,3,4-*de*]quinoline, **14**, also starting directly from Cbz-protected compound **13**, could be explained as follows. The deprotection of benzyloxycarbonyl-protected phenolic oxygens by bases,[30] also in alcoholic medium,[31] is a well-known procedure, and even the system ammonia/methanol was yet successfully used.[31c] Moreover, ammonia and methanol are able to remove the silyl group from the key intermediate **8**[32] and to promote the subsequent 6-*endodig* cycloisomerization, even at room temperature; the driving force in the final step is the formation of pyrano[2,3,4-*de*]quinoline, **14**, a compound strongly stabilized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by resonance (Scheme 5). This sequence is in agreement with related literature findings.[33]

In conclusion, during the study for a new total synthesis of aaptamine **I** two unnatural oxygenated aaptaminoids, **11** and **14**, have been serendipitously discovered. The syntheses took place in five and seven steps, respectively, with the satisfactory overall yields of 31% and 34%, respectively. The common starting material is the cheap and easily available 2,3-dihydroxybenzoic acid. The key steps for the formation of the oxygenated tricycles **11** and **14** are the divergent thermic 5-*exodig* vs base-promoted 6-*endodig* cyclizations of 5-alkynylquinolinone **8**. The biological proprieties of the new aaptaminoids **11** and **14** will be evaluated.

## EXPERIMENTAL SECTION

**General Experimental Methods.** All chemicals and solvents are commercially available and were used without further purification. Microwave-assisted reactions were performed with a MILESTONE microSYNT multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with a fiber-optic sensor. All reactions were performed at least twice. Silica on TLC Alu Foils F254 (Fluka) were employed for thin layer chromatography (TLC). Silica gel 40−63 $\mu$m (SDS - Carlo Erba Reagents) was employed for flash column chromatography. Melting points are uncorrected. Unless otherwise specified, proton NMR spectra were recorded at room temperature in $CDCl_3$, at 200 or 300 MHz. Unless otherwise specified, $^{13}C$ NMR spectra were recorded at room temperature in $CDCl_3$ at 50.3 or 75.45 MHz. The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. All $^{13}C$ NMR spectra were recorded with complete proton decoupling.

*2,3-Dihydroxy-5-bromobenzoic Acid,*[19] ***2***. To a solution of 2,3-dihydroxybenzoic acid (2.50 g, 16.22 mmol) in acetic acid (20 mL) was dropwise added bromine (2.59 g, 0.83 mL, 16.22 mmol). The mixture was stirred at room temperature overnight. The solvent was removed in vacuo to give a solid which was dissolved in EtOAc (30 mL) and washed with brine (2 × 20 mL). The organic layer was dried over anhyd sodium sulfate and the solvent removed at reduced pressure to give 2,3-dihydroxy-5-bromobenzoic acid, **2** (3.75 g, 99%), as a pale-pink solid. The product was sufficiently pure to be used in the next step without further purification. Mp 218−221 °C (lit. 203−204 (EtOAc/hexane)[19] 222−223 ($H_2O$)[34]). $^1H$ NMR (DMSO, 200 MHz): $\delta$ = 7.10 (d, 1H, $J$ = 2.3), 7.30 (d, 1H, $J$ = 2.3), 9.89 (brs, 1H) (2 phenolic OH obscured). $^{13}C$ NMR (DMSO, 50.3 MHz): $\delta$ = 109.7, 115.4, 122.3, 123.3, 148.3, 150.7, 171.7. MS (ESI -): $m/z$ (%) = 231/233 (58, $MH^-$), 485/487 (100, dimer + Na).

*2,3-Dimethoxy-5-bromobenzoic Acid,*[19] ***3***. A mixture of 2,3-dihydroxy-5-bromobenzoic acid **2** (3.50 g, 15.02 mmol), dimethyl sulfate (6.54 g, 51.88 mmol), potassium carbonate (7.17 g, 51.88 mmol) in acetone (25 mL) was refluxed for 20 h. The solid was filtered off on a sintered glass filter, and the solution was concentrated to give a liquid which was dissolved in methanol (25 mL), treated with NaOH (40% aq, 16 mL), and refluxed for 2 h. The solvent was then removed under reduced pressure, and the residue was dissolved in water (30 mL) and extracted with EtOAc (2 × 20 mL). The aqueous phase was adjusted to pH <2 with HCl 37% aq (≅1.5 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were dried over anhyd sodium sulfate, and the solvent was removed at reduced pressure to give 2,3-dimethoxy-5-bromobenzoic acid, **3** (3.57 g, 91%), as white solid. The product was sufficiently pure to be used in the next step without further purification. Mp 104−105 °C (lit. 199−200 (EtOAc/hexane),[19] 122−124 ($H_2O$)[34]). $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ = 3.93 (s, 3H), 4.07 (s, 3H), 7.25 (d, 1H, $J$ = 2.4), 7.86 (d, 1H, $J$ = 2.4), 11.12 (brs, 1H). $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 56.6, 62.5, 117.6, 120.8, 123.9, 126.5, 147.9, 153.2, 164.8. MS ($ESI^+$): $m/z$ (%) = 283/285 (65, $M^+$ + Na), 261/263 (100, $MH^+$), 243/245 (83, $MH^+ - H_2O$).

*Ethyl-(5-bromo-2,3-dimethoxyphenyl)carbamate,* ***4***. To a solution of 2,3-dimethoxy-5-bromobenzoic acid, **3** (3.00 g, 11.49 mmol), in dry THF (40 mL) were added diphenylphosphoryl azide (3.32 g, 2.60 mL, 12.06 mmol), absolute ethanol (6.55 mL, 115 mmol), and anhyd TEA (1.40 g, 1.91 mL, 13.79 mmol). The mixture was stirred at 65 °C for 2 h. A strong evolution of gas was observed. After cooling to room temperature, the reaction was concentrated under reduced pressure, and the crude was dissolved with EtOAc (70 mL). The organic phase was successively washed with saturated aqueous $NaHCO_3$ solution (60 mL), water (60 mL), and brine (60 mL) and was dried over anhyd sodium sulfate and concentrated at reduced pressure. The reaction crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 95:5) to give ethyl-(5-bromo-2,3-dimethoxyphenyl)carbamate, **4** (2.90 g, 83%), as a pale-yellow oil. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ = 1.33 (t, 3H, $J$ = 7.1), 3.83 (s, 3H), 3.85 (s, 3H), 4.24 (q, 2H, $J$ = 7.1), 6.75 (d, 1H, $J$ = 2.2), 7.24 (brs, 1H), 7.98 (d, 1H, $J$ = 2.2). $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 14.7, 56.3, 60.9, 61.6, 110.5, 114.2, 117.1, 133.3, 136.3, 152.6, 153.4. MS ($ESI^+$): $m/z$ (%) = 326/328 (100, $M^+$ + Na), 304/306 (36, $MH^+$), 258/260 (31, $MH^+ - C_2H_6O$). Anal. Calcd (%) for $C_{11}H_{14}BrNO_4$ (304.14): C 43.44, H 4.64, N 4.61. Found: C 43.27, H 4.69, N 4.57.

*5-Bromo-2,3-dimethoxyaniline,* ***5***. To a solution of ethyl (5-bromo-2,3-dimethoxyphenyl)carbamate, **4** (1.64 g, 5.39 mmol), in ethanol (10 mL), was added a solution of potassium hydroxide (3.18 g, 56.6 mmol) in ethanol (16 mL). The mixture was refluxed for 15 h, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (15 mL), washed with brine (15 mL), dried over anhyd sodium sulfate, and concentrated at reduced pressure. The reaction crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 90:10) to give 5-bromo-2,3-dimethoxyaniline, **5** (1.2 g, 96%), as yellow solid. Mp 59−61 °C. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ = 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (brs, 2H), 6.45 (d, 1H, $J$ = 2.2), 6.53 (d, 1H, $J$ = 2.2). $^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 56.2, 60.0, 106.3, 111.8, 116.9, 135.3, 141.9, 153.7. MS ($ESI^+$): $m/z$ (%) = 232/234 (100, $MH^+$), 217/219 (10, $MH^+ - CH_3$). Anal. Calcd (%) for $C_8H_{10}BrNO_2$ (232.07): C 41.40, H 4.34, N 6.04. Found: C 41.52, H 4.39, N 5.98.

*5-[(5-Bromo-2,3-dimethoxyphenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione,* ***6***. 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (0.635 g, 4.39 mmol) and trimethyl orthoformate (15 mL) were refluxed for 2 h. Then a solution of 5-bromo-2,3-dimethoxyaniline, (**5** 1.00 g, 4.31 mmol), in trimethyl orthoformate (15 mL) was added dropwise, and the reaction mixture was refluxed further for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = from 80:20 to 70:30) to give the Meldrum's acid derivative **6** (1.63 g, 98%) as a pale-yellow solid. Mp 165−


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166 °C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 1.75 (s, 6H), 3.89 (s, 3H), 3.94 (s, 3H), 6.90 (d, 1H, $J$ = 2.0), 7.13 (d, 1H, $J$ = 2.0), 8.58 (d, 1H, $J$ = 14.4), 11.58 (bd, 1H, $J$ = 14.4). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 27.3, 56.6, 61.4, 88.6, 100.8, 105.4, 113.7, 117.4, 132.8, 138.5, 151.1, 154.0, 163.7, 165.3. MS (ESI$^+$): $m/z$ (%) = 408/410 (69, MH$^+$), 350/352 (70), 308/310 (100). Anal. Calcd (%) for $C_{15}H_{16}BrNO_6$ (386.20): C 46.65, H 4.18, N 3.63. Found: C 46.74, H 4.21, N 3.63.

*5-Bromo-7,8-dimethoxyquinolin-4(1H)-one,* ***7****.* Meldrum's acid derivative **6** (1.5 g, 3.88 mmol) was refluxed in diphenyl ether (10 mL) with a heating mantle. After 10 min the reaction mixture was cooled and then purified by flash column chromatography on silica gel eluting first with hexane (to remove diphenyl ether) then sequentially with hexane/EtOAc = 50:50, EtOAc, and finally EtOAc/MeOH = 98:2 to give 5-bromo-7,8-dimethoxyquinolin-4(1*H*)-one, **7** (845 mg, 77%), as light-brown solid. Mp 231−234 °C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 3.97 (s, 3H), 3.98 (s, 3H), 6.18 (dd, 1H, $J$ = 7.5, $J$ = 1.7), 7.20 (s, 1H), 7.51 (dd, 1H, $J$ = 7.5, $J$ = 6.0), 8.74 (brs, 1H). $^{13}$C NMR ($CDCl_3$, 75.45 MHz): $\delta$ = 56.8, 61.5, 111.9, 115.9, 116.3, 118.4, 134.9, 136.6, 152.3, 178.1 (one signal obscured). MS (ESI$^+$): $m/z$ (%) = 306/308 (100, M$^+$ + Na), 284 (23, MH$^+$). Anal. Calcd (%) for $C_{11}H_{10}BrNO_3$ (284.11): C 46.50, H 3.55, N 4.93. Found: C 46.41, H 3.60, N 4.99.

*2,3-Dimethoxy-5-[(trimethylsilyl)ethynyl]aniline,* ***9****.* Under a nitrogen atmosphere, to a solution of 5-bromo-2,3-dimethoxyaniline, **5** (200 mg, 0,862 mmol), in anhyd triethylamine (3.4 mL) were added trimethylsilylacetylene (101 mg, 0.143 mL, 1.03 mmol) and $PdCl_2(PPh_3)_2$ (98% w/w; 24.2 mg, 0.0344 mmol). The reaction was stirred at rt for 15 min, and then CuI (99% w/w; 3.1 mg, 0.0172 mmol) was added. The reaction mixture was stirred at 70 °C for 12 h, until no more starting product was detectable by TLC (eluent: hexane/EtOAc = 70:30). The solvent was evaporated under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 90:10) to give 2,3-dimethoxy-5-((trimethylsilyl)ethynyl)aniline, **9** (194 mg, 91%), as an orange oil. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 0.23 (s, 9H), 3.81 (s, 3H), 3.82 (s, 3H), 3.82 (brs, 2H), 6.46 (d, 1H, $J$ = 1.8), 6.53 (d, 1H, $J$ = 1.8). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 0.2, 56.0, 60.1, 92.5, 105.7, 106.7, 112.9, 118.7, 137.1, 140.6, 152.7. MS (ESI$^+$): $m/z$ (%) = 272 (19, M$^+$ + Na), 250 (100, MH$^+$), 178 (10, MH$^+$ − Si$(CH_3)_3$). Anal. Calcd (%) for $C_{13}H_{19}NO_2Si$ (249.39): C 62.61, H 7.68, N 5.62. Found: C 62.71, H 7.66, N 5.65.

*5-[(2,3-Dimethoxy-5-(trimethylsilylethynyl)phenylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione,* ***10****.* 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (73 mg, 0.506 mmol) and trimethyl orthoformate (2.5 mL) were refluxed for 2 h. Then a solution of 2,3-dimethoxy-5-((trimethylsilyl)-ethynyl)aniline **9** (75 mg, 0.301 mmol) in trimethyl orthoformate (2.5 mL) was added dropwise, and the reaction mixture was refluxed for 3 h until no more starting material was detectable by TLC (eluent: hexane/EtOAc = 70:30). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 90:10) to give the Meldrum's acid derivative **10** (112 mg, 93%) as a white solid. Mp 130−134 °C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 0.26 (s, 9H), 1.74 (s, 6H), 3.88 (s, 3H), 3.97 (s, 3H), 6.86 (d, 1H, $J$ = 1.6), 7.11 (d, 1H, $J$ = 1.6), 8.61 (d, 1H, $J$ = 14.5), 11.55 (bd, 1H, $J$ = 14.5). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 0.04, 27.3, 56.4, 61.5, 88.3, 95.3, 103.7, 105.3, 111.5, 113.6, 119.8, 131.7, 139.8, 151.3, 153.0, 163.7, 165.3. MS (ESI$^-$): $m/z$ (%) = 402 (100, MH$^-$). Anal. Calcd (%) for $C_{20}H_{25}NO_6Si$ (403.50): C 59.53, H 6.24, N 3.47. Found: C 59.70, H 6.26, N 3.44.

*(Z)-7,8-Dimethoxy-5-[(trimethylsilyl)methylene]-5H-furo-[2,3,4-de]quinoline,* ***11****.* Meldrum's acid derivative **10** (73 mg, 0.181 mmol) was refluxed in diphenyl ether (5 mL) with a heating mantle. After 10 min the reaction mixture was cooled and was purified by flash column chromatography on silica gel, eluting first with hexane (to remove diphenyl ether), then with hexane/EtOAc = 50:50 to give the tricyclic oxygenated aaptaminoid **11** (28 mg, 51%) as an orange solid. Mp 89−91 °C. $\delta$ = 0.29 (s, 9H), 4.02 (s, 3H), 4.27 (s, 3H), 5.57 (s, 1H), 6.68 (d, 1H, $J$ = 5.1), 7.33 (s, 1H) 8.73 (d, 1H, $J$ = 5.1). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = −0.08, 57.8, 62.3, 97.7, 102.8, 106.4, 121.0, 125.9, 138.8, 144.4, 154.3, 155.6, 162.8, 163.6. MS (ESI$^+$): $m/z$ (%) = 302 (100, MH$^+$), 287 (15, MH$^+$ − $CH_3$). Anal. Calcd (%) for $C_{16}H_{19}NO_3Si$ (301.41): C 63.76, H 6.35, N 4.65. Found: C 63.62, H 6.40, N 4.60.

*Benzyl-(5-bromo-7,8-dimethoxyquinolin-4-yl)carbonate,* ***12****.* To a suspension of NaH 55% mineral oil (160 mg, 3.66 mmol) in anhyd THF (10 mL) was added portionwise the quinolinone **7** (400 mg, 1.41 mmol) at 0 °C. The mixture was stirred for 30 min at 70 °C. Then, benzyl chloroformate (624 mg, 0.515 mL, 3.66 mmol) was slowly added dropwise. The solution was allowed to cool to rt and stirred for 24 h. The mixture was treated with aq 0.1 M HCl (50 mL) and extracted with chloroform (3 × 30 mL). The combined organic layers were dried over anhyd sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 60:40) to give benzyl-(5-bromo-7,8-dimethoxyquinolin-4-yl)carbonate, **12** (531 mg, 90%), as a pale-yellow solid. Mp 87−89 °C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 4.01 (s, 3H), 4.07 (s, 3H), 5.34 (s, 2H), 7.13 (d, 1H, $J$ = 4.7), 7.37−7.47 (m, 5H), 7.63 (s, 1H), 8.92 (d, 1H, $J$ = 4.7). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 57.3, 62.1, 71.3, 109.0, 114.0, 117.4, 122.9, 128.9, 129.2, 134.7, 143.5, 146.6, 151.5, 151.7, 152.9, 154.4 (one signal overlapped). MS (ESI$^+$): $m/z$ (%) = 440/442 (78, M$^+$ + Na), 418/420 (100, MH$^+$), 374/376 (18, MH$^+$ − $CO_2$). Anal. Calcd (%) for $C_{19}H_{16}BrNO_5$ (418.24): C 54.56, H 3.86, N 3.35. Found: C 54.59, H 3.88, N 3.32.

*Benzyl-[7,8-dimethoxy-5-((trimethylsilyl)ethynyl)quinolin-4-yl]carbonate,* ***13****.* Under a nitrogen atmosphere, to a solution of benzyl-(5-bromo-7,8-dimethoxyquinolin-4-yl)carbonate, **12** (142 mg, 0,340 mmol), in anhyd DMF (0.7 mL) were added triethylamine (1.02 g, 1.4 mL, 10.04 mmol), trimethylsilylacetylene (40 mg, 0.056 mL, 0.408 mmol), and $PdCl_2(PPh_3)_2$ (98% w/w; 9.5 mg, 0.014 mmol). The reaction was stirred at rt for 15 min, and then CuI (99% w/w; 1.30 mg, 0.0068 mmol) was added. The reaction mixture was stirred at 70 °C for 12 h until no more starting material was detectable by TLC (eluent: hexane/EtOAc = 20:80). The reaction crude was concentrated under reduced pressure, and the residue was poured in water (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried over anhyd sodium sulfate and concentrated at reduced pressure. The reaction crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 60:40) to give benzyl [7,8-dimethoxy-5-[(trimethylsilyl)-ethynyl]quinolin-4-yl]carbonate, **13** (109 mg, 74%), as a yellow oil. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 0.23 (s, 9H), 4.03 (s, 3H), 4.11 (s, 3H), 5.31 (s, 2H), 7.09 (d, 1H, $J$ = 4.8), 7.38 (m, 5H), 7.56 (s, 1H), 8.87 (d, 1H, $J$ = 4.8). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 0.13, 57.1, 62.3, 71.1, 99.0, 103.5, 112.9, 113.0,


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119.0, 123.5, 128.6, 128.9, 129.0, 134.7, 144.6, 145.9, 151.3, 151.5, 152.6, 155.2. MS (ESI$^+$): $m/z$ (%) = 436 (100, MH$^+$), 392 (45, MH$^+$ − $CO_2$). Anal. Calcd (%) for $C_{24}H_{25}NO_5Si$ (435.55): C 66.18, H 5.79, N 3.22. Found: C 65.94, H 5.76, N 3.19.

*7,8-Dimethoxy-5-[(trimethylsilyl)ethynyl]quinolin-4(1H)-one,* ***8.*** In a screw capped test tube and under a nitrogen atmosphere were added 1,4-cyclohexadiene (1.5 mL) and Pd/C 10% (74 mg, 100 wt %) to a solution of benzyl [7,8-dimethoxy-5-[(trimethylsilyl)ethynyl]quinolin-4-yl]carbonate, **13** (74 mg, 0.170 mmol), in a mixture of EtOAc/EtOH = 1:1 (9.0 mL). The reaction mixture was stirred at 50 °C for 2 h until no more starting material was detectable by TLC (eluent: hexane/EtOAc = 40:60). The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 60:40) to give 7,8-dimethoxy-5-((trimethylsilyl)ethynyl)-quinolin-4(1*H*)-one, **8** (40 mg, 77%), as yellow wax. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 0.29 (s, 9H), 3.97 (s, 3H), 4.00 (s, 3H), 6.17 (d, 1H, $J$ = 7.5), 7.13 (s, 1H), 7.53 (dd, 1H, $J$ = 7.5, $J$ = 5.9), 8.90 (brs, 1H). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 0.20, 56.5, 61.4, 99.6, 104.9, 111.4, 116.7, 117.8, 121.9, 135.5, 135.6, 136.7, 151.7, 178.2. MS (ESI$^+$): $m/z$ (%) = 324 (34, M$^+$ + Na), 302 (100, MH$^+$). Anal. Calcd (%) for $C_{16}H_{19}NO_3Si$ (301.41): C 63.76, H 6.35, N 4.65. Found: C 63.85, H 6.39, N 4.64.

*8,9-Dimethoxypyrano[2,3,4-de]quinoline* ***14****. Method A.* In a screw-capped test tube and under a nitrogen atmosphere, a solution of 7,8-dimethoxy-5-((trimethylsilyl)ethynyl)quinolin-4(1*H*)-one, **8** (40 mg, 0.132 mmol), in dry ammonia in methanol ($NH_3$/MeOH 2 M solution, 2.5 mL) was stirred for 4 h at rt until no more starting material was detectable by TLC (eluent: hexane/EtOAc = 50:50). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 60:40) to give 8,9-dimethoxypyrano[2,3,4-*de*]quinoline, **14** (26 mg, 85%), as yellow solid.

*Method B.* In a screw-capped glass vessel, a well-stirred solution of benzyl-[7,8-dimethoxy-5-[(trimethylsilyl)ethynyl]-quinolin-4-yl]carbonate, **13** (37 mg, 0.085 mmol), in dry ammonia in methanol ($NH_3$/MeOH 2 M solution, 2.5 mL) was heated for 1 h at 120 °C in a multimode microwave oven (ramp time not included = 10 min, max power = 400 W). The reaction mixture was evaporated to dryness and the crude purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 60:40) to give 8,9-dimethoxypyrano[2,3,4-*de*]quinoline, **14** (18 mg, 93%), as yellow solid. Mp 79−81 °C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ = 3.97 (s, 3H), 4.02 (s, 3H), 6.20 (d, 1H, $J$ = 5.9), 6.54 (d, 1H, $J$ = 5.2), 6.68 (s, 1H), 6.85 (d, 1H, $J$ = 5.9), 8.58 (d, 1H, $J$ = 5.2). $^{13}$C NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 56.9, 61.2, 101.9, 104.4, 109.3, 115.8, 124.4, 140.7, 143.5, 145.6, 153.7, 154.1, 159.9. MS (ESI$^+$): $m/z$ (%) = 252 (36, M$^+$ + Na), 230 (100, MH$^+$), 215 (49, MH$^+$ − $CH_3$). Anal. Calcd (%) for $C_{13}H_{11}NO_3$ (229.23): C 68.11, H 4.84, N 6.11. Found: C 67.95, H 4.88, N 6.05.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1$H and $^{13}$C NMR spectra for compounds **2**−**14**. A full listing of crystallographic data for the structures of compounds **11** and **14** including tables of bond distances and bond angles. ORTEPIII figure of the independent molecule in the asymmetric unit showing the numbering schemes for all non-hydrogen atoms. X-ray data as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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