Synthesis of Quinolinone Alkaloids via Aryne Insertions into Unsymmetric Imides in Flow

Johannes Schwan, Merlin Kleoff, Bence Hartmayer, Philipp Heretsch,* and Mathias Christmann*
Freie Universität Berlin, Institut für Chemie und Biochemie, Takustr. 3, 14195 Berlin, Germany

Supporting Information Placeholder

ABSTRACT: A general strategy for the synthesis of 3,4-dioxygenated quinolin-2-one natural products is reported. The key step is a regioselective insertion of arynes into unsymmetric imides. When performed in continuous flow, the reaction proceeded within minutes. The resulting N-acylated 2-aminobenzophenones were transformed to (±)-peniprequinolone, (±)-aflaquinolones E and F, (±)-6-deoxyaflaquinolone E, (±)-quinolinones A and B, and (±)-aniduquinolone C in 1–3 steps.

The growing family of 3,4-dioxygenated quinolin-2-ones constitutes a valuable source of molecules with cytotoxic, nematocidal and antiviral activities.1,2 Biosynthetically, these fungal secondary metabolites are derived from the nonribosomal peptide synthetase (NRPS) product cyclopeptin (1), an adduct of anthranilic acid and either O-methyl-L-tyrosine or phenylalanine (Scheme 1a). Groll and Hintermann demonstrated that a single enzyme, AsqJ, catalyzes a multistep transformation of the benzodiazepine core of 1 into the parent quinoline 2.3 Downstream processing into the final natural products may involve prenylation (n=0), double prenylation (n=1) as well as additional oxidation steps.6 Following this synthetic blueprint, Nature has evolved a “library” of bioactive secondary metabolites3,7 from which only yaequinolone J1, J2, and A2 have been synthesized to date (Scheme 1b).8 Since these natural products share a common heterocyclic core, we decided to develop a step-efficient,9 modular approach to access the entire group of these alkaloids (Scheme 1c). Synthetically, the 3,4-dioxygenated quinolin-2-one core (6) can be obtained by intramolecular glycolate aldolizations.10 We speculated that arylene chemistry11 could provide a straightforward access to N-glycolated 2-aminobenzophenones (5) and thus enable the synthesis of this natural product family. Based on the contributions of Greaney11a (acyclated carbamates), Stoltz11b (symmetric imides), and Xu11d (acrylamides), we speculated that a selective σ-C–N insertion of in-situ generated arynes (3) into unsymmetric imides 4 could deliver 5 in a one-pot operation12 (Scheme 2). With these substrates, the challenge lies in the differentiation of two similar N-acyl groups.

Scheme 1. Outline of the Work

a) anthranic acid
b) (-)-yaequinolone A2
   Panetal, 2009
   (+)-aniduquinolone C
   Hanessian et al., 2018
   (-)-yaequinolone J1
   Hanessian et al., 2018

3

R

4

5

6

Ar

R

KO\text{Bu}

H

R

O\text{R'}
As a starting point, we investigated the insertion of benzene precursor 3a\textsuperscript{13} into the unsymmetric imide 4a. Under the conditions reported by Stoltz et al.,\textsuperscript{11b} benzophenone 5a was formed in 16% yield with only a slight preference for the 5a over its constitutional isomer 7 (Table 1, entry 1). A screening of solvents revealed that acetonitrile gave the best selectivity of 5:7:1 (entry 3). Among different fluoride sources, cesium fluoride gave the highest yield of 5a with 33% and an isomeric ratio of 3:7:1 (entry 4). Upon extended reaction time, 7 undergoes slow thermal decomposition leading to a slightly increased isomer in favor of 5a. Furthermore, it turned out that also imide 4a slowly decomposes to benzamide at elevated temperatures and under basic conditions.

Due to superior heat and mass transfer, reactions performed in flow can significantly be accelerated. Therefore, intermediates such as 8 often react with higher selectivity and yield, enabling reactions that are otherwise impossible.\textsuperscript{14} Surprisingly, only few examples are reported, where arynes are generated and used in a flow reactor.\textsuperscript{15}

Table 1. Reaction Development in Batch\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>F’ Source</th>
<th>5a:7\textsuperscript{b}</th>
<th>5a (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>TBAT</td>
<td>1.3:1</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>TBAT</td>
<td>2.0:1</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>TBAT</td>
<td>5.7:1</td>
<td>25</td>
</tr>
<tr>
<td>4\textsuperscript{d}</td>
<td>MeCN</td>
<td>CsF</td>
<td>3.7:1</td>
<td>33</td>
</tr>
<tr>
<td>5\textsuperscript{d}</td>
<td>MeCN</td>
<td>KF</td>
<td>4.0:1</td>
<td>20</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 4a (0.26 mmol, 1 equiv.), 3a (0.39 mmol, 1.5 equiv.), F’ source (0.52 mmol, 2 equiv.), solvent (2.0 mL), 60 °C, 16 h; \textsuperscript{b}ratios were determined by H NMR integration; \textsuperscript{c}isolated yield; \textsuperscript{d}conducted at 80 °C for 4 h; \textsuperscript{e}18-crown-6 (1 equiv.) and 4 Å mol sieves were used as additives.

In order to suppress thermal imide decomposition by shortening the reaction time, a flow protocol seemed promising. Due to its high solubility, tetrabutylammonium difluorotriphenylsilicate (TBAT) is a better fluoride source for flow reactions than cesium fluoride. An optimization of reaction time, temperature and stoichiometry (see SI, for details), increased the yield of 5a from 25% in batch (Table 1, entry 3), to 52% when conducted at 65 °C with 1.5 equiv. of 3a at a flow rate of 1 mL/min (Table 2, entry 1). Under these conditions, a regioselectivity of 2.9:1 (5a:7) was observed, while the residence time was reduced to 4 minutes.

Using the optimized conditions, a collection of substituted arynes and imides were reacted. According to the proposed mechanism, the aryne insertion proceeds via intermediacy of 8.\textsuperscript{11b,16} Greaney et al.\textsuperscript{11a} showed that a major byproduct results from premature protonation of 8. Remarkably, under flow conditions even the use of wet acetonitrile did not increase the amount of byproduct, thus rendering the flow process more sustainable. As arynes bearing a 3-alkoxy substituent have been reported under regioselective nucleophilic attack in the meta-position,\textsuperscript{17} we expected the resulting benzophenones to provide us with an access to the 5-hydroxyquinolinone cores present in aflaquinolone E (8)\textsuperscript{11} and quinolino B (10).\textsuperscript{19} In agreement with the literature reports,\textsuperscript{11a,b,20} we too observed significantly lower yields with those substrates. Thus, when using 3-O-benzyl and 3-O-allyl substituted aryne precursors 3b and 3c, the yield dropped to 18% to 30% (Table 2, entry 3-6). The insertion was also performed with 4-bromo substituted imide 4c to access an unnatural quinolinone derivative with a handle for cross coupling chemistry as well as O-benzyl substituted imide 4d to access aflaquinolone F (11).\textsuperscript{18} In all cases, benzophenones 5a-h were obtained as the major product along with unreacted imide 4a-d.

Table 2. Aryne Insertion in Flow\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>5 (%)\textsuperscript{b}</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>52</td>
</tr>
<tr>
<td>2\textsuperscript{c}</td>
<td>b</td>
<td>H</td>
<td>OMe</td>
<td>Me</td>
<td>60</td>
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<td>H</td>
<td>Br</td>
<td>Me</td>
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</tr>
<tr>
<td>4</td>
<td>d</td>
<td>OBn</td>
<td>H</td>
<td>Me</td>
<td>35</td>
</tr>
<tr>
<td>5\textsuperscript{c}</td>
<td>e</td>
<td>OBn</td>
<td>OMe</td>
<td>Me</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>H</td>
<td>H</td>
<td>Bn</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>OAllyl</td>
<td>H</td>
<td>Me</td>
<td>18</td>
</tr>
<tr>
<td>8\textsuperscript{c}</td>
<td>h</td>
<td>OAllyl</td>
<td>OMe</td>
<td>Me</td>
<td>30</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 4 (0.20 mmol, 1 equiv., 0.1 min MeCN), 3 (0.30 mmol, 1.5 equiv., 0.15 min in MeCN), TBAT (0.36 mmol, 1.8 equiv., 0.18 min in MeCN), 4 mL reactor volume, 65 °C; \textsuperscript{b}isolated yield; \textsuperscript{c}4b (c = 0.01 mmol in MeCN), 3a-c (c = 0.015 mmol in MeCN), TBAT (c = 0.018 mmol in MeCN).

With the benzophenones 5a-h in hand, we next investigated an intramolecular reaction\textsuperscript{13} to forge the 3,4-dioxygenated quinoline-2-one core. Using an excess of potassium tert-butoxide in tetrahydrofuran at 0 °C, the quinolines 6a-g were obtained as single diastereomers (Scheme 2).
Following this procedure, the natural products (±)-6-deoxyyaflaquinolone E (6a)\textsuperscript{21} and (±)-quinolinone A (6b)\textsuperscript{20c} were prepared in 91% and 84% yield, respectively.

**Scheme 2. Intramolecular Aldolization**

![Scheme 2](image)

Cyclization of 5d, 5e, and 5f delivered the benzyl protected quinolinones 6d, 6e, and 6f which were subjected to hydrogenolysis to afford the natural products (±)-aflaquinolone E (9), F (11)\textsuperscript{18} and (±)-quinolinone B (10)\textsuperscript{20c} in up to 82% yield over two steps. Quinolinones 6g and 6h underwent Claisen rearrangement at 150 °C in 1,2-dichlorobenzene for 10 hours to give 12a and 12b in 71% and 63% yield, respectively (Scheme 3)\textsuperscript{22}. At higher temperature and prolonged reaction time, elimination of the tertiary alcohol was observed. Olefin metathesis of 12a using Umicore M71SIMes as catalyst and an excess of 2-methylbut-2-ene gave (±)-aniduquinolone C (13a)\textsuperscript{21} in 81% yield, whereas (±)-peniprequinolone (13b)\textsuperscript{20} was obtained in 80% yield starting from 12b.

**Scheme 3. Synthesis of Aniduquinolone C and Peniprequinolone**

![Scheme 3](image)

In conclusion, we have devised a general approach for the synthesis of 3,4-dioxygenated quinolin-2-one natural products. The sequence proceeds through an insertion of arynes into unsymmetric imides followed by a diastereoselective intramolecular aldolization. A flow protocol for the aryne insertion was developed giving access to N-glycolated 2-aminoazabenzenophenes within minutes. By this not immediately evident, yet powerful disconnection, the quinolinone natural products peniprequinolone, aflaquinolone E, F, quinolone A, B, and aniduquinolone C were synthesized in three to six steps\textsuperscript{23}. Future work will focus on the synthesis of quinolinone natural products with other side chains and higher oxidation levels.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

**AUTHOR INFORMATION**

* Corresponding Authors
  * E-mail: mathias.christmann@fu-berlin.de
  * E-mail: philipp.heretsch@fu-berlin.de

* Notes
  The authors declare no competing financial interest.

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**REFERENCES**


(23) All spectra of prepared natural products are in agreement with those reported in ref. (18), (19) and (21).
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Supporting Information

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General working methods

The analytical data was obtained with the help of the following equipment.

**NMR spectroscopy**

$^1$H and $^{13}$C NMR spectra were acquired on a JEOL ECX 400 (400 MHz), JEOL ECP 500 (500 MHz) and a Bruker Avance 700 (700 MHz) in CDCl$_3$ as a solvent. The chemical shifts were reported relative to CDCl$_3$ ($\delta$ = $^1$H: 7.26 ppm, $^{13}$C: 77.16 ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = quintuplet, br = broad and combinations thereof.

The spectra were evaluated with the software MestReC.

**Mass spectra** were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian), or a HR-EI-MS: Autospec Premier (Waters).

**GC-MS**: were recorded on a GC system Agilent Technologies 7890-A series/Mass selective detector, Agilent Technologies 5975 C (column: HP-5MS (J&W Scientific, Agilent); 30 m, 0.250 mm i.D., Film 0.25 μm).

**IR: spectra** were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavelengths $\tilde{\nu}$ in cm$^{-1}$ and were analyzed with the software Spectral Manager from JASCO.

**Melting points** were measured on a Thermovar from the company Reichert and are not corrected.

**Chromatography** Reaction progress was monitored by thin layer chromatography on aluminum backed silica gel plates (silica gel 60 F 254 from E. Merck), visualizing with UV light ($\lambda = 254$ nm). The plates were developed using vanillin dip solution (170 mL methanol, 20.0 ml conc. acetic acid, 10.0 mL conc. sulfuric acid with 1.0 g vanillin), KMnO$_4$ dip solution (3.0 g potassium permanganate, 5.0 mL NaOH-solution (5 w/w), 300 mL dest. water) or an anisaldehyde solution (450 mL ethanol, 25.0 mL anisaldehyde, 25.0 mL conc. sulfuric acid, 8.0 mL acetic acid).

Flash chromatography was performed using silica gel M60 from Macherey & Nagel (particle size: 40–63 μm).

**HPLC**: were conducted on a modular Knauer HPLC system with a UV detector at 254 nm and differential refractometer on a 4 x 250 mm column packed with Nucleosil 50-5 from Macherey-Nagel.

**Flow Reactions**: Flow reactions were performed in 1/16 inch PTFE tubing with an inner diameter of 1.0 mm. The tubing was embedded in an aluminum block from ThalesNano and heated with an Ika stirring plate. A stainless-steel T-piece from Vici or static mixer (Upchurch Scientific) was used to mix the reagents. Fittings were either coned 10/32 stainless steel fittings from Upchurch scientific or flat bottom 1/4-28 gripper fittings from Dibafit. A kdScientific syringe pump (model no. KDS 200CE) was used to pump the reagents through the reactor.

**Microwave Reactions**: Reactions in a microwave were performed in a sealed tube using a Biotage Initiator Microwave with a maximum power of 400 W.
Reagents and Solvents Reactions with air or moisture-sensitive substances were, if not otherwise indicated, carried out under an argon atmosphere with the help of the Schlenk technique. All other reagents and solvents were used as purchased from commercial suppliers unless otherwise noted. Anhydrous solvents were purified with the solvent purification system MB-SPS-800 (Braun). Water free Acetonitrile was purchased from Acros Organics in AcroSeal®-bottles under Argon atmosphere with molecular sieves (3 Å) or HPLC-grade acetonitrile from Fischer Scientific was used. The solvents (ethyl acetate, pentane) used for column chromatography and work up were purified from commercially available technical grade solvents by distillation under reduced pressure with the help of rotatory evaporators (Heidolph or IKA) at 40 °C water bath temperature. Benzamides,\textsuperscript{1} benzylxy acetic acid,\textsuperscript{2} benzyloxyacetyl chloride\textsuperscript{3} and 3-hydroxy-2-(trimethylsilyl)phenyl triflate\textsuperscript{4} were prepared according to literature procedures. Compound names are derived from Chemdraw and are not necessarily identical with the IUPAC nomenclature.
Synthesis of Compounds

**N-(2-Methoxycetyl)-benzamide (4a)**

![Chemical structure of N-(2-Methoxycetyl)-benzamide (4a)](image)

Benzamide (2.00 g, 16.5 mmol, 1 equiv.) was dissolved in anhydrous pyridine (26 mL) and 2-methoxycetyl chloride (3.01 mL, 33.0 mmol, 2 equiv.) was added in one portion at room temperature. The yellow mixture was stirred in a sealed tube at 80 °C for 2 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure to 1/4 of its volume and diluted with NH₄Cl (sat. aq., 50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with NH₄Cl (sat. aq., 3 × 150 mL) and NaCl (sat. aq., 100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, n-pentane/EtOAc = 1:1) affording the title compound (Ia, 1.77 g, 9.17 mmol, 56%) as a colorless solid.

**Rf = 0.41 (n-pentane/EtOAc = 1:1); m.p.: 105 °C; ^1H NMR (500 MHz, CDCl₃): δ = 9.44 (s, 1H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.38 (s, 2H), 3.49 (s, 3H) ppm; ^13C NMR (126 MHz, CDCl₃): δ = 171.1, 165.2, 133.4, 132.5, 129.0, 127.9, 73.1, 59.5 ppm; IR (neat): ν = 3378, 3280, 3168, 3071, 2990, 2963, 2938, 2920, 2825, 2748, 2600, 1909, 1771, 1709, 1685, 1636, 1602, 1584, 1555, 1508, 1469, 1448, 1396, 1384, 1346, 1327, 1310, 1287, 1250, 1239, 1196, 1169, 1120, 1090, 1069, 1031, 1012, 1002, 973, 933, 907, 842, 818, 805, 751, 701 cm⁻¹; HRMS (ESI): m/z calculated for C₁₀H₁₁NNaO₃⁺ ([M+Na]⁺): 216.0631; found: 216.0641.

**4-methoxy-N-(2-methoxycetyl)-benzamide (4b)**

![Chemical structure of 4-methoxy-N-(2-methoxycetyl)-benzamide (4b)](image)

4-Methoxybenzamide (2.00 g, 13.2 mmol, 1 equiv.) was dissolved in anhydrous pyridine (20 mL) and 2-methoxycetyl chloride (1.50 mL, 16.5 mmol, 2 equiv.) was added at room temperature. The orange mixture was stirred in a sealed tube at 60 °C for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was suspended in NaHCO₃ (sat. aq., 250 mL) and EtOAc (250 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with NaCl (sat. aq., 2 × 400 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was recrystallized from hot EtOAc affording the title compound (Ib, 1.45 g, 6.48 mmol, 49%) as a colorless solid.

**Rf = 0.42 (n-pentane/EtOAc = 1:2); m.p.: 156 °C; ^1H NMR (400 MHz, DMSO-d₆): δ = 11.00 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 4.44 (s, 2H), 3.83 (s, 3H), 3.34 (s, 3H) ppm; ^13C NMR (101 MHz, DMSO-d₆): δ = 171.1, 165.2, 133.4, 132.5, 129.0, 127.9, 73.1, 59.5 ppm; IR (neat): ν = 3378, 3280, 3168, 3071, 2990, 2963, 2938, 2920, 2825, 2748, 2600, 1909, 1771, 1709, 1685, 1636, 1602, 1584, 1555, 1508, 1469, 1448, 1396, 1384, 1346, 1327, 1310, 1287, 1250, 1239, 1196, 1169, 1120, 1090, 1069, 1031, 1012, 1002, 973, 933, 907, 842, 818, 805, 751, 701 cm⁻¹; HRMS (ESI): m/z calculated for C₁₁H₁₂NNaO₃⁺ ([M+Na]⁺): 222.0631; found: 222.0641.
MHz, DMSO-\(\delta\)): \(\delta = 172.9, 165.7, 163.0, 130.7, 124.6, 113.8, 72.8, 58.5, 55.6\) ppm; \textbf{IR} (neat): \(\tilde{\nu} = 3390, 3291, 3169, 3094, 3080, 3014, 2970, 2942, 2843, 1769, 1710, 1685, 1645, 1618, 1607, 1574, 1517, 1458, 1422, 1394, 1311, 1254, 1182, 1146, 1124, 1025, 849, 809, 764\) cm\(^{-1}\); \textbf{HRMS} (ESI): m/z calculated for C\(_{11}\)H\(_{13}\)NNaO\(_4\)+ ([M+Na]+): 246.0737; found 246.0738.

\textbf{4-bromo-N-(2-methoxycarbonyl)benzamide (4c)}

4-Bromobenzamide (150 mg, 0.992 mmol, 1 equiv.) was dissolved in anhydrous pyridine (1.6 mL) and 2-methoxycarbonyl chloride (0.181 mL, 1.99 mmol, 2 equiv.) was added at room temperature. The orange mixture was stirred in a sealed tube at 60 \(^\circ\)C for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was suspended in NaHCO\(_3\) (sat. aq., 20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 \times 20 mL). The combined organic layers were washed with NaCl (sat. aq., 2 \times 50 mL), dried (\(\text{MgSO}_4\)), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, \(n\)-pentane/EtOAc 2:1) to afford the title compound (I\(_c\), 74.0 mg, 0.332 mmol, 34%) as a colorless solid.

\(R_t = 0.30\) (\(n\)-pentane/EtOAc 1:2); m.p.: 141 \(^\circ\)C; \textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)) \(\delta = 9.37\) (s, 1H), 7.73 (d, \(J = 8.1\) Hz, 2H), 7.64 (d, \(J = 8.2\) Hz, 2H), 4.35 (s, 2H), 3.51 (s, 3H) ppm; \textbf{\(^{13}\)C NMR} (126 MHz, CDCl\(_3\)) \(\delta = 170.7, 164.5, 132.4, 131.5, 129.5, 128.6, 73.0, 59.6\) ppm; \textbf{IR} (neat): \(\tilde{\nu} = 3240, 3196, 3160, 2970, 2952, 2926, 2823, 1731, 16696, 1591, 1524, 1502, 1479, 1400, 1386, 1257, 1232, 1202, 1136, 1110, 1069, 1012, 939, 907, 840, 818, 772, 763, 744, 717, 684, 661\) cm\(^{-1}\); \textbf{HRMS} (ESI): m/z calculated for C\(_{10}\)H\(_{10}\)BrNO\(_3\)Na\(_+\) ([M+Na]+): 293.9736; found: 293.9745.

\textbf{N-(2-(benzyloxy)acetyl)benzamide (4d)}

Benzamide (800 mg, 6.60 mmol, 1 equiv.) was dissolved in anhydrous pyridine (11 mL). Benzyloxyacetyl chloride (2.44 g, 13.2 mmol, 2 equiv.) was added and the mixture was stirred in a sealed tube at 60 \(^\circ\)C for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and NaHCO\(_3\) (sat. aq., 10 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with NaCl (sat. aq., 2 \times 10 mL) and dried (\(\text{MgSO}_4\)). The solvents were removed under reduced pressure. The crude product was recrystallized from hot EtOAc affording the title compound (I\(_d\), 300 mg, 1.10 mmol, 17%) as a colorless solid.
m.p.: 113 °C; ¹H NMR (700 MHz, CDCl₃) δ = 9.32 (s, 1H), 7.82 – 7.80 (m, 2H), 7.60 (td, J = 7.3, 1.3 Hz, 1H), 7.50 – 7.47 (m, 2H), 7.39 (s, 2H), 7.38 (d, J = 1.6 Hz, 2H), 7.36 – 7.33 (m, 1H), 4.70 (s, 2H), 4.43 (s, 2H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ = 170.5, 165.0, 136.8, 133.5, 132.6, 129.2, 128.8, 128.5, 128.2, 127.8, 73.9, 70.5 ppm; IR (neat): ν = 3284, 2951, 2922, 2868, 1712, 1688, 1599, 1582, 1500, 1469, 1406, 1390, 1324, 1304, 1244, 1216, 1115, 1102, 1072, 1028, 1001, 975, 949, 933, 908, 872, 862, 841, 822, 800, 785, 757, 702, 657 cm⁻¹; HRMS (ESI): m/z calculated for C₁₆H₁₅NNaO₃⁺ ([M+Na⁺]): 292.0944; found: 292.0951.

3-(benzyloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3b)

3-Hydroxy-2-trimethylsilyl-phenyl trifluoromethanesulfonate (500 mg, 1.59 mmol, 1 equiv.) was suspended in water (15 mL) and BnBr (0.472 mL, 3.98 mmol, 2.5 equiv.), TBAB (513 mg, 1.59 mmol, 1 equiv.) and K₃PO₄ (1.01 g, 4.77 mmol, 3 equiv.) were added at room temperature. The suspension was stirred vigorously at room temperature for two hours, diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, n-pentane/EtOAc = 20:1) to afford the title compound (IVb, 555 mg, 1.37 mmol, 86%) as a colorless oil.

Rₓ = 0.83 (n-pentane/EtOAc = 10:1); ¹H NMR (500 MHz, CDCl₃) δ = 7.41 (s, 4H), 7.39 – 7.32 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.09 (s, 2H), 0.34 (s, 9H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ = 164.8, 154.9, 136.2, 131.7, 128.8, 128.4, 127.9, 121.2, 120.1, 117.5, 113.1, 110.6, 71.1, 1.1 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ = -73.98 ppm; IR (neat): ν = 3067, 3036, 2954, 2901, 2876, 1594, 1565, 1434, 1417, 1247, 1207, 1160, 1137, 1116, 1024, 934, 842, 826, 785, 735 cm⁻¹; HRMS (ESI): m/z calculated for C₁₇H₁₉F₃SSiNa ([M+Na⁺]): 427.0617, found 427.0667.

3-(allyloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3c)

3-Hydroxy-2-trimethylsilyl-phenyl trifluoromethanesulfonate (1.47 g, 4.66 mmol, 1 equiv.) was suspended in water (150 mL). Allyl bromide (2.42 mL, 28.0 mmol, 6.0 equiv.), TBAB (1.50 g, 6.0 mmol, 1.0 equiv.) and K₃PO₄ (2.97 g, 14.0 mmol, 3 equiv.) were added at room temperature. The suspension was stirred vigorously at room temperature for one hour, diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, n-pentane) to afford the title compound (IVc, 1.12 g, 3.16 mmol, 68%) as a colorless oil.
Rf = 0.65 (n-pentane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.34 (t, $J$ = 8.4 Hz, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 6.61 (d, $J$ = 8.3 Hz, 1H), 6.09 – 5.98 (m, 1H), 5.45 – 5.35 (m, 1H), 5.34 – 5.30 (m, 1H), 4.56 (d, $J$ = 5.4 Hz, 2H), 0.38 (s, 9H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 164.6, 154.8, 132.7, 131.7, 121.2, 118.5, 117.5, 113.0, 110.6, 69.7, 1.1 ppm; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -72.77 ppm; IR (neat): $\tilde{\nu}$ = 3089, 2988, 2955, 2901, 2865, 1595, 1565, 1436, 1420, 1362, 1247, 1206, 1160, 1140, 1117, 1057, 1034, 996, 939, 924, 894, 837, 787, 769, 738, 712, 693, 668 cm$^{-1}$; HRMS (ESI): m/z calculated for C$_{13}$H$_{17}$F$_3$O$_4$SSiNa$^+$ ([M+Na$^+$]): 377.0461, found: 377.0461.

Table S1. Analysis of main parameters for the synthesis of benzophenone 5a and acetophenone 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>v [ml/min]</th>
<th>Residence time [min]</th>
<th>Lewis acid</th>
<th>C$_{imid}$ [mol/L]</th>
<th>C$_{Acin}$ [mol/L]</th>
<th>C$_{TBAT}$ [mol/L]</th>
<th>T [°C]</th>
<th>IIa : IIIa</th>
<th>Solvent/cond.</th>
<th>5a$^a$ [%]</th>
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<td>4</td>
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<td>0.05</td>
<td>0.06</td>
<td>0.10</td>
<td>55</td>
<td>-</td>
<td>no workup</td>
<td>32</td>
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<td>0.05</td>
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<td>0.10</td>
<td>55</td>
<td>-</td>
<td>aqueous workup</td>
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<td>-</td>
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<tr>
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<td>0.05</td>
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<td>55</td>
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<td>0.06</td>
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<td>-</td>
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<td>-</td>
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<td>-</td>
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<td>80</td>
<td>-</td>
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<tr>
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<td>4.2 : 1</td>
<td>PhMe/MeCN (1:1); 40 psi BPR</td>
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<td>65</td>
<td>-</td>
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<td>42$^c$</td>
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<td>3.8 : 1$^b$</td>
<td>dry MeCN</td>
<td>39$^c$</td>
</tr>
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</table>

$^a$The ratio of 5a:7 as well as the yield of IIa were determined via GC-MS acetanilid as standard. An aliquot of the reactor output (100 µL or 500 µL) was taken, diluted to yield a volume of 900 µL and treated with a solution of acetanilide (100 µL, 0.05 M). $^b$Determined by $^1$H NMR integration. $^c$Isolated yield.

**General Procedure for the Aryne Insertion in Flow (GP1)**

Prior use, the flow reactor was washed with three reactor volumes of acetonitrile using a syringe pumps. A stock solution of aryne precursor (3a-c, 0.150 M in MeCN, 1.5 equiv.) and imide (4a-d, 0.100 M in
MeCN, 1.0 equiv.) was loaded on a sample loop with a volume of 1 mL. Then, a stock solution of TBAT (0.180 m in acetonitrile, 1.8 equiv.) was loaded on a sample loop with a volume of 1 mL. Both solutions were pumped simultaneously at a rate of 0.5 mL/min, driven by MeCN. The stock solutions were combined at a T-piece to react in a 4.0 mL PTFE coil, preheated to 65 °C using an aluminum block. The reaction mixture was collected, concentrated under reduced pressure and purified by column chromatography to afford the ortho-aminobenzophenones 5a-h.

\[
N-(2\text{-benzoylphenyl})-2\text{-methoxyacetamide (5a)}
\]

![Chemical structure of 5a](image)

Compound 5a was prepared according to GP1 starting from 3a (127 mg, 0.427 mmol, 1.5 equiv.) and 4a (55.0 mg, 0.285 mmol, 1 equiv.). Column chromatography (silica gel, n-pentane/EtOAc = 4:1) afforded the title compound (5a, 40.0 mg, 0.148 mmol, 52%) as a colorless oil that solidified in the fridge and compound 7 (14.5 mg, 0.054 mmol, 19%) as a colorless solid.

5a:

\[
R_f = 0.40 \quad (n\text{-pentane}/\text{EtOAc} = 3:1); \quad ^1H\ \text{NMR} \ (700 \text{ MHz, CDCl}_3): \delta = 11.39 \ (s, 1H), 8.69 \ (d, J = 8.3 \text{ Hz, 1H}), 7.73 \text{ – 7.70 (m, 2H), 7.60 – 7.54 (m, 3H), 7.47 (t, J = 7.8 \text{ Hz, 2H}), 7.11 (td, J = 7.6, 1.2 \text{ Hz, 1H}), 4.04 (s, 2H), 3.55 (s, 3H) ppm;} \quad ^{13}C\ \text{NMR} \ (176 \text{ MHz, CDCl}_3): \delta = 199.1, 169.2, 139.4, 138.7, 134.1, 133.5, 132.5, 130.0, 128.4, 124.3, 122.6, 121.7, 72.7, 59.8 \text{ ppm;} \quad \text{IR (neat): } \tilde{\nu} = 3286, 3060, 3033, 2996, 2934, 2828, 2756, 2249, 1832, 1692, 1639, 1598, 1577, 1515, 1446, 1432, 1362, 1293, 1196, 1180, 1158, 1114, 1076, 1048, 1028, 987, 959, 935, 917, 880, 852, 805, 752, 728 \text{ cm}^{-1}; \quad \text{HRMS (ESI): } m/z \text{ calculated for } C_{16}H_{14}N_{2}NaO_{3}^+: 292.0944; \quad \text{found: 292.0959.}
\]

7:

\[
R_f = 0.35 \quad (n\text{-pentane}/\text{EtOAc} = 3:1); \quad \text{m.p.: } 138\text{–}139 \ ^\circ \text{C}; \quad ^1H\ \text{NMR} \ (500 \text{ MHz, CDCl}_3): \delta = 12.57 \ (s, 1H), 9.02 \ (dd, J = 8.6, 1.1 \text{ Hz, 1H}), 8.12 \text{ – 8.08 (m, 2H), 7.82 (dd, J = 8.0, 1.4 \text{ Hz, 1H}), 7.64 (ddd, J = 8.7, 7.3, 1.5 \text{ Hz, 1H}), 7.58 – 7.54 (m, 1H), 7.53 – 7.49 (m, 2H), 7.14 (t, J = 8.2 \text{ Hz, 1H}), 4.81 (s, 2H), 3.55 (s, 3H) ppm;} \quad ^{13}C\ \text{NMR} \ (126 \text{ MHz, CDCl}_3): \delta = 200.2, 166.2, 141.8, 135.9, 134.6, 132.2, 129.6, 129.0, 127.7, 122.6, 121.3, 119.7, 75.5, 59.7 \text{ ppm;} \quad \text{IR (neat): } \tilde{\nu} = 3268, 3236, 3130, 3062, 2995, 2942, 2829, 1672, 1653, 1610, 1585, 1559, 1537, 1496, 1448, 1368, 1322, 1311, 1258, 1216, 1196, 1139, 1120, 1029, 978, 925, 699, 661 \text{ cm}^{-1}; \quad \text{HRMS (ESI): } m/z \text{ calculated for } C_{16}H_{15}N_{2}NaO_{2}^+: 292.0944; \quad \text{found: 292.0944.}
\]
2-methoxy-N-(2-(4-methoxybenzoyl)phenyl)acetamide (5b)

Compound 5b was prepared according to GP1 starting from 3a (90.4 mg, 0.303 mmol, 1.5 equiv., 0.015 M) and and 4b (45.0 mg, 0.202 mmol, 1 equiv., 0.010 M). Column chromatography (silica gel, n-pentane/EtOAc = 3:1) afforded the title compound (5b, 32.8 mg, 0.122 mmol, 60%) as a slightly yellow oil.

Rf = 0.49 (n-pentane/EtOAc = 2:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 11.09\) (s, 1H), 8.62 (dt, \(J = 8.1, 1.0\) Hz, 1H), 7.78 – 7.72 (m, 2H), 7.58 – 7.52 (m, 2H), 7.16 – 7.09 (m, 1H), 6.99 – 6.93 (m, 2H), 4.03 (s, 2H), 3.89 (s, 3H), 3.53 (s, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 197.3, 169.1, 163.5, 138.8, 133.4, 132.8, 132.7, 125.3, 122.7, 121.9, 113.7, 72.7, 59.8, 55.7\) ppm; IR (neat): \(\tilde{\nu} = 3310, 3006, 2931, 2840, 1687, 1633, 1597, 1578, 1510, 1447, 1419, 1315, 1306, 1293, 1253, 1196, 1172, 1154, 1110, 1026, 986, 925, 844, 788, 760, 739, 696\) cm\(^{-1}\); HRMS (ESI): m/z calculated for C\(_{16}\)H\(_{15}\)NNaO\(_3\)^+ ([M+Na]^+): 322.1050; found: 322.1062.

\(\text{N-(2-(4-bromobenzoyl)phenyl)}\)-2-methoxyacetamide (5c)

Compound 5c was prepared according to GP1 starting from 3a (44.8 mg, 0.150 mmol, 1.5 equiv.) 4c (27.2 mg, 0.100 mmol, 1 equiv.). Column chromatography (silica gel, n-pentane/EtOAc 3:1) afforded the title compound (5c, 8.10 mg, 0.023 mmol, 23%) as a slightly yellow oil.

Rf = 0.33 (n-pentane/EtOAc = 3:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 11.31\) (s, 1H), 8.68 (dd, \(J = 8.4, 1.0\) Hz, 1H), 7.67 – 7.54 (m, 5H), 7.52 (dd, \(J = 7.9, 1.6\) Hz, 1H), 7.15 – 7.11 (m, 1H), 4.05 (s, 2H), 3.56 (s, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 197.9, 169.2, 139.5, 137.5, 134.4, 133.2, 131.8, 127.7, 124.0, 122.8, 121.9, 72.7, 59.9\) ppm; IR (neat): \(\tilde{\nu} = 3298, 3081, 3033, 2995, 2932, 2827, 1692, 1641, 1601, 1577, 1515, 1483, 1446, 1432, 1394, 1361, 1314, 1293, 1262, 1196, 1178, 1167, 1157, 1114, 1068, 1051, 1010, 987, 959, 921, 880, 841, 783, 758, 725, 675, 654 cm\(^{-1}\)); HRMS (ESI): m/z calculated for C\(_{16}\)H\(_{14}\)BrNaO\(_3\)^+ ([M+Na]^+): 370.0049; found: 370.0063.
**N-(2-benzoyl-3-(benzylxy)phenyl)-2-methoxyacetamide (5d)**

Compound 5d was prepared according to GP1 starting from 3b (62.0 mg, 0.153 mmol, 1.5 equiv.) and 4a (44.6 mg, 0.230 mmol, 1 equiv.). Column chromatography (silica gel, n-pentane/EtOAc = 3:1) afforded the title compound (5d, 30.6 mg, 0.082 mmol, 35%) as a slightly yellow oil.

R_f = 0.25 (n-pentane/EtOAc = 4:1); ^1H NMR (700 MHz, CDCl_3): \( \delta = 9.51 \) (s, 1H), 8.03 (dd, \( J = 8.4, 0.8 \) Hz, 1H), 7.80 – 7.77 (m, 2H), 7.55 (tt, \( J = 8.7, 1.3 \) Hz, 1H), 7.47 – 7.41 (m, 3H), 7.21 – 7.17 (m, 1H), 7.16 – 7.13 (m, 2H), 6.81 (dd, \( J = 8.4, 0.8 \) Hz, 1H), 6.77 (d, \( J = 7.5 \) Hz, 2H), 4.90 (s, 2H), 3.93 (s, 2H), 3.41 (s, 3H) ppm; ^13C NMR (176 MHz, CDCl_3): \( \delta = 197.1, 168.6, 157.4, 139.4, 137.1, 136.1, 133.1, 132.5, 129.4, 128.5, 128.4, 127.8, 118.8, 115.2, 108.5, 72.4, 70.4, 59.6 \) ppm; IR (neat): \( \tilde{\nu} = 3359, 3061, 3031, 3003, 2929, 2829, 1802, 1691, 1646, 1597, 1581, 1523, 1497, 1466, 1460, 1428, 1381, 1313, 1275, 1256, 1196, 1146, 1112, 1087, 1071, 1028, 986, 925, 875, 865, 846, 807, 782, 739 \) cm\(^{-1}\); HRMS (ESI): m/z calculated for C_{23}H_{21}NNaO_4\(^+\) ([M+Na]^+): 398.1363; found: 398.1367.

**N-(3-(benzyloxy)-2-(4-methoxybenzoyl)phenyl)-2-methoxyacetamide (5e)**

Compound 5e was prepared according to GP1 starting from 3b (571 mg, 1.41 mmol, 1.5 equiv., 0.015 M) and 4b (210 mg, 0.941 mmol, 1 equiv., 0.010 M). Column chromatography (silica gel, n-pentane/EtOAc = 3:1) afforded the title compound (5e, 90.6 mg, 0.122 mmol, 24%) as a slightly yellow oil.

R_f = 0.18 (n-pentane/EtOAc = 3:1); ^1H NMR (700 MHz, CD_3CN): \( \delta = 8.96 \) (s, 1H), 7.87 (dd, \( J = 8.3, 0.8 \) Hz, 1H), 7.76 – 7.73 (m, 2H), 7.47 (t, \( J = 8.3 \) Hz, 1H), 7.24 – 7.18 (m, 3H), 6.99 – 6.96 (m, 3H), 6.95 – 6.93 (m, 2H), 4.98 (s, 2H), 3.85 (s, 3H), 3.84 (s, 2H), 3.30 (s, 3H) ppm; ^13C NMR (176 MHz, CD_3CN): \( \delta = 195.8, 169.1, 165.2, 157.6, 137.4, 137.3, 132.6, 132.2, 129.2, 128.7, 128.1, 120.7, 115.9, 114.9, 109.8, 72.7, 71.1, 59.7, 56.4 \) ppm; IR (neat): \( \tilde{\nu} = 3360, 3062, 3034, 3009, 2935, 2840, 1691, 1645, 1593, 1509, 1461, 1382, 1280, 1254, 1173, 1145, 1111, 1070, 1028, 986, 927, 844, 793, 735, 696, 668 \) cm\(^{-1}\); HRMS (ESI): m/z calculated for C_{24}H_{23}NNaO_5\(^+\) ([M+Na]^+): 428.1468; found: 428.1461.
**N-(2-benzoylphenyl)-2-(benzyloxy)acetamide (5f)**

![Chemical Structure](image)

Compound 5f was prepared according to GP1 starting from 3a (44.8 mg, 0.150 mmol, 1.5 equiv.) and 4d (29.0 mg, 0.100 mmol, 1 equiv.). Column chromatography (silica gel, n-pentane/EtOAc 6:1) afforded the title compound (5f, 14.1 mg, 0.0404 mmol, 40%) as a colorless oil.

Rf = 0.60 (n-pentane/EtOAc = 4:1); ¹H NMR (700 MHz, CDCl₃): δ = 11.46 (s, 1H), 8.67 (dd, J = 8.4, 1.1 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.62 – 7.55 (m, 3H), 7.52 – 7.45 (m, 4H), 7.37 – 7.33 (m, 2H), 7.30 – 7.26 (m, 1H), 7.15 – 7.10 (m, 1H), 4.73 (s, 2H), 4.10 (s, 2H) ppm; ¹³C NMR (176 MHz, CDCl₃): δ = 198.8, 169.2, 139.3, 138.7, 136.9, 134.0, 133.3, 132.6, 130.2, 128.7, 128.4, 128.2, 128.1, 124.6, 122.7, 121.8, 73.8, 69.8 ppm; IR (neat): ν = 3300, 3061, 3029, 2955, 2924, 2867, 1694, 1641, 1599, 1578, 1519, 1447, 1397, 1373, 1317, 1293, 1265, 1207, 1163, 1099, 1027, 1000, 974, 936, 921, 852, 805, 75 cm⁻¹; HRMS (ESI): m/z calculated for C₂₂H₁₉NO₃Na⁺ ([M+Na⁺]⁺): 368.1263; found: 368.1263.

**N-(3-(allyloxy)-2-benzoylphenyl)-2-methoxyacetamide (5g)**

![Chemical Structure](image)

Compound 5g was prepared according to GP1 starting from 3c (107 mg, 0.303 mmol, 1.5 equiv.) and 4a (45.0 mg, 0.202 mmol, 1 equiv.). Column chromatography (silica gel, n-pentane/EtOAc = 3:1) afforded the title compound (5g, 12.0 mg, 0.0371 mmol, 18%) as a slightly yellow oil.

Rf = 0.29 (n-pentane/EtOAc = 3:1); ¹H NMR (500 MHz, CDCl₃): δ = 9.52 (s, 1H), 8.01 (dd, J = 8.4, 0.8 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.56 – 7.51 (m, 1H), 7.47 – 7.38 (m, 3H), 6.73 (dd, J = 8.4, 0.9 Hz, 1H), 5.53 (ddt, J = 17.2, 10.7, 4.9 Hz, 1H), 4.97 (dq, J = 10.7, 1.5 Hz, 1H), 4.87 (dq, J = 17.3, 1.7 Hz, 1H), 4.35 (dt, J = 5.0, 1.7 Hz, 2H), 3.93 (s, 2H), 3.40 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 197.1, 168.6, 157.4, 139.3, 137.1, 133.1, 132.5, 132.1, 129.3, 128.4, 118.6, 117.1, 115.1, 108.6, 72.4, 69.3, 59.6 ppm; IR (neat): ν = 3356, 3066, 2951, 2922, 2850, 1696, 1648, 1597, 1584, 1522, 1468, 1422, 1370, 1362, 1314, 1277, 1197, 1178, 1145, 1144, 1076, 986, 926, 853, 808, 782, 746, 718, 702, 671, 661 cm⁻¹; HRMS (ESI): m/z calculated for C₁₉H₁₉NO₄Na⁺ ([M+Na⁺]⁺): 348.1206; found: 348.1207.
Compound 5h was prepared according to GP1 starting from 3c (198 mg, 0.555 mmol, 1.5 equiv., 0.015 M) and 4b (83.0 mg, 0.370 mmol, 1 equiv., 0.010 M). Column chromatography (silica gel, n-pentane/EtOAc = 2:1) afforded the title compound (5h, 39.3 mg, 0.111 mmol, 30%) as a slightly yellow oil.

Rf = 0.32 (n-pentane/EtOAc = 2:1); **1H NMR** (500 MHz, CDCl3): δ = 9.25 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.40 (t, J = 8.3 Hz, 1H), 6.89 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 9.1 Hz, 1H), 5.65 (ddt, J = 17.2, 10.6, 4.9 Hz, 1H), 5.02 (dq, J = 10.7, 1.5 Hz, 1H), 4.96 (dq, J = 17.3, 1.7 Hz, 1H), 4.40 (dt, J = 4.8, 1.7 Hz, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.37 (s, 3H) ppm; **13C NMR** (126 MHz, CDCl3): δ = 195.1, 168.5, 164.0, 156.8, 136.5, 132.4, 132.0, 131.8, 131.6, 119.5, 117.1, 115.2, 113.7, 108.7, 72.3, 69.3, 59.6, 55.7 ppm; **IR** (neat): ν = 3359, 3075, 2931, 2840, 1810, 1693, 1646, 1594, 1522, 1509, 1467, 1421, 1382, 1362, 1315, 1281, 1256, 1196, 1173, 1146, 1113, 1073, 986, 929, 880, 846, 817, 792, 768, 734, 709, 693, 672, 663 cm⁻¹; **HRMS** (ESI): m/z calculated for C₂₀H₂₁NNaO₆⁺ ([M+Na]⁺): 378.1312; found: 378.1331.
General Procedure for the Aldol Reaction (GP2)

The ortho-aminobenzophenone (5a-h, 1 equiv.) was dissolved in anhydrous THF (50 mL/mmol substrate) and a solution of KO{\text{Bu}} (7 equiv., 1 M in THF) was added dropwise at 0 °C. Upon addition of KO{\text{Bu}} the solution turned bright yellow. After stirring at 0 °C for 1.5 h, water (50 mL/mmol substrate) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL/mmol substrate). The combined organic layers were dried (MgSO{\text{4}}), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the quinolinones 6a-g.

(±)-6-Deoxyaflaquinolone E (6a)

6-Deoxyaflaquinolone E was prepared according to GP2 starting from 5a (20 mg, 0.075 mmol, 1 equiv.) and KO{\text{Bu}} (59 mg, 0.53 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_{2}Cl_{2}/MeOH = 100:3) to afford the title compound (6a, 18 mg, 0.068 mmol, 92%) as a colorless solid.

R_f = 0.21 (n-pentane/EtOAc = 1:1); m.p.: 160 °C – 165 °C; \textsuperscript{1}H NMR (700 MHz, DMSO-\text{d}_{6}): δ = 10.21 (s, 1H), 7.33 (d, J = 4.4 Hz, 4H), 7.28 (dt, J = 8.5, 4.2 Hz, 1H), 7.24 – 7.20 (m, 1H), 6.93 – 6.90 (m, 2H), 6.88 (dd, J = 7.5, 1.6 Hz, 1H), 5.81 (s, 1H), 4.18 (s, 1H), 3.34 (s, 3H) ppm; \textsuperscript{13}C NMR (176 MHz, DMSO-\text{d}_{6}): δ = 168.4, 142.3, 136.8, 129.2, 128.7, 127.8, 127.5, 127.3, 126.7, 122.1, 115.1, 83.9, 76.7, 59.1 ppm; IR (neat): \tilde{\nu} = 3446, 3361, 3211, 3085, 3022, 2993, 2931, 2845, 2831, 1681, 1609, 1593, 1559, 1486, 1446, 1433, 1397, 1318, 1285, 1263, 1246, 1226, 1203, 1181, 1157, 1157, 1142, 1119, 1107, 1069, 1048, 1020, 1001, 953, 940, 910, 871, 858, 824, 791, 762, 752, 704, 674, 658 cm\textsuperscript{-1}; HRMS (ESI): m/z calculated for C_{16}H_{15}NaO_{3}\textsuperscript{+} ([M+Na]\textsuperscript{+}): 292.0944; found: 292.0945. The NMR data match those reported for 6-deoxyaflaquinolone E.\textsuperscript{5}
Quinolinone A was prepared according to GP2 starting from 5b (20 mg, 0.067 mmol, 1 equiv.) and KOtBu (53 mg, 0.47 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH2Cl2/MeOH = 100:3) to afford the title compound (6b, 16.7 mg, 0.056 mmol, 84%) as a colorless solid.

\[ R_f = 0.22 \text{ (n-pentane/EtOAc = 1:1); m.p.: } 172^\circ \text{C} - 175^\circ \text{C}; ^1H \text{ NMR (500 MHz, acetone-}d_6\text{)}: \delta = 9.29 (s, 1H), 7.35 - 7.20 (m, 4H), 7.07 - 6.97 (m, 2H), 6.91 - 6.81 (m, 2H), 4.61 (s, 1H), 3.93 (s, 1H), 3.76 (s, 3H) \text{ ppm; } ^13C \text{ NMR (126 MHz, acetone-}d_6\text{)}: \delta = 168.2, 160.3, 137.6, 134.5, 129.6, 129.0, 128.4, 123.6, 115.9, 115.9, 114.2, 85.7, 77.3, 59.4, 55.5 \text{ ppm; } IR (\text{neat}): \tilde{\nu} = 3249, 3081, 3002, 2931, 2836, 1687, 1611, 1595, 1512, 1483, 1463, 1379, 1306, 1252, 1173, 1146, 1106, 1081, 1033, 991, 942, 903, 860, 833, 812, 757 \text{ cm}^{-1}; \text{HRMS (ESI): m/z calculated for } C_{17}H_{17}NO_4^+ ([M+Na]^+): 322.1050; \text{ found: 322.1047}. \]

The NMR data match those reported for Quinolinone A.6

cis-4-(4-bromophenyl)-4-hydroxy-3-methoxy-3,4-dihydroquinolin-2(1H)-one (6c)

Compound 6c was prepared according to GP2 starting from 5c (8.0 mg, 0.021 mmol, 1 equiv.) and KOtBu (16 mg, 0.15 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH2Cl2/MeOH = 100:3) to afford the title compound (6c, 7.2 mg, 0.019 mmol, 90%) as a colorless oil.

\[ R_f = 0.21 \text{ (n-pentane/EtOAc = 1:1); } ^1H \text{ NMR (700 MHz, CD_3OD): } \delta = 7.51 (d, J = 8.8 \text{ Hz, 2H}), 7.36 - 7.33 (m, 2H), 7.28 (ddd, J = 8.0, 5.8, 3.0 \text{ Hz, 1H}), 7.00 - 6.98 (m, 2H), 6.95 (dt, J = 7.9, 0.8 \text{ Hz, 1H}), 4.23 (s, 1H), 3.40 (s, 3H) \text{ ppm; } ^13C \text{ NMR (176 MHz, CDCl}_3\text{)}: \delta = 170.9, 142.4, 138.0, 132.2, 130.5, 130.2, 129.7, 129.1, 124.3, 122.7, 116.8, 85.4, 78.4, 60.6 \text{ ppm; IR (neat): } \tilde{\nu} = 3241, 3069, 2954, 2927, 2853, 2358, 1685, 1607, 1592, 1488, 1467, 1394, 1309, 1205, 1173, 1143, 989, 802, 759 \text{ cm}^{-1}; \text{HRMS (ESI): m/z calculated for } C_{16}H_{14}BrNO_3Na^+ ([M+Na]^+): 370.0049; \text{ found: 370.0051}. \]
cis-5-(benzyloxy)-4-hydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one (6d)

Compound 6d was prepared according to GP2 starting from 5d (28 mg, 0.075 mmol, 1 equiv.) and KOtBu (59 mg, 0.53 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH = 100:2) to afford the title compound (6d, 23 mg, 0.062 mmol, 84%) as a colorless oil.

Rᵣ = 0.25 (n-pentane/EtOAc = 1:1); ¹H NMR (700 MHz, CDCl₃): δ = 8.58 (s, 1H), 7.28 – 7.21 (m, 5H), 7.07 (dd, J = 7.6, 1.9 Hz, 2H), 6.73 (dd, J = 8.5, 0.9 Hz, 1H), 6.57 (dd, J = 8.0, 0.9 Hz, 1H), 5.29 (s, 1H), 5.05 (d, J = 11.5 Hz, 1H), 4.97 (d, J = 11.6 Hz, 1H), 3.85 (d, J = 1.4 Hz, 1H), 3.61 (s, 3H) ppm; ¹³C NMR (176 MHz, CDCl₃): δ = 168.0, 158.0, 142.0, 137.2, 135.7, 130.1, 128.7, 128.7, 128.4, 127.5, 126.2, 115.2, 109.6, 108.8, 85.0, 78.4, 71.1, 59.8 ppm; IR (neat): ν̃ = 3503, 3232, 3062, 3031, 2930, 2829, 2248, 1691, 1595, 1498, 1471, 1448, 1383, 1315, 1277, 1259, 1222, 1176, 1138, 1102, 1059, 1028, 993, 910, 846, 783, 730, 697, 654 cm⁻¹; HRMS (ESI): m/z calculated for C₂₃H₂₁NNaO₄⁺ ([M+Na⁺]): 398.1363; found: 398.1368.

cis-5-(benzyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1H)-one (6e)

Compound 6e was prepared according to GP2 starting from 5e (30 mg, 0.080 mmol, 1 equiv.) and KOtBu (63 mg, 0.56 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH = 100:3) to afford the title compound (6e, 25 mg, 0.067 mmol, 84%) as a colorless oil.

Rᵣ = 0.25 (n-pentane/EtOAc = 1:1); ¹H NMR (700 MHz, CDCl₃): δ = 8.33 (s, 1H), 7.29 – 7.23 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 7.11 – 7.08 (m, 2H), 6.79 (d, J = 7.5 Hz, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.28 (s, 1H), 5.05 (d, J = 11.5 Hz, 1H), 4.97 (d, J = 11.5 Hz, 1H), 3.80 (s, 1H), 3.76 (s, 3H), 3.59 (s, 3H) ppm; ¹³C NMR (176 MHz, CDCl₃): δ = 168.0, 159.7, 158.1, 137.1, 135.7, 133.6, 129.9, 128.8, 128.4, 127.6, 127.5, 115.4, 114.1, 109.5, 108.8, 85.2, 80.6, 78.2, 71.1, 59.7, 55.4 ppm; IR (neat): ν̃ = 3502, 3237, 3066, 3034, 2999, 2930, 2834, 1693, 1596, 1508, 1471, 1388, 1302, 1280, 1253, 1231, 1172, 1103, 1061, 1031, 993, 913, 895, 834, 778, 734, 698, 656 cm⁻¹; HRMS (ESI): m/z calculated for C₂₄H₂₃NNaO₅⁺ ([M+Na⁺]): 428.1468; found: 428.1467.
cis-3-(benzyloxy)-4-hydroxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one (6f)

Compound 6f was prepared according to GP2 starting from 5f (14 mg, 0.043 mmol, 1 equiv.) and KOtBu (34 mg, 0.30 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH = 100:3) to afford the title compound (6f, 12 mg, 0.031 mmol, 72%) as a colorless oil.

\[ R_f = 0.23 \text{ (Pentane/EtOAc = 1:1); } ^1\text{H NMR (500 MHz, CD₃OD): } \delta = 7.40 - 7.32 (m, 5H), 7.27 (ddd, } J = 7.9, 6.3, 2.6 \text{ Hz, 1H}), 7.20 - 7.15 (m, 3H), 7.03 - 6.99 (m, 2H), 6.99 - 6.93 (m, 3H), 4.81 (d, } J = 11.5 \text{ Hz, 1H}), 4.50 (s, 1H), 4.45 (d, } J = 11.5 \text{ Hz, 1H}) \text{ ppm;} ^{13}\text{C NMR (176 MHz, CDCl}_3): \delta = 168.5, 140.7, 136.7, 135.7, 129.7, 128.8, 128.6, 128.5, 128.5, 128.2, 128.1, 126.8, 124.1, 115.5, 81.1, 73.8 ppm; IR (neat): } \tilde{\nu} = 3263, 3087, 3060, 3029, 2923, 2854, 1692, 1610, 1595, 1485, 1448, 1375, 1296, 1265, 1241, 1174, 1143, 1125, 1096, 1070, 1044, 1028, 989, 936, 907, 853, 811, 753 \text{ cm}^{-1}; \text{ HRMS (ESI): } m/z \text{ calculated for } \text{C}_{22}\text{H}_{19}\text{NO}_3\text{K}^+ ([M+K]^+): 384.0997; \text{ found: 384.1002.}

cis-5-(allyloxy)-4-hydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one (6g)

Compound 6g was prepared according to GP2 starting from 5g (35 mg, 0.11 mmol, 1 equiv.) and KOtBu (86 mg, 0.77 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH = 100:2) to afford the title compound (6g, 27 mg, 0.072 mmol, 67%) as a colorless oil.

\[ R_f = 0.23 \text{ (n-pentane/EtOAc = 1:1); } ^1\text{H NMR (500 MHz, CDCl}_3): \delta = 8.07 (s, 1H), 7.29 - 7.26 (m, 5H), 7.22 (t, } J = 8.2 \text{ Hz, 1H}), 6.65 (dd, } J = 8.4, 1.0 \text{ Hz, 1H}), 6.52 (dd, } J = 8.0, 0.9 \text{ Hz, 1H}), 5.78 (ddt, } J = 17.2, 10.6, 5.4 \text{ Hz, 1H}), 5.34 (s, 1H), 5.21 - 5.15 (m, 2H), 4.52 - 4.41 (m, 2H), 3.84 (d, } J = 1.4 \text{ Hz, 1H}), 3.58 (s, 3H) \text{ ppm;} ^{13}\text{C NMR (126 MHz, CDCl}_3): \delta = 167.7, 158.0, 141.9, 137.2, 132.1, 130.0, 128.7, 128.5, 126.1, 118.8, 115.0, 109.4, 108.7, 83.1, 81.4, 74.8, 59.8 \text{ ppm; IR (neat): } \tilde{\nu} = 3494, 3249, 3235, 3083, 3002, 2928, 2829, 1692, 1596, 1502, 1473, 1447, 1421, 1391, 1324, 1313, 1278, 1259, 1224, 1179, 1103, 1059, 1028, 992, 930, 887, 824, 784, 750, 731, 699, 674, 665, 654 \text{ cm}^{-1}; \text{ HRMS (ESI): } m/z \text{ calculated for } \text{C}_{19}\text{H}_{19}\text{NO}_4\text{Na}^+ ([M+Na]^+): 348.1206; \text{ found: 348.1195.}

cis-5-(allyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1H)-one (6h)

Compound 6h was prepared according to GP2 starting from 5h (43 mg, 0.12 mmol, 1 equiv.) and KOtBu (94 mg, 0.84 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel CH2Cl2/MeOH = 100:3) to afford the title compound (6h, 25 mg, 0.070 mmol, 58%) as a colorless oil.

Rf = 0.23 (n-pentane/EtOAc = 1:1); ¹H NMR (500 MHz, CDCl₃): δ = 8.34 (s, 1H), 7.21 (t, J = 8.2 Hz, 1H), 7.18 – 7.15 (m, 2H), 6.81 – 6.77 (m, 2H), 6.65 (d, J = 8.5 Hz, 1H), 6.51 (dd, J = 8.0, 0.8 Hz, 1H), 5.83 (ddt, J = 17.0, 10.4, 5.3 Hz, 1H), 5.40 (s, 1H), 5.25 – 5.16 (m, 2H), 4.54 – 4.44 (m, 2H), 3.81 (d, J = 1.5 Hz, 1H), 3.74 (s, 3H), 3.59 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 167.9, 159.7, 158.0, 137.0, 133.6, 129.8, 127.5, 118.8, 115.2, 114.1, 109.5, 108.7, 85.2, 78.2, 69.8, 59.6, 55.3 ppm; IR (neat): ν = 3697, 3251, 3237, 3196, 3101, 3087 3039, 2997, 2932, 2833, 2246, 1691, 1595, 1508, 1471, 1442, 1417, 1392, 1303, 1280, 1251, 1224, 1172, 1101, 993, 928, 912, 893, 833, 809, 779, 729, 693, 670, 661 cm⁻¹; HRMS (ESI): m/z calculated for C₂₀H₂₁NO₅⁺ ([M+Na]⁺): 378.1312; found: 378.1317.
(±)-Aflaquinolone E (9)

To a solution of 6d (23 mg, 0.060 mmol, 1 equiv.) EtOH/EtOAc (1:1, 1 mL) was added Pd/C (6.4 mg, 0.0061 mmol, 10 w% Pd, 10 mol%) and the atmosphere was changed from Ar to H₂ by short evacuation and backfilling with H₂. The reaction mixture was then stirred vigorously at room temperature for 2 h under an atmosphere of H₂. Then the reaction mixture was then filtered over a short pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH = 50:1) to afford the title compound (9, 15 mg, 0.051 mmol, 85%) as a colorless solid.

Rᵣ = 0.21 (n-pentane/EtOAc = 3:1); m.p.: 143 °C – 148 °C; \(^1\)H NMR (700 MHz, CD₃OD): δ = 7.32 – 7.29 (m, 3H), 7.29 – 7.26 (m, 2H), 7.15 (t, J = 8.1 Hz, 1H), 6.54 (dd, J = 8.3, 1.1 Hz, 1H), 6.46 (dd, J = 8.0, 1.1 Hz, 1H), 3.66 (s, 1H), 3.53 (s, 3H) ppm; \(^1^3\)C NMR (176 MHz, CD₃OD): δ = 169.1, 159.1, 140.9, 138.1, 131.0, 129.8, 129.6, 127.5, 113.2, 113.0, 108.2, 86.3, 79.9, 59.2 ppm; IR (neat): ν = 3281, 3061, 2998, 2935, 2832, 1681, 1620, 1595, 1475, 1448, 1387, 1243, 1207, 1169, 1099, 1021, 879, 791, 745, 725, 698, 659 cm⁻¹; HRMS (ESI): m/z calculated for C₁₆H₁₆NNaO₄+ ([M+Na]+): 308.0893; found: 308.0900.
The NMR data match those reported for Aflaquinolone E.⁷

(±)-Quinolinone B (10)

To a solution of 6e (12 mg, 0.028 mmol, 1 equiv.) in EtOH/EtOAc (1:1, 1 mL) was added Pd/C (3.0 mg, 0.0029 mmol, 10 w% Pd, 10 mol%) and the atmosphere was changed from Ar to H₂ by short evacuation and backfilling with H₂. The reaction mixture was then stirred vigorously at room temperature for 2 h under an atmosphere of H₂. The reaction mixture was then filtered over a short pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel CH₂Cl₂/MeOH = 50:1) to afford the title compound (10, 8.8 mg, 0.028 mmol, 98%) as a colorless oil.

Rᵣ = 0.60 (CH₂Cl₂/MeOH = 50:1); \(^1\)H NMR (700 MHz, acetone-d₆): δ = 9.28 (s, 1H), 9.16 (s, 1H), 7.22 (d, J = 8.9 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 6.55 (dd, J = 8.0, 1.1 Hz, 1H), 6.49 (dd, J = 8.2, 1.1 Hz, 1H), 6.14 (s, 1H), 3.77 (s, 3H), 3.67 (d, J = 1.6 Hz, 1H), 3.50 (s, 3H) ppm; \(^1^3\)C NMR
(176 MHz, acetone-d₆): δ = 166.5, 161.0, 159.2, 138.1, 131.9, 130.7, 128.8, 114.7, 112.5, 112.4, 107.4, 85.8, 79.6, 58.9, 55.5 ppm; IR (neat): ν = 3294, 3066, 2993, 2932, 2837, 1685, 1626, 1595, 1510, 1439, 1379, 1207, 1170, 1103, 1076, 1051, 1025, 989, 936, 884, 834, 783, 756, 716 cm⁻¹; HRMS (ESI): m/z calculated for C₁₇H₁₇NNaO₅⁺ ([M+Na⁺]: 338.0999; found: 338.1006. The NMR data match those reported for Quinolinone B.⁶

(±)-Aflaquinolone F (11)

To a solution of 6f (12 mg, 0.034 mmol, 1 equiv.) in EtOH/EtOAc (1:1, 1 mL) was added Pd/C (3.6 mg, 0.0031 mmol, 10 w% Pd, 10 mol%) and the atmosphere was changed from Ar to H₂ by short evacuation and backfilling with H₂. The reaction mixture was then stirred vigorously at room temperature for 16 h under an atmosphere of H₂. The reaction mixture was then filtered over a short pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH = 100:3) to afford the title compound (11, 8.7 mg, 0.034 mmol, 99%) as a colorless oil.

R₁ = 0.30 (CH₂Cl₂/MeOH = 50:1); ¹H NMR (600 MHz, CD₃OD): δ = 7.50 (d, J = 8.2 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.29 – 7.20 (m, 1H), 6.96 (s, 1H), 6.98 – 6.85 (m, 1H), 6.73 – 6.70 (m, 1H), 5.48 (s, 1H), 4.75 (s, 1H) ppm; ¹³C NMR (151 MHz, CD₃OD): δ = 172.7, 143.2, 138.4, 130.6, 130.1, 129.0, 128.4, 128.3, 124.0, 117.0, 78.7, 75.8, 49.4 ppm; IR (neat): ν = 3294, 2954, 2922, 2853, 1727, 1707, 1606, 1464, 1376, 1282, 1248, 1116, 1031, 824, 762, 722 cm⁻¹; HRMS (ESI): m/z calculated for C₁₅H₁₃NNaO₃⁺ ([M+Na⁺]: 278.0787; found: 278.0795. The NMR data match those reported for Aflaquinolone F.⁷

**cis-6-allyl-4,5-dihydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one (12a)**

6g (14 mg, 0.040 mmol, 1 equiv.) was dissolved in 1,2-dichlorobenzene (1 mL) and heated in a microwave at 150 °C for 10 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, n-pentane/EtOAc = 1:2) to afford the title compound (12a, 9.9 mg, 0.030 mmol, 71%) as a colorless oil.

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S20
$R_f = 0.32 \ (CH_2Cl_2/MeOH = 50:1);^1 \ H \ NMR \ (500 \ MHz, \ CDCl_3): \ \delta = 8.90 \ (d, \ J = 0.5 \ Hz, \ 1H), \ 7.85 \ (s, \ 1H), \ 7.33 - 7.29 \ (m, \ 3H), \ 7.28 - 7.25 \ (m, \ 2H), \ 7.05 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 6.32 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 5.97 \ (dtd, \ J = 16.8, \ 10.1, \ 6.6 \ Hz, \ 1H), \ 5.07 - 5.02 \ (m, \ 2H), \ 4.60 \ (s, \ 1H), \ 3.69 \ (d, \ J = 1.5 \ Hz, \ 1H), \ 3.62 \ (s, \ 3H), \ 3.31 \ (qdt, \ J = 15.7, \ 6.7, \ 1.7 \ Hz, \ 2H) \ ppm; \ ^{13}C \ NMR \ (126 \ MHz, \ CDCl_3): \ \delta = 165.7, \ 155.7, \ 137.7, \ 136.9, \ 133.8, \ 130.8, \ 129.3, \ 129.0, \ 126.5, \ 124.4, \ 115.7, \ 110.5, \ 106.5, \ 84.3, \ 79.1, \ 59.1, \ 33.7 \ ppm; \ IR \ (neat): \ \tilde{\nu} = 3465, \ 3290, \ 3074, \ 2954, \ 2924, \ 2869, \ 1683, \ 1638, \ 1622, \ 1602, \ 1505, \ 1493, \ 1463, \ 1449, \ 1421, \ 1378, \ 1346, \ 1272, \ 1174, \ 1102, \ 1077, \ 1036, \ 1027, \ 992, \ 947, \ 916, \ 892, \ 856, \ 846, \ 815, \ 754, \ 697, \ 673, \ 666 \ cm^{-1}; \ HRMS \ (ESI): \ m/z \ calculated \ for \ C_{19}H_{19}NNaO_4^+ ([M+Na]^+): \ 348.1206; \ found: \ 348.1216.\]

**cis-6-allyl-4,5-dihydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1H)-one (12b)**

6h (39 mg, 0.11 mmol, 1 equiv.) was dissolved in 1,2-dichlorobenzene (1 mL) and heated in a microwave at 150 °C for 10 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, $n$-pentane/EtOAc = 1:2) to afford the title compound (12b, 25 mg, 0.070 mmol, 63%) as a colorless oil.

$R_f = 0.32 \ (n$-Pentane/EtOAc = 1:1); $^1H \ NMR \ (400 \ MHz, \ acetone-d$_6$): $\delta = 9.45 \ (s, \ 1H), \ 9.25 \ (s, \ 1H), \ 7.28 - 7.15 \ (m, \ 2H), \ 7.04 \ (dt, \ J = 8.1, \ 0.7 \ Hz, \ 1H), \ 6.93 - 6.82 \ (m, \ 2H), \ 6.51 \ (d, \ J = 8.5 \ Hz, \ 1H), \ 6.23 \ (s, \ 1H), \ 6.01 - 5.89 \ (m, \ 1H), \ 5.08 - 5.00 \ (m, \ 1H), \ 4.96 \ (ddtd, \ J = 10.1, \ 2.0, \ 1.4, \ 0.5 \ Hz, \ 1H), \ 3.76 \ (s, \ 2H), \ 3.65 \ (dd, \ J = 1.5, \ 0.5 \ Hz, \ 1H), \ 3.50 \ (s, \ 1H), \ 3.33 - 3.20 \ (m, \ 2H) \ ppm; \ ^{13}C \ NMR \ (126 \ MHz, \ acetone-d$_6$): \ $\delta = 166.4, \ 161.0, \ 156.6, \ 138.1, \ 136.3, \ 131.9, \ 130.8, \ 128.8, \ 123.2, \ 115.4, \ 114.7, \ 112.0, \ 107.1, \ 85.8, \ 79.7, \ 58.8, \ 55.5, \ 34.2 \ ppm; \ IR \ (neat): \ \tilde{\nu} = 3280, \ 3069, \ 2955, \ 2924, \ 2853, \ 1683, \ 1638, \ 1623, \ 1603, \ 1509, \ 1463, \ 1418, \ 1379, \ 1306, \ 1253, \ 1224, \ 1172, \ 1103, \ 1077, \ 1028, \ 993, \ 944, \ 909, \ 891, \ 860, \ 830, \ 812, \ 798, \ 765, \ 754, \ 730, \ 709, \ 701, \ 687, \ 681, \ 666 \ cm^{-1}; \ HMRS \ (ESI): \ m/z \ calculated \ for \ C_{20}H_{21}NNaO_5^+ ([M+Na]^+): \ 378.1312; \ found: \ 378.1328.

(±)-Aniduquinolone C (13a)

12a (9.9 mg, 0.030 mmol, 1 equiv.) and Umicore M71 SIMes (1.1 mg, 0.0015 mmol, 5 mol%) were dissolved in CH$_2$Cl$_2$ (0.5 mL), 2-methylbut-2-ene (0.030 mL, 0.30 mmol, 10 equiv.) was added and the reaction mixture was heated to reflux for 5 h in a sealed tube. After cooling to room temperature, the
reaction mixture was filtered through a short pad of silica gel. All volatiles were removed under reduced pressure, and the crude product was purified by HPLC (EtOH/n-pentane = 1:10, 1 mL/min, tᵣ = 7.00 min) to afford the title compound (13a, 8.0 mg, 0.024 mmol, 81%) as a colorless oil.

Rᵣ = 0.35 (CH₂Cl₂/MeOH 50:1); ¹H NMR (700 MHz, DMSO-d₆): δ = 10.15 (s, 1H), 7.37 – 7.28 (m, 3H), 7.19 (dd, J = 5.8, 3.6 Hz, 2H), 6.95 (d, J = 7.9 Hz, 1H), 6.37 (d, J = 7.9 Hz, 1H), 5.24 (t, J = 7.4 Hz, 1H), 3.58 (s, 1H), 3.43 (s, 3H), 3.19 (dd, J = 15.4, 7.4 Hz, 1H), 3.08 (dd, J = 15.4, 7.3 Hz, 1H), 1.68 (s, 3H), 1.65 (s, 3H) ppm; ¹³C NMR (176 MHz, DMSO-d₆): δ = 166.1, 155.0, 140.0, 135.0, 131.3, 129.2, 128.6, 126.2, 123.0, 122.8, 110.9, 106.3, 84.4, 78.7, 58.3, 27.5, 25.6, 17.7 ppm; IR (neat): ν̃ = 3218, 3142, 3062, 2912, 2832, 2255, 1685, 1623, 1602, 1506, 1493, 1447, 1422, 1375, 1274, 1224, 1174, 1105, 1076, 1024, 943, 902, 867, 767, 734 cm⁻¹; HRMS (ESI): m/z calculated for C₂₂H₂₃NNaO₄⁺ ([M+Na⁺]: 376.1519; found: 376.1513. The NMR data match those reported for Aniduquinolone C⁵.

(±)-Peniprequinolone (13b)

12b (11 mg, 0.030 mmol, 1 equiv.) and Umicore M71 SiMes (1.1 mg, 0.0015 mmol, 5 mol%) were dissolved in CH₂Cl₂ (0.5 mL). 2-methylbut-2-ene (0.030 mL, 0.30 mmol, 10 equiv.) was added and the reaction mixture was heated to reflux for 5 h in a sealed tube. After cooling to room temperature, the reaction mixture was filtered through a short pad of silica gel. All volatiles were removed under reduced pressure, and the crude product was purified by HPLC (EtOH/n-pentane = 1:10, 1 mL/min, tᵣ = 8.60 min) to afford the title compound (13b, 9.0 mg, 0.024 mmol, 80%) as a colorless solid.

Rᵣ = 0.40 (CH₂Cl₂/MeOH 50:1); m.p.: 59°C; ¹H NMR (500 MHz, CDCl₃): δ = 8.91 (s, 1H), 7.91 (s, 1H), 7.19 – 7.14 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.28 (d, J = 8.0 Hz, 1H), 5.30 – 5.26 (m, 1H), 4.54 (s, 1H), 3.76 (s, 3H), 3.68 (d, J = 1.5 Hz, 1H), 3.60 (s, 3H), 3.29 (dd, J = 16.0, 7.5 Hz, 1H), 3.20 (dd, J = 16.0, 7.2 Hz, 1H), 1.74 (s, 3H), 1.68 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 166.0, 160.3, 155.7, 133.3, 132.8, 130.1, 129.5, 128.0, 125.8, 122.4, 114.4, 110.5, 106.4, 84.5, 84.5, 78.9, 59.0, 55.4, 27.8, 25.9, 17.9 ppm; IR (neat): ν̃ = 3277, 3059, 2954, 2923, 2869, 2853, 1684, 1621, 1603, 1510, 1462, 1419, 1377, 1306, 1254, 1221, 1188, 1172, 1105, 1079, 1032, 989, 974, 940, 929, 903, 867, 829, 810, 767, 755, 734, 707, 698, 974, 661, 652 cm⁻¹; HRMS (ESI): m/z calculated for C₂₂H₂₃NNaO₄⁺ ([M+Na⁺]: 406.1625; found: 406.1627. The NMR data match those reported for Peniprequinolone.⁶
References


Appendix

$^{1}$H NMR (500 MHz, CDCl₃)

$^{13}$C NMR (126 MHz, CDCl₃)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$\text{MeO}$

$4b$

$^1\text{H NMR (400 MHz, DMSO-$d_6$)}$

$\text{MeO}$

$4b$

$^{13}\text{C NMR (101 MHz, DMSO-$d_6$)}$
$^{1}H$ NMR (700 MHz, CDCl$_3$)

$^{13}C$ NMR (176 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CDCl$_3$)

$^{13}$C NMR (176 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CDCl$_3$)

$^{13}$C NMR (176 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CD$_3$CN)

$^{13}$C NMR (176 MHz, CD$_3$CN)
$^1$H NMR (700 MHz, CDCl$_3$)

$^{13}$C NMR (176 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^{1}H$ NMR (700 MHz, DMSO-$_d_6$)

$^{13}C$ NMR (176 MHz, DMSO-$_d_6$)

S39
$^1$H NMR (500 MHz, acetone-$d_6$)

$^{13}$C NMR (126 MHz, acetone-$d_6$)
$^{1}H$ NMR (700 MHz, CDCl$_3$)

$^{13}$C NMR (176 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CDCl$_3$)

$^{13}$C NMR (176 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CD$_2$OD)

$^{13}$C NMR (126 MHz, CD$_2$OD)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CD$_3$OD)

$^{13}$C NMR (176 MHz, CD$_3$OD)
$^1$H NMR (700 MHz, acetone-d$_6$)

$^{13}$C NMR (176 MHz, acetone-d$_6$)
$^1$H NMR (600 MHz, CD$_3$OD)

$^{13}$C NMR (151 MHz, CD$_3$OD)
$^{1}H$ NMR (400 MHz, acetone-$d_{6}$)

$^{13}C$ NMR (126 MHz, acetone-$d_{6}$)
$^{1}$H NMR (700 MHz, DMSO-d$_6$)

$^{13}$C NMR (176 MHz, DMSO-d$_6$)
$^{1}H$ NMR (500 MHz, CDCl$_3$)

$^{13}C$ NMR (126 MHz, CDCl$_3$)