

Supporting Information

Microwave-Assisted “Click Chemistry” for the Preparation of 3- and 4-Triazolo-2(1*H*)-quinolones as Potential Fluorescent Probes

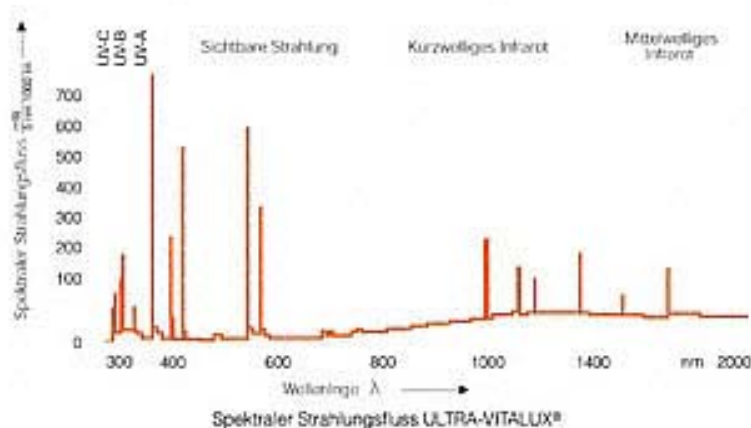
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General Experimental Details:

^1H - and ^{13}C -NMR spectra were recorded on a Bruker AMX 360 (360 and 90 MHz respectively). Low resolution mass spectra were obtained in the atmospheric pressure chemical ionization (positive or negative APCI mode). Analytical HPLC analysis was carried out on a LiChrospher 100 C18 reversed-phase analytical column (119 × 3 mm, 5 μm particle size) at 25 °C, using mobile phase A (water/MeCN 9:1 (v/v) + 0.1% TFA) and phase B (MeCN + 0.1% TFA), with linear gradient from 30% B to 100% B in 8 min and 2 min with 100% phase B. Whenever needed, chromatographic purification was performed either by “dry-flash” silica gel chromatography on silica gel 60H (Merck) with petroleum ether/ethyl acetate = 1:1 to 1:2 as eluting solvent or by automated flash chromatography on a Biotage SP1 chromatography system using pre-packed silica gel cartridges (Biotage) with petroleum ether/ethyl acetate in linear gradient regime from 0% EtOAc to 100% EtOAc. IR spectroscopy (KBr or NaCl) was performed on a FT-IR Mattson Instruments 6030 Galaxy Series Spectrometer. Microwave-assisted reactions were performed in an Initiator 8 (Biotage AB) single mode microwave instrument at 2450 MHz controlled irradiation using standard sealed microwave glass vials. Reaction temperatures were monitored by an IR sensor on the outside wall of the reaction vials. Reaction times refer to hold times at the selected set temperature, not to total irradiation times. UV-Irradiation was performed with an OSRAM Ultra-Vitalux[®] 300W lamp (see light spectrum below).



Synthetic Procedures and Analytical Data

General Procedure 1: 1,3-Dipolar Azide-Alkyne Cycloaddition - To a stirred mixture of the corresponding ethynyl- or azidoquinolin-2(1*H*)-one (1 eq), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.1 eq), sodium ascorbate (0.1 eq) and 2 mL dimethylformamide in a 5 mL microwave vial, 1.1 eq of phenylazide or phenylacetylene is added in one portion. The vial is sealed and subjected to

microwave irradiation at 150 °C or 110 °C for 30 min. The reaction mixture is then poured onto ice-water, stirred for 20 min and filtered to give the desired product.

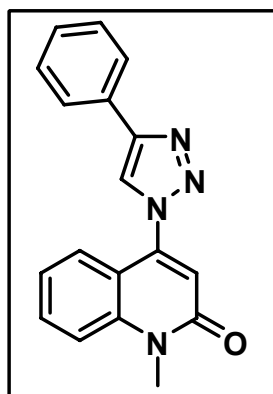
General Procedure 2 : N-Oxidation of Quinolines - To a stirred solution of quinolines **7**, **14** or **19** (1 eq) in 15 mL of CHCl₃ inside a 25 mL round bottom flask, 1.1 eq of 3-chloroperbenzoic acid (*m*-CPBA) is added in portions. The resulted mixture is then stirred for 1 h (quinoline **7**), or 3 h (quinolines **14** and **19**), correspondingly. The reaction mixture is then diluted with saturated aq. NaHCO₃ (10 mL) and 1N NaOH (3 mL). The biphasic mixture is separated, and the aqueous phase extracted with two additional portions of CHCl₃ (15 mL each). The combined organic layers were washed with 5 wt% aq. NaHSO₃ (50 mL), saturated aq. NaHCO₃ (100 mL) and water (100 mL). After drying over MgSO₄ and filtration, the solvent is removed under reduced pressure to give the corresponding products **8**, **15** or **20**.

General Procedure 3: Sonogashira C-C Coupling Reaction - To a stirred mixture of the corresponding 3-bromo compounds **3** or **7** (1 eq), Pd(PPh₃)₂Cl₂ 0.1 eq (10 mol%), CuI (0.1 eq) and 1.5 eq (*i*-Pr)₂NEt in 10 mL of dioxane in a 25 mL round bottom flask, 1.1 eq trimethylsilylacetylene is added dropwise. The reaction mixture thus formed is stirred for 3h (compound **3**), or 24h (compound **7**), correspondingly until conversion is complete (HPLC). The solvent is then removed under reduced pressure and the residue subjected to flash chromatography (petroleum ether:EtOAc = 1:2 or 2:1) to give the desired products **4** (72%) or **13** (73%).

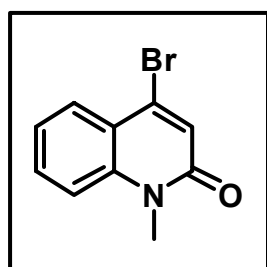
General Procedure 4: Desilylation - To a stirred suspension of the corresponding trimethylsilyl derivatives **4** or **13** (1 eq) in 10 mL MeOH in a 25 mL round bottom flask, 2 eq of KF is added in one portion and the resulting mixture is further stirred at room temperature for 30 min. The reaction mixture is then poured onto ice-water, stirred for 20 min and filtered to give the desired products.

General Procedure 5: UV-Induced Intramolecular Rearrangement – A stirred solution (suspension in the case of **21**) of the corresponding quinoline-N-oxides **11**, **16** or **21** (0.3-0.5 mmol) in 20 mL of MeOH placed in a crystallization dish was irradiated with an OSRAM Ultra-Vitalux[®] 300W lamp (see above) for the corresponding time (1h 40 min or 17h – for compound **21**). The addition of a several 5 mL portions of MeOH is needed to prevent the reaction mixture from running dry. After the rearrangement is complete, the reaction mixture

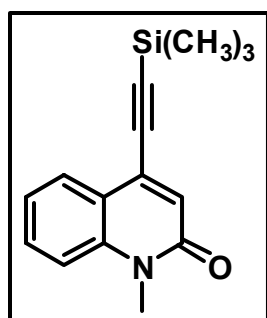
is concentrated under vacuum and the residue is poured onto cold water, stirred for 15 min and filtered to give the pure products **12**, **17** and **22**.



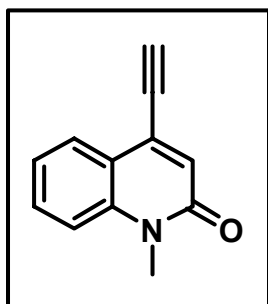
1-Methyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one (2). Prepared according to general procedure 1 (see above). Mp 201-203 °C (CH₃CN), 98% yield. ¹H-NMR (360 MHz, DMSO-d₆) δ 3.17 (s, 3H), 7.04 (s, 1H), 7.32 – 7.42 (m, 2H), 7.51 (t, *J* = 7.52, 2H), 7.63 (d, *J* = 8.02, 1H), 7.70 – 7.79 (m, 2H), 7.97 (d, *J* = 7.58, 2H), 9.19 (s, 1H); ¹³C NMR (90 MHz, DMSO-d₆) δ 30.09, 115.83, 116.06, 117.31, 123.26, 124.07, 125.26, 126.0, 128.94, 129.52, 130.33, 132.84, 140.67, 143.14, 147.28, 160.84; MS (pos APCI) *m/z* 302 (92, M), 274 (100, M – 28), 279 (19, M – 59).



4-Bromo-1-methylquinolin-2(1H)-one (3). To a mixture of 2 g (11.42 mmol) of 4-hydroxy-1-methylquinolin-2(1H)-one and 10 mL dimethylformamide in a 20 mL microwave vial, 1.13 mL (11.99 mmol, 1.05 eq) of PBr₃ are added slowly while stirring and cooling at the same time. After the addition is completed (5-10 min), the vial is sealed and subjected to microwave irradiation at 125 °C for 25 min. The reaction mixture is then poured onto ice-water, stirred for 20 min and filtered. The solid residue is purified by flash chromatography to give 1.93 g of compound **3**. Mp 125-127 °C (*i*-propanol), 71% yield. ¹H-NMR (360 MHz, CDCl₃) δ 3.69 (s, 3H), 7.13 (s, 1H), 7.28 – 7.37 (m, 2H), 7.61 (t, *J* = 7.23, 1H), 7.97 (d, *J* = 7.01, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 29.65, 114.31, 120.15, 122.72, 125.05, 128.88, 131.78, 135.91, 139.37, 160.70; MS (pos APCI) *m/z* 238 (100, M), 159 (28, M – 79).

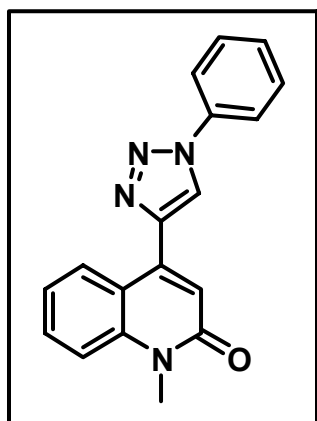


1-Methyl-4-[(trimethylsilyl)ethynyl]quinolin-2(1H)-one (4). Prepared according to general procedure 3 (see above). Mp 75-77 °C, 72% yield. ¹H-NMR (360 MHz, CDCl₃) δ 0.37 (s, 9H), 3.71 (s, 1H), 6.89 (s, 1H), 7.3 (t, *J* = 7.78, 1H), 7.36 (d, *J* = 8.57, 1H), 7.6 (d, *J* = 7.80, 1H), 8.03 (d, *J* = 7.75, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 0.28, 29.61, 99.02, 105.26, 114.22, 120.00, 122.28, 124.90, 127.65, 131.08, 132.26, 139.80, 161.46; MS (pos APCI) *m/z* 255 (100, M).



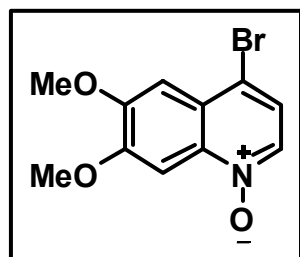
183 (100, M).

4-Ethynyl-1-methylquinolin-2(1H)-one (5). Prepared according to general procedure 4 (see above). Mp 149-151 °C, 76% yield. ¹H-NMR (360 MHz, CDCl₃) δ 3.61 (s, 1H), 3.71 (s, 3H), 6.94 (s, 1H), 7.28 – 7.37 (m, 2H), 7.60 (t, *J* = 7.82, 1H), 8.04 (d, *J* = 7.89, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 29.50, 78.24, 86.49, 114.30, 119.91, 122.43, 126.03, 127.36, 131.278, 131.49, 139.79, 161.25; MS (pos APCI) *m/z*



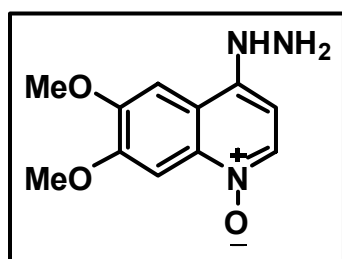
274 (38, M – 28).

1-Methyl-4-(1-phenyl-1H-1,2,3-triazol-4-yl)quinolin-2(1H)-one (6). Prepared according to general procedure 1 (see above). Mp 235-237 °C (DMF), 92% yield. ¹H-NMR (360 MHz, CDCl₃) δ 3.79 (s, 3H), 6.99 (s, 1H), 7.31 (t, *J* = 7.26, 1H), 7.45 – 7.53 (m, 2H), 7.57 – 7.66 (m, 2H), 7.83 (d, *J* = 7.83, 2H), 8.29 (s, 1H), 8.43 (d, *J* = 7.05, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 29.58, 114.49, 119.06, 120.67, 121.15, 121.57, 122.40, 127.78, 129.22, 129.92, 131.06, 136.66, 128.69, 140.45, 144.98, 161.70; MS (pos APCI) *m/z* 302 (100, M),



(pos APCI) *m/z* 283 (100, M), 205 (22, M – 78).

4-Bromo-6,7-dimethoxyquinoline 1-oxide (8). Prepared according to general procedure 2 (see above). Mp 183-185 °C (decomp.) (*i*-propanol), 77% yield. ¹H-NMR (360 MHz, CDCl₃) δ 4.05 (s, 3H), 4.08 (s, 3H), 7.30 (s, 1H), 7.40 (d, *J* = 6.59, 1H), 8.07 (s, 1H), 8.23 (d, *J* = 6.58, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 56.37, 56.79, 99.54, 105.52, 118.30, 122.64, 124.99, 133.96, 138.24, 152.19, 154.00; MS

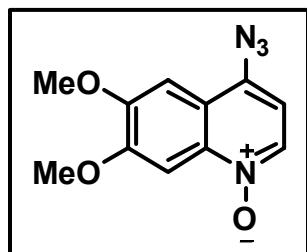


(3.97 mmol) of the desired product. Mp 174 °C (decomp.) (*i*-propanol), 75% yield. ¹H-NMR

4-Hydrazinyl-6,7-dimethoxyquinoline 1-oxide (9). A stirred suspension of 1.5 g (5.28 mmol, 1 eq) 4-bromo-6,7-dimethoxyquinoline 1-oxide (8) in 7 mL EtOH and 5 mL 98% NH₂NH₂·H₂O in a 25 mL round bottom flask is heated at 80 °C for 4h. The reaction mixture is then concentrated under reduced

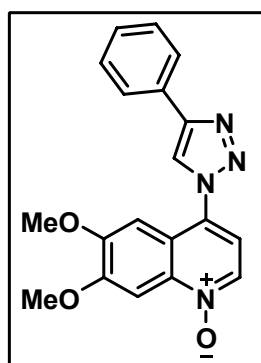
pressure, cooled down, filtered and the residue washed with 2 mL cold EtOH to give 0.94 g

(360 MHz, CD₃OD) δ 3.93 (s, 3H), 4.00 (s, 3H), 6.88 (d, $J = 7.12$, 1H), 7.29 (s, 1H), 7.79 (s, 1H), 8.17 (d, $J = 7.11$, 1H); ¹³C NMR (90 MHz, CD₃OD) δ 55.69, 56.82, 97.81, 99.46, 102.00, 113.11, 136.72, 137.76, 150.56, 151.15, 155.20; MS (pos APCI) m/z 235 (100, M), 205 (12, M – 30).



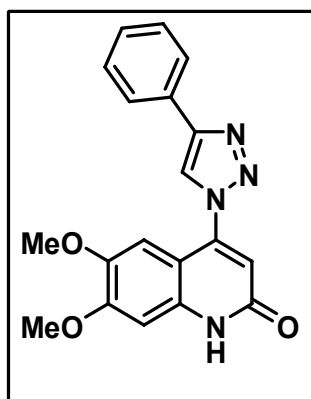
4-Azido-6,7-dimethoxyquinoline 1-oxide (10). A stirred solution of 545 mg (2.32 mmol, 1 eq) of 4-hydrazinyl-6,7-dimethoxyquinoline 1-oxide (9) in 20 mL 10% HCl in a 50 mL round bottom flask is cooled-down to -5 °C (ice bath) and 210 mg (3 mmol, 1.3 eq) of NaNO₂ dissolved in 10 mL of H₂O was added

dropwise so that the temperature does not exceed 5 °C. After the addition was finished, the reaction mixture is stirred for 45 min and left to reach room temperature. The reaction mixture is then basified with Na₂CO₃ and extracted with CHCl₃. The biphasic mixture is separated, the aqueous phase extracted with two additional portions of CHCl₃ (15 mL each) and the combined organics washed with water (50 mL). After drying over MgSO₄ and filtration, the solvent is removed under reduced pressure to give 371 mg (1.51 mmol) of product 10. Mp 154 °C (decomp.), 65% yield. IR (KBr) ν_{\max} 3376, 2126, 1624, 1496, 1433, 1352, 1271, 1198; ¹H-NMR (360 MHz, CDCl₃) δ 3.99 (s, 3H), 4.06 (s, 3H), 6.90 (d, $J = 6.65$, 1H), 7.19 (s, 1H), 8.01 (s, 1H), 8.36 (d, $J = 6.65$, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 56.28, 56.66, 99.31, 101.02, 107.24, 118.24, 134.22, 134.28, 138.01, 151.27, 154.21; MS (pos APCI) m/z 220 (100, M – 30), 204 (68, M – 16).

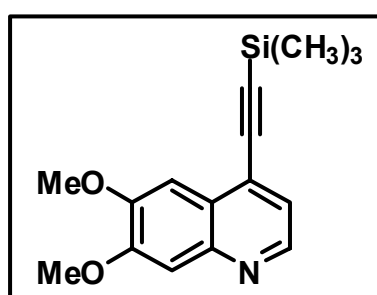


6,7-Dimethoxy-4-(4-phenyl-1H-1,2,3-triazol-1-yl)quinoline 1-oxide (11).

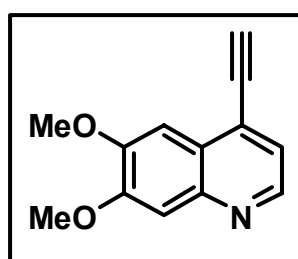
Prepared according to general procedure 1 (see above). Mp 115 °C (decomp.), 91% yield. IR (KBr) ν_{\max} 3387, 3235, 1498, 1436, 1206, 1022; ¹H-NMR (360 MHz, DMSO-d₆) δ 3.85 (s, 3H), 4.01 (s, 3H), 7.29 (s, 1H), 7.40 (t, $J = 7.38$, 1H), 7.52 (t, $J = 7.55$, 1H), 7.66 (d, $J = 6.63$, 1H), 8.00 (s, 2H), 8.01 (s, 1H), 8.64 (d, $J = 6.63$, 1H), 9.26 (s, 1H); ¹³C NMR (90 MHz, DMSO-d₆) δ 25.37, 55.82, 56.15, 61.90, 98.84, 101.77, 116.26, 119.52, 123.46, 125.37, 127.97, 128.29, 128.93, 129.91, 133.43, 137.85, 146.83, 151.72, 153.34; MS (neg APCI) m/z 348 (100, M), 320 (72, M – 28).



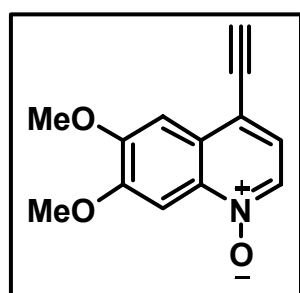
6,7-Dimethoxy-4-(4-phenyl-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one (12). Prepared according to general procedure 5 (see above). Mp 286 °C (decomp.) (MeCN), 89% yield. ¹H-NMR (360 MHz, DMSO-d₆) δ 3.70 (s, 3H), 3.87 (s, 3H), 6.71 (s, 1H), 7.03 (s, 1H), 7.16 (s, 1H), 7.40 (t, *J* = 7.36, 1H), 7.51 (t, *J* = 7.54, 2H), 7.99 (d, *J* = 7.28, 2H), 9.24 (s, 1H), 12.07 (s, 1H); ¹³C NMR (90 MHz, DMSO-d₆) δ 55.33, 55.44, 97.90, 104.69, 106.55, 113.27, 122.79, 125.18, 128.11, 128.71, 129.58, 135.51, 142.88, 144.96, 146.44, 152.74, 160.68; MS (neg APCI) *m/z* 348 (100, M).



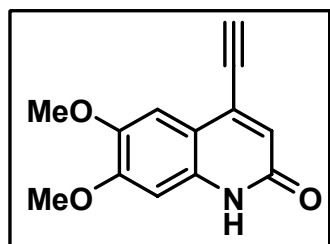
6,7-Dimethoxy-4-((trimethylsilyl)ethynyl)quinoline (13). Prepared according to general procedure 3 (see above). Mp 104-106 °C, 73% yield. ¹H-NMR (360 MHz, CDCl₃) δ 0.33 (s, 9H), 4.01 (s, 3H), 4.04 (s, 3H), 7.35 (s, 1H), 7.41 (s, 1H), 7.49 (s, 1H), 8.67 (bs, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 0.15, 55.82, 56.13, 100.87, 103.54, 104.35, 108.25, 121.92, 127.20, 145.14, 147.18, 150.42, 152.62; MS (pos APCI) *m/z* 285 (100, M), 213 (11, M – 72).



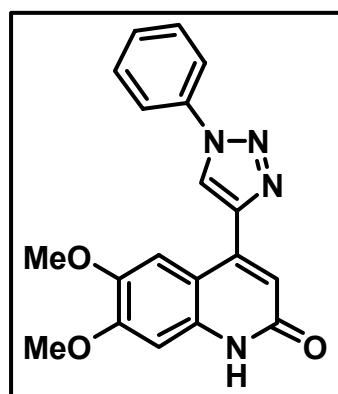
4-Ethynyl-6,7-dimethoxyquinoline (14). Prepared according to general procedure 4 (see above). Mp 137-139 °C (ethanol), 98% yield. ¹H-NMR (360 MHz, CDCl₃) δ 3.63 (s, 1H), 4.03 (s, 3H), 4.05 (s, 3H), 7.39-7.46 (m, 3H), 8.66 (d, *J* = 3.68, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 56.07, 56.14, 79.81, 85.65, 103.25, 108.25, 122.63, 123.83, 126.30, 145.20, 147.21, 150.65, 152.76; MS (pos APCI) *m/z* 213 (100, M).



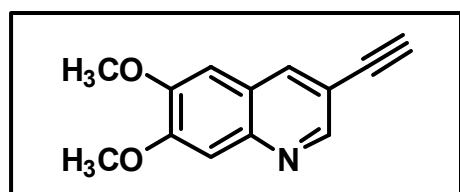
4-Ethynyl-6,7-dimethoxyquinoline 1-oxide (15). Prepared as described in general procedure 2 (see above). Mp 177 °C (decomp.), 64% yield. ¹H-NMR (360 MHz, CDCl₃) δ 3.69 (s, 1H), 4.05 (s, 3H), 4.08 (s, 3H), 7.32 (d, *J* = 6.36, 1H), 7.45 (s, 1H), 8.05 (s, 1H), 8.33 (d, *J* = 6.36, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 56.50, 79.35, 86.55, 98.95, 104.24, 116.39, 122.94, 126.33, 133.51, 137.63, 151.95, 153.71; MS (pos APCI) *m/z* 229 (100, M).



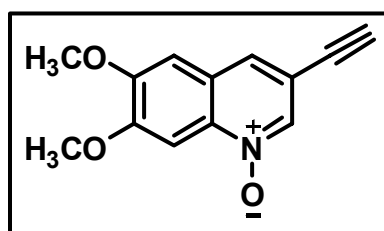
4-Ethynyl-6,7-dimethoxyquinolin-2(1H)-one (16). Prepared as described in general procedure 5 (see above). 83% yield. $^1\text{H-NMR}$ (360 MHz, DMSO-d_6) δ 3.80 (s, 3H), 3.83 (s, 3H), 4.92 (s, 1H), 6.54 (s, 1H), 6.88 (s, 1H), 7.19 (s, 1H), 11.77 (s, 1H); $^{13}\text{C NMR}$ (90 MHz, DMSO-d_6) δ 55.59, 78.46, 89.72, 98.01, 106.13, 111.24, 122.48, 128.74, 131.30, 134.49, 145.13, 152.43, 160.62; MS (pos APCI) m/z 229 (100, M), 213 (21, M – 16).



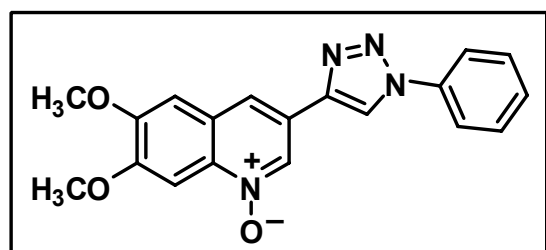
6,7-Dimethoxy-4-(1-phenyl-1H-1,2,3-triazol-4-yl)quinolin-2(1H)-one (17). Prepared according to general procedure 1 (see above). 90% yield. $^1\text{H-NMR}$ (360 MHz, DMSO-d_6) δ 3.80 (s, 3H), 3.85 (s, 3H), 6.70 (s, 1H), 6.78 (s, 1H), 6.97 (s, 1H), 7.54 (t, $J = 7.27$, 1H), 7.7 (t, $J = 7.17$, 2H), 9.47 (s, 1H), 11.72 (s, 1H); $^{13}\text{C NMR}$ (90 MHz, DMSO-d_6) δ 55.21, 55.36, 97.77, 107.48, 109.59, 120.00, 123.19, 128.70, 129.63, 135.22, 136.07, 138.81, 144.45, 151.73, 160.94; MS (pos APCI) m/z 348 (100, M), 332 (86, M – 16), 320 (23, M – 28), 304 (22, M – 56).



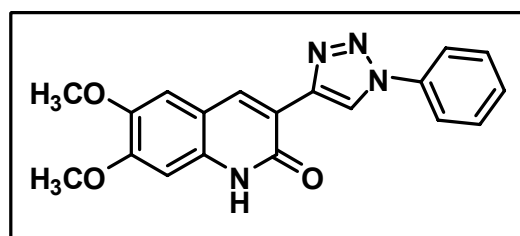
3-Ethynyl-6,7-dimethoxyquinoline (19). To a stirred suspension of 640 mg (1.84 mmol, 2 eq) of (chloromethyl)triphenylphosphonium chloride in 5 mL of THF, 72 mg (1.84 mmol, 2 eq) of NaNH_2 are added in one portion. The reaction mixture is then stirred at room temperature, until the yellowish-brown colour of the formed phosphorus ylide appears and then for an additional 30 min. 200 mg (0.92 mmol, 1 eq) of aldehyde **16** are added and the mixture heated under reflux for 12h. After cooling to room temperature, 207 mg (1.84 mmol, 2 eq) of $t\text{-BuOK}$ are added and the mixture was again refluxed for another one hour. The solvent is then removed under reduced pressure and the residue subjected to flash chromatography (petroleum ether:EtOAc = 1:1) to give 53 mg (0.25 mmol) of compound **17**. Mp 162-164 °C (*i*-propanol), 27% yield. $^1\text{H-NMR}$ (360 MHz, DMSO-d_6) δ 3.90 (s, 3H), 3.94 (s, 3H), 4.38 (s, 1H), 7.34 (s, 1H), 7.37 (s, 1H), 8.31 (s, 1H), 8.68 (s, 1H); $^{13}\text{C NMR}$ (90 MHz, DMSO-d_6) δ 56.03, 81.19, 82.90, 105.22, 107.52, 113.54, 122.32, 136.71, 143.78, 149.07, 149.94, 152.86; MS (pos APCI) m/z 213 (100, M).



3-Ethynyl-6,7-dimethoxyquinoline 1-oxide (20). Prepared as described in general procedure 2 (see above). Mp 211 °C (decomp.) (*i*-propanol), 84% yield. ¹H-NMR (360 MHz, CDCl₃) δ 3.20 (s, 1H), 3.99 (s, 3H), 4.06 (s, 3H), 7.00 (s, 1H), 7.67 (s, 1H), 8.02 (s, 1H), 8.43 (d, *J* = 1, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 56.48, 78.85, 80.43, 99.25, 105.22, 114.55, 125.25, 127.85, 135.86, 137.69, 151.72, 154.11; MS (pos APCI) *m/z* 229 (100, M), 212 (8, M – 17).



6,7-Dimethoxy-3-(1-phenyl-1H-1,2,3-triazol-4-yl)quinoline 1-oxide (21). Prepared according to general procedure 1 (see above). Mp > 295 °C (decomp.) (DMF), 98% yield. ¹H-NMR (360 MHz, CDCl₃) δ 4.05 (s, 3H), 4.11 (s, 3H), 7.16 (s, 1H), 7.50 (t, *J* = 7.43, 1H), 7.58 (t, *J* = 7.64, 2H), 7.80 (d, *J* = 7.79, 2H), 8.09 (s, 1H), 8.25 (s, 1H), 8.28 (s, 1H), 8.92 (1H); MS (pos APCI) *m/z* 348 (100, M).



6,7-Dimethoxy-3-(1-phenyl-1H-1,2,3-triazol-4-yl)quinolin-2(1H)-one (22). Prepared according to general procedure 5 (see above). Mp > 235 °C (decomp.), 75% yield. ¹H-NMR (360 MHz, DMSO-*d*₆) δ 3.82 (s, 3H), 3.91 (s, 3H), 6.93 (s, 1H), 7.44 (s, 1H), 7.51 (t, *J* = 7.38, 1H), 7.61 (t, *J* = 7.52, 2H), 7.98 (d, *J* = 7.29, 2H), 8.74 (s, 1H), 9.14 (s, 1H), 12.03 (1H); ¹³C NMR (90 MHz, DMSO-*d*₆) δ 55.33, 55.44, 97.90, 104.69, 106.55, 113.27, 122.79, 125.18, 128.11, 128.71, 129.58, 135.51, 142.88, 144.96, 146.44, 152.74, 160.68; MS (pos APCI) *m/z* 348 (100, M).

Starting materials **1**, **7** and **18** were prepared using literature procedures [1-3].

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