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SYNTHESIS OF NEOAMPHIMEDINE

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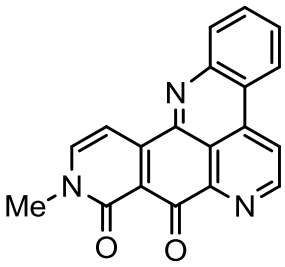
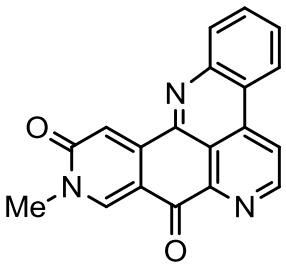
Abstract – The synthesis of neoamphimedine (from *Xestospongia* sp.), which is a potent antitumor agent both *in vitro* and *in vivo*, also can induce topoisomerase II-mediated catenation of plasmid DNA *in vitro*. The synthesis was achieved in twelve steps from 2,5-dimethoxyphenethylamine in 6% overall yield.

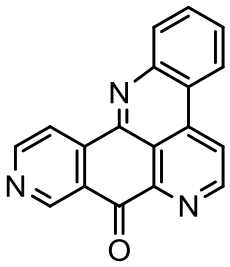
A series of structurally related polycyclic aromatic alkaloids containing a pyrido[2,3,4-*kl*]acridine subunit has been isolated from marine sources; more than 100 compounds are now known.[1] Almost all of them are cytotoxic and their regulation of cellular growth and differentiation, their effect on cAMP-mediated processes, inhibition[2] of topoisomerase II, and anti-HIV activity have been reported.[3]



neoamphimedine (1)



amphimedine (2)



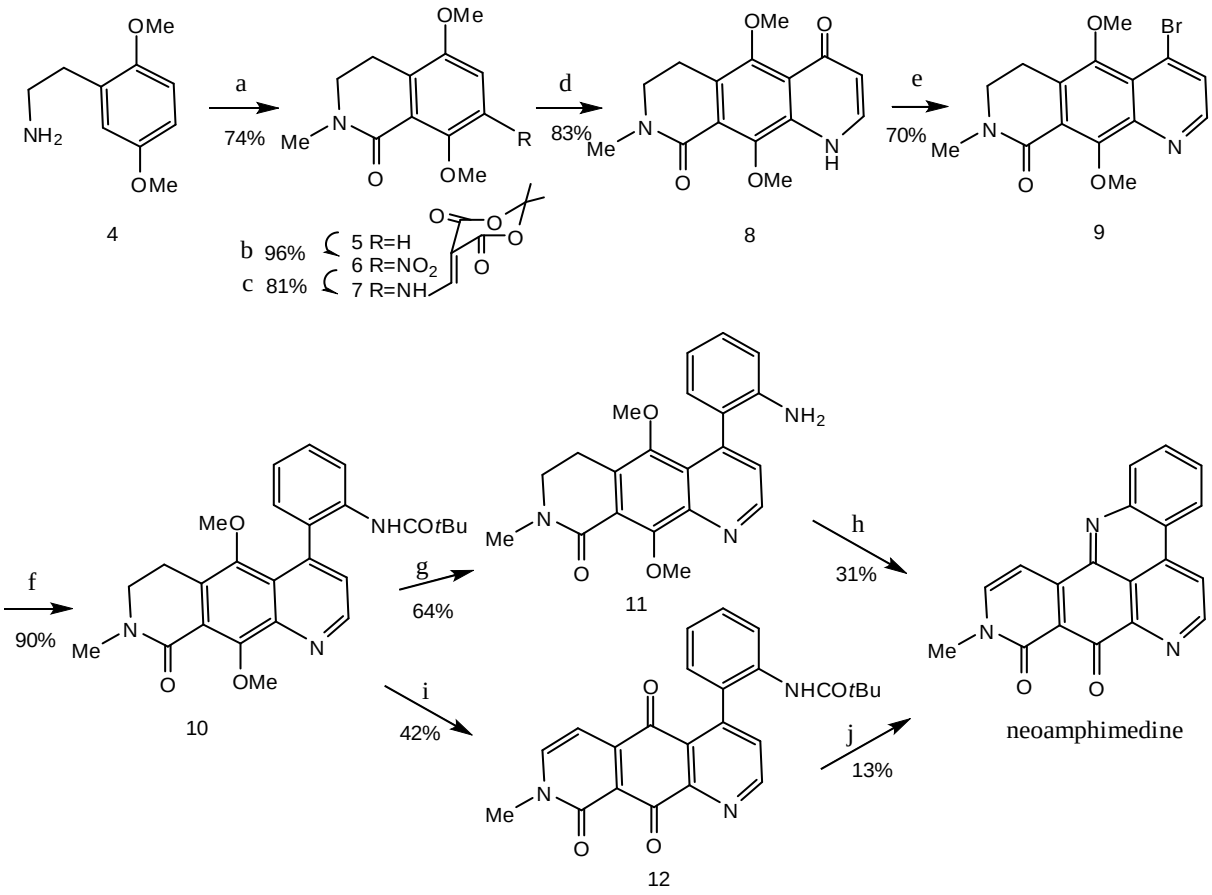
demethyldeoxyamphimedine (3)

In 1983, Schmitz *et al*. reported the first isolation of a novel cytotoxic pentacyclic aromatic alkaloid amphimedine (**2**) from an *Amphimedon* sp. of sponge found near the island of Guam, and its structure was assigned on the basis of extensive long-range heterocorrelation and carbon-carbon correlation analyses.[4] Later, neoamphimedine (**1**) was isolated from *Xestospongia* sp.[2] and demethyldeoxyamphimedine (**3**), which contains a pyridine ring fused to a pyridoacridine ring system, was isolated from the purple morph of the ascidian *Cystodytes dellechiajei*[5] and their structures were determined on the basis of NMR and heteronuclear multiple bond correlation (HMBC) experiments. Neoamphimedine (**1**) and amphimedine (**2**) are regioisomers in which a pyridinone moiety and acridinone are fused in different positions.

Neoamphimedine (**1**) is a potent antitumor agent both *in vitro* and *in vivo*, and can also induce topoisomerase II-mediated catenation of plasmid DNA *in vitro*; therefore, its synthesis and bioactivity are of interest.

In 2007, Ireland and co-workers accomplished the first synthesis of neoamphimedine (**1**) using the Knorr cyclization and Sandmeyer reaction.[6]

In this study we report the synthesis of neoamphimedine from 2,5-dimethoxyphenethylamine in twelve steps using the Bischler-Napieralski cyclization reaction, thermolysis of arylaminomethylene Meldrum's acid derivative, and the biaryl cross-coupling reaction.



a) i $ClCO_2Et$, Et_3N, THF, rt, 17 h ii MeI, NaH, THF, rt, 3 h iii DMAP, $(CF_3SO_2)O$, CH_2Cl_2, rt, 16 h b) $Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O, 21 °C, 1.5 h c) i Pd-C, H_2, MeOH, 3 h ii Meldrum's acid, $HC(OMe)_3$, 120 °C, 2 h d) Ph_2O, reflux, 25 min e) $POBr_3$, THF, 50-55 °C, 15 min f) 2-(pivaloylamino)phenylboronic acid, $[(C_6H_5)_3P]_4Pd$, K_2CO_3/H_2O, EtOH, toluene, 100 °C, 1 h g) H_2SO_4/H_2O, 105 °C, 6 h h) i BBr_3, CH_2Cl_2, rt, 2 h ii CAN/H_2O, MeCN, 0-5 °C, 10 min i) i BBr_3, CH_2Cl_2, 4 °C, 30 min ii CAN/H_2O, MeCN, 0 °C, 10 min j) H_2SO_4/H_2O, 100 °C, 2 h

The preparation of dihydroisoquinoline-1-one (**5**) from commercially available 2,5-dimethoxy-phenethylamine (**4**) was first examined using the Bischler-Napieralski cyclization reaction in three steps. A solution of phenethylamine (**4**), ethyl chloroformate, and triethylamine in THF was stirred at room temperature for 17 h to afford the *N*-carbethoxy derivative, which was used without purification in the next step. *N*-Methylation of the crude *N*-carbethoxy derivative was performed using methyl iodide and

sodium hydride in dry THF at room temperature for 3 h, followed by Bischler-Napieralski cyclization reaction[7] with triflic anhydride and dimethylaminopyridine in dry dichloromethane at room temperature for 16 h to yield dihydroisoquinoline-1-one (**5**) in 74% yield from **4**. Nitration of **5** with cupric nitrate trihydrate in acetic anhydride gave 7-nitrodihydroisoquinolin-1-one (**6**) selectively with an electron-drawing carbonyl group in excellent yield. Enamine (**7**) was prepared by catalytic hydrogenation of **6** over 10% Pd-C in methanol, followed by reaction with Meldrum's acid in trimethyl orthoformate[8] in 81% yield. Cyclization of **7** in refluxing diphenyl ether for 25 min afforded piperidoquinoline-4,9-dione (**8**) *via* unstable aminoketene[9] in 83% yield. Treatment of **8** with phosphorus oxybromide in THF at 50-55 °C for 15 min afforded bromopiperidoquinoline-9-one (**9**) in 70% yield. Palladium(0)-catalyzed cross-coupling reaction of **9** with 2-pivaloylaminophenyl boronic acid gave the pivaloylaminophenyl quinoline (**10**) in 90% yield.[10] Direct oxidative demethylation of **10** with ceric ammonium nitrate (CAN)[11] afforded many spots on TLC and did not give the corresponding quinoline quinone. Hydrolysis of **10** with 20% aq. H_2SO_4 solution at 105 °C for 6 h gave aminophenyl quinoline (**11**) in 64% yield. Finally, demethylation of 5,10-dimethoxyquinoline (**11**) with BBr_3 in methylene chloride at room temperature for 2 h followed by oxidative demethylation and dehydriding with CAN at 0-5 °C for 10 min afforded neoamphimedine (**1**) in 31% yield; with HNO_3 at room temperature for 50 min, neoamphimedine (**1**) was obtained in only 6% yield. The other piridoquinoline-5,9,10-trione (**12**) was prepared by demethylation with BBr_3 in methylene chloride at 4 °C for 30 min followed by oxidative demethylation with CAN at 0 °C for 10 min in 42% yield. In addition, hydrolysis of **12** with 20% aq. H_2SO_4 solution at 100 °C for 2 h gave **1** in 13% yield. The spectroscopic data of synthetic **1** matched those of authentic samples[2] in all respects.

In summary, neoamphimedine (**1**) was synthesized from commercially available 2,5-dimethoxy-phenethylamine using the Bischler-Napieralski cyclization reaction, thermolysis of arylaminomethylene Meldrum's acid derivative, and biaryl cross-coupling reaction in twelve steps in 6% overall yield.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra at 270 MHz were measured in $CDCl_3$ with tetramethylsilane as an internal standard. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column chromatography (flash chromatography) was performed with silica gel 60 (Merck, 230-400 mesh).

5,8-Dimethoxy-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-one (5). To a solution of 2,5-dimethoxy-phenethylamine (**4**) (1.81 g, 1.0 mmol) and 1.21 g (12 mmol) of triethylamine in THF (50 mL) was carefully added ethyl chloroformate (5.89 g, 54 mmol) at 0 ℃ under N_2. The reaction mixture was stirred at room temperature under N_2 for 17 h. H_2O (250 mL) was added and extracted with $CHCl_3$ (3 x 30 mL). The extract was washed with brine, dried, filtered, and concentrated in vacuo. A solution of the residue in dry THF (30 mL) was added dropwise under N_2 to a stirred suspension of NaH (2.16 g, 90 mmol) in dry THF (70 mL). The stirring was continued at room temperature for 30 min and methyl iodide (5.1 g, 360 mmol) was added. The resulting mixture was stirred for a further 3 h, diluted with water (250 mL), and extracted with $CHCl_3$ (1 x 100 mL, 2 x 50 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo, and to a solution of the resulting residue and DMAP (3.66 g, 30 mmol) in dry CH_2Cl_2 (100 mL), triflic anhydride (14.1 g, 50 mmol) was added dropwise for over 15 min at 0 ℃. The mixture was stirred for 16 h at room temperature under N_2, diluted with water (100 mL), adjusted to pH 8 with saturated aq. $NaHCO_3$ solution, the aqueous and organic layers were separated, and the former was extracted with $CHCl_3$ (1 x 30 mL). The combined organic fractions were washed with brine, dried, filtered, concentrated in vacuo. The residue was chromatographed (eluting with EtOAc) to afford **5** (1.64 g, 74%). mp 99.5-100.5 ℃ (colorless crystals from $CHCl_3$-hexane). HRMS Calcd for $C_{12}H_{15}NO_3$: 221.1052, Found: 221.1049. Ms *m/z* (%): 221 (M^+, 100), 192 (66), 163 (21), 148 (23). IR (KBr) cm^{-1}: 1653, 1489, 1262, 1073. ^{1}H-NMR ($CDCl_3$) δ : 2.90 (2H, t, *J*=6.6 Hz), 3.14 (3H, s), 3.45 (2H, t, *J*=6.6 Hz), 3.80 (3H, s), 3.88 (3H, s), 6.83 (1H, d, *J*=8.9 Hz), 6.92 (1H, d, *J*=8.9 Hz).

5,8-Dimethoxy-2-methyl-7-nitro-3,4-dihydro-2*H*-isoquinolin-1-one (6).

Cupric nitrate trihydrate (362 mg, 1.5 mmol) was added to a stirred solution of quinolone (**5**) (221 mg, 1 mmol) in acetic anhydride (5 mL) at 21 ℃. The mixture was stirred for an additional 1.5 h, poured into ice-cooled water, and extracted with $CHCl_3$ (3 x 30 mL). The extract was successively washed with water (100 mL), 1% aq. $NaHCO_3$ solution (100 mL), and brine. The solution was dried, filtered, concentrated in vacuo, and the residue was recrystallized from $CHCl_3$-hexane to give **6** (255 mg, 96%) as light yellow prisms. mp 98.5-99.5 ℃. HRMS Calcd for $C_{12}H_{14}N_2O_5$: 266.0903, Found: 266.0900. Ms *m/z* (%): 266 (M^+, 4), 236 (100), 150 (10), 135 (48). IR (KBr) cm^{-1}: 1652, 1521, 1342, 1051. ^{1}H-NMR ($CDCl_3$) δ : 2.96 (2H, t, *J*=6.6 Hz), 3.17 (3H, s), 3.50 (2H, t, *J*=6.6 Hz), 3.88 (3H, s), 4.01 (3H, s), 7.33 (1H, s).

5-[(5,8-Dimethoxy-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-one-7-ylamino)methylene]-2,2-dimethyl-4,6-dione-1,3-dioxane (7).

5,8-Dimethoxy-7-nitro-1-isoquinolone (**6**) (1.05 g, 3.95 mmol) in MeOH (50 mL) was hydrogenated for 3 h using 10% Pd-C (300 mg) as a catalyst under H_2 atomsphere. The catalyst was filtered off and the solvent was removed. A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (635 mg, 4.4 mmol) in methyl

orthoformate (6 mL) was refluxed for 2 h and the crude aminoisoquinolone was immediately added. The mixture was stirred at 120 ℃ for another 2 h. After the reaction mixture was cooled, the precipitated crystals were collected by filtration and recrystallized from $CHCl_3$-hexane to give **7** (1.24 mg, 81%) as light yellow needles. mp 212-213 ℃. HRMS Calcd for $C_{19}H_{22}N_2O_7$: 390.1427, Found: 390.1424. Ms *m/z* (%): 390 (M^+, 14), 332 (5), 257 (100), 241 (9). IR (KBr) cm^{-1}: 1718, 1683, 1654, 1615, 1578, 1457, 1337, 1271, 1205, 1051. ^{1}H-NMR ($CDCl_3$) δ : 1.76 (6H, s), 2.91 (2H, t, *J*=6.6 Hz), 3.17 (3H, s), 3.50 (2H, t, *J*=6.6 Hz), 3.89 (3H, s), 3.98 (3H, s), 6.92 (1H, s), 8.65 (1H, d, *J*=4.9 Hz), 11.85 (1H, d, *J*=4.9 Hz).

5,10-Dimethoxy-8-methyl-piperido[4,3-g]quinolin-4,9-dione (8).

A mixture of **7** (1.17 g, 3 mmol) and diphenyl ether (50 mL) was refluxed for 25 min. The reaction mixture was cooled and diluted with hexane (100 mL). The precipitated crystals were collected by filtration, washed with hexane (3 x 30 mL), and recrystallized from EtOH to give **8** (720 mg, 83%) as light yellow prisms. mp 276-277 ℃. HRMS Calcd for $C_{15}H_{16}N_2O_4$: 288.1110, Found: 288.1109. Ms *m/z* (%): 288 (M^+, 58), 273 (100), 258 (20), 230 (16), 212 (12), 188 (11). IR (KBr) cm^{-1}: 1654, 1646, 1508, 1050. ^{1}H-NMR ($CDCl_3$) δ : 3.12 (2H, t, *J*=6.3 Hz), 3.21 (3H, s), 3.55 (2H, t, *J*=6.3 Hz), 3.87 (3H, s), 4.07 (3H, s), 6.42 (1H, d, *J*=7.3 Hz), 7.77 (1H, d, *J*=7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 22.30, 35.29, 47.92, 62.05, 63.09, 112.35, 121.87, 123.47, 126.60, 135.67, 137.47, 145.57, 150.28, 161.80, 177.05.

4-Bromo-5,10-dimethoxy-8-methyl-piperido[4,3-g]quinolin-9-one (9).

A solution of piperidoquinoline dione (**8**) (144 mg, 0.5 mmol) and $POBr_3$ (450 mg, 1.5 mmol) in THF (4 mL) was stirred at 50-55 ℃ for 15 min, poured into cold water (20 mL), adjusted to pH 8 with saturated aq. $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 20 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo. The residue was recrystallized from *i*-PrOH to give **9** (123 mg, 70%) as light yellow prisms. mp 137-138 ℃. HRMS Calcd for $C_{15}H_{15}N_2O_3Br$: 350.0266, Found: 350.0263. Ms *m/z* (%): 352 (M^++2, 99), 350 (M^+, 100), 337 (36), 335 (40), 323 (51), 321 (52), 309 (51), 307 (71), 294 (39), 292 (41). IR (KBr) cm^{-1}: 1654, 1362, 1039. ^{1}H-NMR ($CDCl_3$) δ : 3.18 (2H, t, *J*=6.6 Hz), 3.23 (3H, s), 3.55 (2H, t, *J*=6.6 Hz), 3.80 (3H, s), 4.23 (3H, s), 7.80 (1H, d, *J*=4.6 Hz), 8.67 (1H, d, *J*=4.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 23.79, 35.17, 47.59, 62.36, 63.76, 123.70, 124.24, 127.80, 129.29, 130.19, 144.96, 146.38, 148.61, 153.91, 162.19.

5,10-Dimethoxy-8-methyl-4-(2-pivaloylamino)phenyl-piperido[4,3-g]quinolin-9-one (10).

2 M Aqueous K_2CO_3 (0.7 mL, 1.4 mmol) was added to a mixture of 4-bromo-piperidoquinoline (**9**) (246 mg, 0.7 mmol) and 2-pivaloylaminophenyl boronic acid (464 mg, 2.1 mmol) in toluene (10.5 mL) and EtOH (0.7 mL) under N_2. Tetrakis(triphenylphosphine)palladium(0) (162 mg, 0.14 mmol) was added to the vigorously stirred two-phase mixture and the resulting mixture was keeped at 100 ℃ for 1 h. The

reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The extract was washed with brine, dried, and concentrated. The residue was chromatographed (eluting with MeOH-EtOAc 1 : 40) to afford **10** (281 mg, 90%). mp 214-215 ℃ (light yellow prisms from *i*-PrOH-hexane). HRMS Calcd for $C_{26}H_{29}N_3O_4$: 447.2158, Found: 447.2156. Ms *m/z* (%): 447 (M^+, 100), 432 (36), 418 (72), 404 (19), 302 (22). IR (KBr) cm^{-1}: 3446, 1687, 1652, 1445, 1366, 1067. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (9H, s), 2.96-3.01 (1H, m,), 3.03 (3H, s), 3.10-3.20 (1H, m), 3.23 (3H, s), 3.45-3.55 (2H, m), 4.30 (3H, s), 6.92 (1H, br s), 7.24 (1H, t, *J*=7.9 Hz), 7.34 (1H, d, *J*=4.3 Hz), 7.35 (1H, d, *J*=7.9 Hz), 7.45 (1H, t, *J*=7.9 Hz), 8.10 (1H, d, *J*=7.9 Hz), 9.06 (1H, d, *J*=4.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.70, 26.95, 35.26, 39.26, 47.69, 61.47, 64.01, 122.06, 123.41, 123.95, 124.15, 126.07, 128.50, 129.02, 129.70, 133.19, 135.85, 143.40, 143.56, 146.72, 149.40, 154.41, 162.28, 176.12.

4-(2-Amino)phenyl 5,10-dimethoxy-8-methyl-piperido[4,3-g]quinolin-9-one (11).

A mixture of **10** (45 mg, 0.1 mmol) and 20% aq. H_2SO_4 solution (1 mL) was stirred at 105 ℃ for 6 h, poured into cold water (9 mL), adjusted to pH 8 with saturated aq. $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 2 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo. The residue was chromatographed (eluting with MeOH-EtOAc 1 : 30) to afford **11** (23 mg, 64%). mp 200-201 ℃ (yellow prisms from $CHCl_3$-hexane). HRMS Calcd for $C_{21}H_{21}N_3O_3$: 363.1583, Found: 363.1580. Ms *m/z* (%): 363 (M^+, 100), 348 (19), 334 (60), 320 (30), 302 (33). IR (KBr) cm^{-1}: 3463, 3369, 2360, 1651, 1455, 1365, 1039. ^{1}H-NMR ($CDCl_3$) δ: 2.95-3.10 (1H, m), 3.13 (3H, s), 3.15-3.30 (1H, m), 3.23 (3H, s), 3.48-3.60 (2H, m), 4.30 (3H, s), 6.79 (1H, d, *J*=7.6 Hz), 6.86 (1H, t, *J*=7.6 Hz), 7.14 (1H, d, *J*=7.6 Hz), 7.24 (1H, t, *J*=7.6 Hz), 7.32 (1H, d, *J*=4.3 Hz), 9.01 (1H, d, *J*=4.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.75, 35.17, 47.75, 61.38, 63.75, 114.83, 117.89, 123.14, 124.48, 125.75, 127.55, 128.88, 128.93, 128.98, 143.74, 143.89, 144.51, 147.33, 149.63, 154.46, 162.65.

Neoamphimedine from 11

[Method A: oxidation used CAN] To 2-aminophenylpiperidoquinoline (**11**) (110 mg, 0.3 mmol) was added a solution of BBr_3 (1 M /CH_2Cl_2 4 mL) at 0 ℃ under a dry nitrogen atmosphere. The solution was stirred at rt for 2 h, poured into cold water (40 mL), adjusted to pH 8 with saturated aq. $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 15 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo. A solution of CAN (411 mg, 0.75 mmol) in water (3 mL) was added drop wise to the residue suspended in acetonitrile-water (2 : 1, 9 mL) with stirring at 0-5 ℃. The mixture was stirred for an additional 10 min, diluted with water (60 mL), adjusted to pH 7 with saturated aq. $NaHCO_3$ solution and extracted with $CHCl_3$ (4 x 30 mL). The extract was washed with brine, dried and concentrated. The residue was chromatographed (eluting with MeOH-$CHCl_3$ 1 : 20) to afford **1** (29 mg, 31%). mp >300 ℃ (yellow needles from $CHCl_3$-MeOH). HRMS Calcd for $C_{19}H_{11}N_3O_2$: 313.0851, Found: 313.0850. Ms *m/z*

(%): 313 (M^+, 100), 285 (98), 215 (19). IR (KBr) cm^{-1}: 1686, 1619, 1607, 1595, 1526, 1339, 1070, 999, 777, 754, 728. ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 3.74 (3H, s), 7.81 (1H, d, *J*=7.0 Hz), 7.84 (1H, d, *J*=7.0 Hz), 7.87 (1H, dd, *J*=7.0, 1.2 Hz), 7.97 (1H, dd, *J*=7.0, 1.2 Hz), 8.36 (1H, dd, *J*=7.3, 0.9 Hz), 8.55 (1H, d, *J*=5.8 Hz), 8.62 (1H, d, *J*=7.9 Hz), 9.31 (1H, d, *J*=5.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$/CD_3OD 2:1 v/v) δ : 38.76, 102.09, 118.18, 119.91, 120.03, 122.73, 123.68, 130.75, 132.24, 132.42, 138.07, 145.33, 145.90, 147.27, 147.36, 149.89, 150.25, 160.42, 179.88.

[Method B: oxidation used HNO_3] To 2-aminophenylpiperidoquinoline (**11**) (145 mg, 0.4 mmol) was added a solution of BBr_3 (1 M /CH_2Cl_2, 5 mL) at 0 ℃ under a dry nitrogen atmosphere. The solution was stirred at rt for 2 h, poured into cold water (50 mL), adjusted to pH 8 with saturated aq. $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 20 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo. A mixture of the residue and 10 N HNO_3 (5 mL) was stirring at rt for 50 min, diluted with water (50 mL), adjusted to pH 7 with saturated aq. $NaHCO_3$ solution and extracted with $CHCl_3$ (4 x 30 mL). The extract was washed with brine, dried and concentrated. The residue was chromatographed (eluting with MeOH-$CHCl_3$ 1 : 20) to afford **1** (8 mg, 6%).

8-Methyl-4-(2-pivaloylamino)phenyl-pirido[4,3-g]quinoline-5,9,10-trione (12).

To pivaloylaminophenylpiperidoquinoline (**10**) (179 mg, 0.4 mmol) was added a solution of BBr_3 (1 M /CH_2Cl_2 5 mL) at 0 ℃ under a dry nitrogen atmosphere. The solution was stirred at 4 ℃ for 30 min, poured into cold water (40 mL), adjusted to pH 7 with saturated aq. $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 15 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo. A solution of CAN (548 mg, 1 mmol) in water (4 mL) was added drop wise to the residue in acetonitrile (4 mL) with stirring at 0 ℃. The mixture was stirred for an additional 10 min, diluted with water (60 mL), adjusted to pH 7 with saturated aq. $NaHCO_3$ solution and extracted with $CHCl_3$ (3 x 20 mL). The extract was washed with brine, dried and concentrated. The residue was chromatographed (eluting with MeOH-EtOAc 1 : 50) to afford **12** (70 mg, 42%). mp 299-300 ℃ (yellow-red powder from *i*-PrOH). HRMS Calcd for $C_{24}H_{21}N_3O_4$: 415.1532, Found: 415.1527. Ms *m/z* (%): 415 (M^+, 32), 358 (7), 331 (100), 314 (12), 260 (8). IR (KBr) cm^{-1}: 3436, 1697, 1686, 1654, 1542, 1475, 1296. ^{1}H-NMR ($CDCl_3$) δ : 0.94 (9H, s), 3.70 (3H, s), 6.76 (1H, d, *J*=7.0 Hz), 7.00 (1H, br s), 7.15 (1H, d, *J*=7.6 Hz), 7.33 (1H, t, *J*=7.6 Hz), 7.51 (1H, t, *J*=7.6 Hz), 7.53 (1H, d, *J*=4.9 Hz), 7.74 (1H, d, *J*=7.6 Hz), 7.84 (1H, d, *J*=7.0 Hz), 9.12 (1H, d, *J*=4.9 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ : 27.25, 39.02, 39.14, 100.61, 119.77, 124.95, 125.98, 126.31, 128.31, 129.60, 130.30, 133.04, 134.45, 144.91, 145.63, 148.51, 149.58, 154.85, 158.39, 176.42, 178.31, 183.34.

Neoamphimedine from 12

A mixture of **12** (21 mg, 0.05 mmol) and 20% aq. H_2SO_4 solution (1 mL) was stirred at 100 ℃ for 2 h, poured into cold water (9 mL), adjusted to pH 7 with saturated aq. $NaHCO_3$ solution, and extracted with

$CHCl_3$ (4 x 4 mL). The extract was washed with brine, dried, filtered, concentrated in vacuo. The residue was chromatographed (eluting with MeOH-$CHCl_3$ 1 : 20) to afford **1** (2.0 mg, 13%).

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