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Total Synthesis of Neuroprotective Dictyoquinazol A, B, and C

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Abstract: A new protective compound, dictyoquinazol **A**, was synthesized starting from 5-methoxy-2-nitrobenzoic acid in six-steps in 36% overall yield. Two derivatives **B** and **C**, isolated from the mushroom *Dictyophora indusiata*, were also synthesized from Dictyoquinazole **A**.

Keywords: dictyoquinazol, natural products, neuroprotection, synthesis

Neurodegenerative diseases are one of the main leading causes of social problems and death resulting from ischemic stroke, brain injury, and epilepsy throughout the world.[1] Despite extensive research to slow down the speed of degradation of neuron cells or alleviate the symptoms caused by neurodegenerative diseases, an effective chemotherapeutic treatment is still needed. NMDA (N-methyl-D-asparate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleprop-ionic acid) receptors have been proposed as two of the most important contributors to neuronal death in the brain.[2] Methaqualone derivatives with a C-2 enol side chain have been reported as potent noncompetative AMPA receptor antagonists.[3] Recently, three new quinazoline compounds, named dictyoquinazoles **A**–**C**, were isolated from the mushroom *Dictyophora indusiata*, which is an edible mushroom used in Chinese food and medicine.[4]

Compounds **A**–**C** have an unique quinazoline moiety rarely found in natural products that protects neurons from glutamate-induced neurotoxicity to a significant degree at concentrations ranging from 5 to 10 μM, protects

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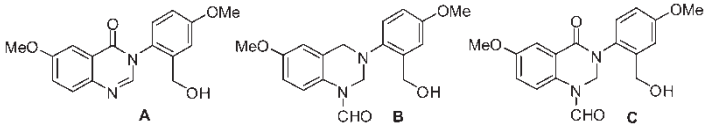
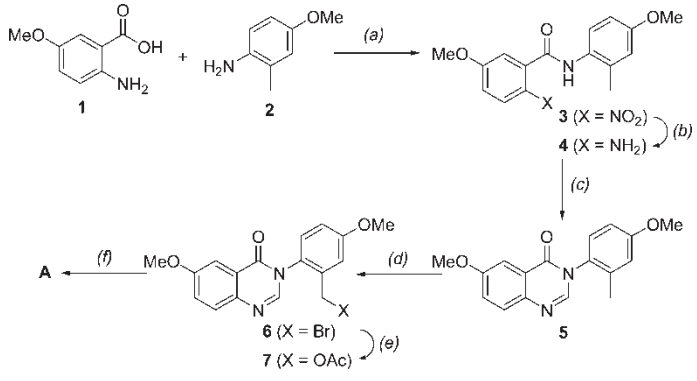
from toxicity induced by NMDA in a dose-dependent manner at concentrations ranging from 10 to 30 μM, and has moderate MAO (monoamine oxidase) inhibitory activity in the range 60–100 μM. In an effort to evaluate the mode of action of these compounds for neuroprotection and to develop potent neuroprotective compounds, we initiated research on an efficient syntheses for these compounds. Here we report the first total synthesis of compounds **A**–**C**. A synthetic scheme of dictyoquinazole **A** is given in Scheme 1.

A standard EDC coupling of 3-methoxy-5-nitrobenzoic acid (**1**) with 4-methoxy-2-methylaniline (**2**) in DMF solvent afforded the amide **3** in 77% yield in 10–20 g. Nitro group reduction of **3** was quantitatively carried out in methanol using an atmosphere of hydrogen over Pd-C catalyst to give the amino amide **4**. The amino amide **4** was refluxed in HCOOH for an hour to give quinazoline-4-one 5 in 75% yield based on 1. Bromination of **5** was problemic at the beginning of this research. When a mixture of *N*-bromosuccinimide and 5 was irradiated under a 200-W sun lamp at 10°C in the presence of a catalytic amount of benzoyl peroxide (BPO), the corresponding bromide **6** was obtained as an inseparable mixture with tetracyclic compound **6a** in 90% yield (3:1 ratio). The benzylic radical 5-rad, produced under the reaction conditions, showed two pathways: one for coupling with NBS to form **6** and the other for radical cyclization to form **6a** as shown in Eq. (1).



The mixture containing bromide **6** was directly subjected to potassium acetate suspended in DMF and then treated with sodium methoxide in



Scheme 1. Conditions: (a) EDC, HOBt, Et_3N, DMF, rt, 5 h, 77%; (b) Pd/C, H2 (1 atm), MeOH, rt, 1 h, 100%; (c) HCOOH, reflux, 1 h, 100%; (d) NBS, $(PhCOO)_2$, 200 W sun lamp, CCl_4, 10°C, 24 h, 68%; (e) KOAc, DMF, rt, 24 h, 62%; (f) NaOMe, MeOH, rt, 3 h, 98%.

methanol for methanolysis to give the corresponding alcohol, dictyoquinazole **A**, in 98% yield. Consequently, dictyoquinazole **A** was synthesized in overall 32% yield based on **1**. Because of the close structural similarity of dictyoquinazol **A**, **B**, and **C**, the dictyoquinazol **B** and **C** could be synthesized from **A** via two more simple chemical reactions (Scheme 2).

Thus, several reducing agents were treated for reduction of **A**. Of AlH_3, $LiAlH_4$, BH_3-SMe_2, Cl_3SiH-NaOH, and $LiBH(t\text{-}Bu)_3$-Et_3SiH, only AlH_3 gave the fully reduced compounds **7** in good yield (63%). The reduced compound **7** was formylated with acetic formic anhydride at room temperature to give dictyoquinazol **B** in 67% yield. Selective imine reduction of **A** was carried out through activation of **A** by oxalyl chloride followed by mild reduction with sodium cyanoborohydride to give **8** in 57% yield. Formylation of **8** was carried out as before to afford dictyoquinazol **C** in 78% yield. ^1H NMR spectra of dictyoquinazole **A**, **B** and **C** are identical to those reported in Ref. 4.

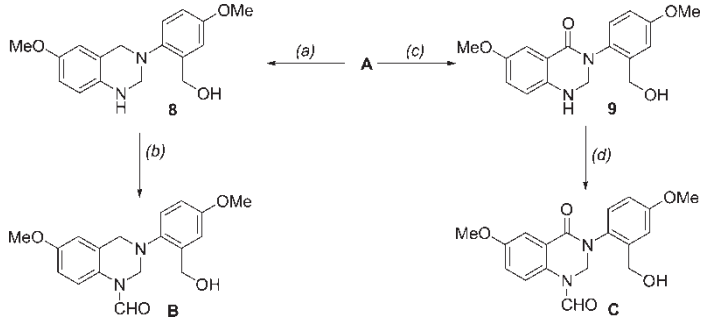
In conclusion, we have accomplished the first total syntheses of quinazol **A**–**C**, novel neuroprotective compounds against excitatory neurotoxins including glutamate, NMDA, and AMPA. Considering the fact that methaqualone derivatives did not block NMDA, and glutamate receptor antagonist, dictyoquinazols with the C-2 enol side chain might have important implications for design of NMDA, glutamate, and AMPA receptor antagonists.

EXPERIMENTAL

Synthesis of Dictyoquinazol A

Preparation of **3**

In a 100-mL, one-necked, round-bottomed flask, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.92 g, 15.22 mmol) and 5-methoxy-2-



Scheme 2. Conditions: (a) AlH3 (2 eq), THF, rt, 0.5 h, 63%; (b) HCOOAc, THF, rt, 3 h, 67%; (c) $(COCl)_2$, $CHCl_3$, reflux, then NaBH3CN, rt, 6 h, 57%; (d) HCOOAc, THF, rt, 3 h, 78%.

nitrobenzoic acid (**1**, 2.50 g, 12.68 mmol) were dissolved in DMF (20 mL). To this solution, 1-hydroxybenzotriazole (**2**, 2.06 g, 15.22 mmol) and subsequently 4-methoxy-2-methylaniline (1.91 g, 13.95 mmol) in DMF (10 mL) and triethylamine (2.7 mL, 19.02 mmol) were added. After 5 h, a 20-mL portion of water was added to the reaction mixture at 0°C, and 2 *N* HCl solution was added until pH 4. The precipitate was collected by filtration. The crude product was washed with EtOAc (30 mL). The solvent was removed in vacuo to give 3.09 g (77%) of **3** as a dark ivory solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $J = 9.2$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.13 (br, 1H), 7.06 (d, $J = 2.4$ Hz, 1H), 7.01 (dd, $J = 9.2$, 2.4 Hz, 1H), 6.80 (dd, $J = 9.2$, 2.4 Hz, 1H), 6.78 (s, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.89, 163.68, 157.73, 138.62, 135.50, 133.25, 127.38, 127.26, 126.24, 115.95, 114.79, 114.02, 111.72, 56.31, 55.48, 18.24.

Reduction of the Nitro Group to **4**

A mixture of **3** (3.00 g, 9.48 mmol) and 5% Pd on charcoal (379 mg) in MeOH (60 mL) was stirred with hydrogen for 1 h. The catalyst was filtered off, and the filtrate was concentrated. Subsequent drying in vacuo yielded **4** (2.72 g, 100%) as an ivory solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br, 1H), 7.54 (d, $J = 9.2$ Hz, 1H), 7.07 (d, $J = 2.8$ Hz, 1H), 6.91 (dd, $J = 8.8$, 2.8 Hz, 1H), 6.79 (dd, $J = 8.8$, 2.8 Hz, 1H), 6.78 (s, 1H), 6.71 (d, $J = 8.8$ Hz, 1H), 4.93 (br, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.13, 157.20, 151.26, 142.06, 132.87, 128.33, 125.77, 119.28, 119.09, 117.67, 115.91, 112.14, 111.52, 55.05, 55.44, 18.41.

Preparation of qunazoline-4-one **5**

A mixture of **4** (2.70 g, 9.43 mmol) and formic acid (5 mL) was refluxed for 1 h and treated with 5 N NaOH solution (30 mL). The precipitate was collected by filtration. The crude product was dissolved in $CHCl_3$. The organic layer was dried over MgSO4. The solvent was evaporated in vacuo to give the product **5** as an ivory solid (2.79 g, quantitatively): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, $J = 3.2$ Hz, 1H), 7.70 (d, $J = 9.2$ Hz, 1H), 7.39 (dd, $J = 8.8$, 2.8 Hz, 1H), 7.16 (d, $J = 8.8$ Hz, 1H), 6.90 (d, $J = 2.4$ Hz, 1H), 6.87 (dd, $J = 8.8$, 2.4 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.43, 159.93, 158.68, 144.49, 142.47, 136.94, 129.42, 128.97, 128.64, 124.48, 123.12, 116.29, 112.30, 106.43, 55.89, 55.51, 18.12.

Bromination of the Tolyl Compound **5** to **6** and **6a**

To **5** (2.70 g, 9.11 mmol) in CCl_4 (20 mL), *N*-bromosuccinimide (1.78 g, 10.02 mmol) were a catalytic amount of benzoyl peroxide (221 mg,

0.91 mmol) were added. The reaction mixture was stirred at 10°C for 1 day in the presence of a 200-W sun lamp. The succinimide was filtered off, and the filtrate was concentrated under reduced pressure. The crude oil was purified by using flash column chromatography (EtOAc–*n*-Hex = 1:1) to give the mixture (**6**:**6a** = 8:2) as a clear foam. ^{1}H NMR (400 MHz, $CDCl_3$) **6**: δ 7.98 (s, 1H), 7.72 (d, J = 12.8 Hz, 1H), 7.72 (s, 1H), 7.42 (dd, J = 8.8, 3.2 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 2.8 Hz, 1H), 7.01 (dd, J = 8.8, 2.8 Hz, 1H), 4.33 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), **6a**: δ 7.85 (s, 1H), 7.70 (s, 1H), 7.69 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.39 (dd, J = 8.8, 2.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 8.8, 2.8 Hz, 1H), 6.43 (s, 1H), 3.92 (s, 6H).

Preparation of Benzyl Acetate **7**

To a suspension of potassium acetate (933 mg, 9.51 mmol) in DMF (7 mL), **6** (2.38 g, 6.34 mmol) in DMF (5 mL) was added dropwise. After being stirred at rt for 1 day, the reaction mixture was cooled to 0°C, diluted with EtOAc (5 mL), quenched with water (10 mL), and extracted with EtOAc (twice). The combined organic layer was washed with water (twice), then dried over MgSO4, and filtered. The residue was purified by flash-column chromatography (EtOAc–*n*-Hex = 1:1) to obtain the product **7** as a clear foam (1.39 g, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.70 (d, J = 6.4 Hz, 1H), 7.67 (s, 1H), 7.39 (dd, J = 8.8, 3.2 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 3.2 Hz, 1H), 7.01 (dd, J = 8.8, 2.8 Hz, 1H), 4.95 (q, J = 12.8, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.98, 160.58, 160.09, 158.72, 144.42, 142.33, 135.00, 129.27, 129.03, 129.00, 124.55, 122.84, 115.59, 114.53, 106.40, 62.63, 55.86, 55.64, 20.74.

Preparation of Dictyoquinazole **A**

In a 25-mL, one-necked, round-bottomed flask, **7** (1.30 g, 3.67 mmol) and sodium methoxide (20 mg, 0.37 mmol) were dissolved in methanol (5 mL). The reaction mixture was stirred at rt for 3 h. The precipitate was collected by filtration to give dictyoquinazole A as a white solid (1.15 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.71 (d, J = 11.2 Hz, 1H), 7.70 (s, 1H), 7.42 (dd, J = 8.8, 2.8 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.8, 2.8 Hz, 1H), 4.46 (dd, J = 12.4, 3.6 Hz, 1H), 4.40 (dd, J = 12.0, 8.8 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.03 (dd, J = 8.8, 3.6 Hz, 1H).

Synthesis of Dictyoquinazol B

To **A** (100 mg, 0.3202 mmol) in THF (4 mL), a 1 M AlH3 solution in THF (640 μL, 0.6404 mmol) was added at 0°C. The reaction mixture was stirred at rt for 30 min. The reaction mixture was cooled to 0°C, diluted with

EtOAc (3 mL), and quenched with water (5 mL). The aqueous layer was extracted with EtOAc, and the organic layer was collected, then dried over MgSO4. The residue was purified by flash-column chromatography (EtOAc–*n*-Hex = 1:1) to allow the product **8** as a clear oil (11.5 mg, 12%). To a solution of acetic formic anhydride (12.8 mg, 0.0952 mmol) in THF (2 mL), **6** (11.0 mg, 0.0366 mmol) in THF (1 mL) was added via cannula. The reaction mixture was stiired at rt for 3 h. The reaction mixture was cooled to 0°C, diluted with EtOAc (2 mL), and quenched with water (2 mL). The aqueous layer was extracted with EtOAc, and the organic layer was collected, then dried over MgSO4. The residue was purified by flash-column chromatography (EtOAc–*n*-Hex = 1:1) to allow the product **B** as a mixture of rotamers **Ba** and **Bb** (8.1 mg, 67%): ^{1}H NMR (400 MHz, CD_3OD) **Ba**: δ 8.66 (s, 1H), 7.28 (d, $J = 9.0$ Hz, 1H), 7.07 (d, $J = 3.0$ Hz, 1H), 6.88 (dd, $J = 9.0$, 3.0 Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 1H), 6.81 (d, $J = 3.0$ Hz, 1H), 6.67 (dd, $J = 8.7$, 3.0 Hz, 1H), 4.84 (s, 2H), 4.76 (s, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H); **Bb**: δ 7.92 (s, 1H), 7.98 (d, $J = 9.0$ Hz, 1H), 7.06 (d, $J = 3.0$ Hz, 1H), 6.86 (dd, $J = 9.0$, 3.0 Hz, 1H), 6.81 (d, $J = 3.0$ Hz, 1H), 6.78 (d, $J = 8.6$ Hz, 1H), 6.69 (dd, $J = 8.6$, 3.0 Hz, 1H), 4.80 (s, 2H), 4.74 (s, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) **Ba**: δ 162.4, 158.9, 158.6, 141.2, 139.4, 130.9, 129.0, 123.6, 119.2, 114.8, 114.6, 113.7, 112.6, 61.5, 61.2, 56.0, 55.8, 54.3; **Bb**: δ 162.9, 158.7, 158.5, 141.2, 139.3, 130.5, 129.8, 124.9, 124.8, 115.8, 114.0, 113.5, 111.7, 68.0, 61.5, 56.0, 55.9, 54.7.

Synthesis of Dictyoquinazol C

To a suspension of **A** (500 mg, 1.60 mmol) in $CHCl_3$ (4 mL), oxalyl chloride (349 μL, 4.80 mmol) was added dropwise at 0°C. After refluxing for 1 h, the solvent was evaporated at 50°C. The imidazolyl chloride compound was dissolved in THF (5 mL), and sodium cyanoborohydride (503 mg, 8.00 mmol) was added at 0°C. The reaction mixture was stirred at rt for 6 h, then cooled to 0°C, and treated with 5 N NaOH solution (10 mL). The aqueous layer was extracted with EtOAc, and the organic layer was collected, washed with 5 N NaOH solution, and then dried over $MgSO_4$. The residue was purified by flash-column chromatography (EtOAc–*n*-Hex = 1:1) to obtain the product **9** as a white solid (503 mg, 100%): ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, $J = 2.8$ Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 1H), 6.99 (d, $J = 2.8$ Hz, 1H), 6.98 (dd, $J = 8.8$, 3.2 Hz, 1H), 6.85 (dd, $J = 8.8$, 3.2 Hz, 1H), 6.75 (d, $J = 8.8$ Hz, 1H), 4.85 (d, $J = 10.0$ Hz, 1H), 4.59 (d, $J = 10.0$ Hz, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 4.42 (br, 1H), 4.34 (d, $J = 12.0$ Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.53, 159.08, 153.87, 141.47, 138.83, 131.60, 127.59, 122.15, 118.89, 118.05, 115.21, 114.81, 111.17, 63.30, 61.84, 55.80, 55.51. To a solution of acetic formic anhydride (94.9 mg, 0.7046 mmol) in THF (3 mL),

9 (85.2 mg, 0.2710 mmol) in THF (2 mL) was added via cannula. The reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled to 0°C, and diluted with EtOAc (2 mL), and quenched with water (3 mL). The aqueous layer was extracted with EtOAc, and the organic layer was collected, then dried over MgSO4. The residue was purified by flash column chromatography (EtOAc–*n*-Hex = 1:1) to give the product **C** as a mixture of rotamers **Ca** and **Cb** (16.1 mg, 17%). ^{1}H NMR (400 MHz, CD_3OD) **Ca**: δ 8.69 (s, 1H), 7.59 (d, $J = 3.0$ Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.25 (dd, $J = 8.8$, 3.0 Hz, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 7.16 (d, $J = 2.8$ Hz, 1H), 6.94 (dd, $J = 8.7$, 2.8 Hz, 1H), 5.41 (d, $J = 11.5$ Hz, 1H), 5.36 (d, $J = 11.5$ Hz, 1H), 4.53 (d, $J = 13.7$ Hz, 1H), 4.49 (d, $J = 13.7$ Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H); **Cb**: δ 8.48 (s, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.57 (d, $J = 3.0$ Hz, 1H), 7.26 (d, $J = 8.6$ Hz, 1H), 7.24 (dd, $J = 8.8$, 3.0 Hz, 1H), 7.13 (d, $J = 2.9$ Hz, 1H), 6.97 (dd, $J = 8.6$, 2.9 Hz, 1H), 5.35 (d, $J = 11.5$ Hz, 1H), 5.27 (d, $J = 11.5$ Hz, 1H), 4.51 (d, $J = 13.7$ Hz, 1H), 4.47 (d, $J = 13.7$ Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H).

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