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PHOTO- AND ELECTROCHEMICAL PROPERTIES OF NOVEL 7-SUBSTITUTED NAPHTHYRIDINE DERIVATIVES

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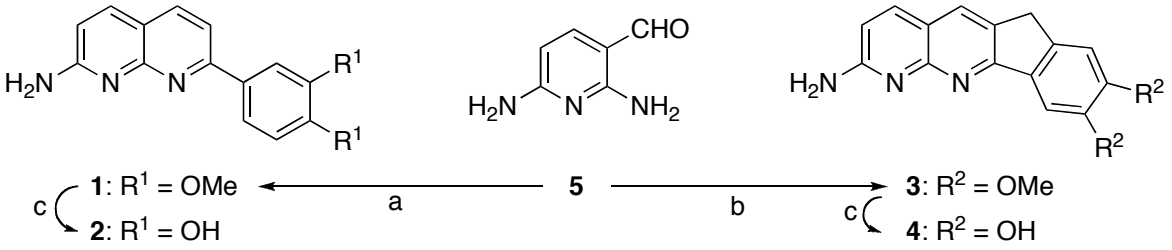
Abstract – Here we report a new class of 1,8-naphthyridine derivatives, 2-amino-7-(3,4-dimethoxyphenyl)-1,8-naphthyridine, 2-amino-7-(3,4-dihydroxy phenyl)-1,8-naphthyridine, 2-amino-(5,6-dimethoxy-1*H*-indenyl[2,3-*b*])-1,8-naphthyridine, and 2-amino-(5,6-dihydroxy-1*H*-indenyl[2,3-*b*])-1,8-naphthyridine. All of these compounds were synthesized via naphthyridine-ring forming reaction with 2,6-diaminopyridine-3-carboxaldehyde as a key step. The two dimethoxy derivatives showed predominant fluorescent emission around 400 nm in MeCN. Cyclic voltammetry of the two dihydroxy derivatives in phosphate buffer showed oxidation potentials of 0.21~0.25 V vs. Ag/AgCl.

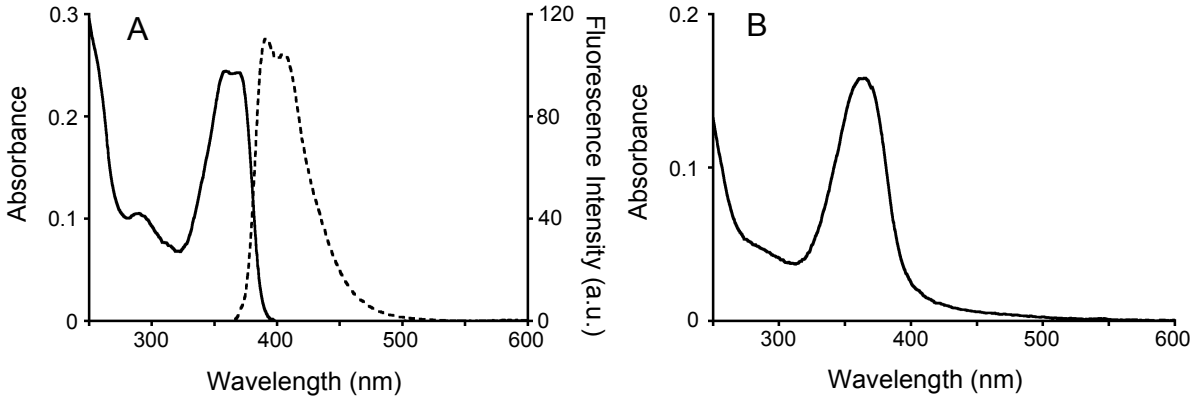
Naphthyridines have been widely developed and are in clinical trials for low-toxic medicine such as analgesic,[1] anitibiotics,[2] and antitumor agent,[3] etc. These heterocyclic compounds have a basic skeleton of 2-amino-1,8-naphthyridine which serves a hydrogen-bonding array of a donor–acceptor–acceptor (DAA, D: donor; A: acceptor) fashion. Therefore, 1,8-naphthyridine derivatives which selectively bind to nucleobases could recently be utilized as an important probe for detecting single nucleotide polymorphisms (SNPs) concerning with various gene disease or trinucleotide repeats as seen in Huntington disease.[4,5] With this in mind, development of new naphthyridine derivatives having photochemical and/or electrochemical activities is highly desired for providing useful detection probes as well as candidates of novel drugs. Herein, we would like to communicate synthesis and photo- and electrochemical properties of new 7-substituted 1,8-naphthyridine derivatives, 2-amino-7-(3,4-dimethoxyphenyl)-1,8-naphthyridine (**1**), 2-amino-7-(3,4-dihydroxyphenyl)-1,8-naphthyridine (**2**), 2-amino-(5,6-dimethoxy-1*H*-indenyl[2,3-*b*])-1,8-naphthyridine (**3**), and 2-amino-(5,6-dihydroxy-1*H*-indenyl[2,3-*b*])-1,8- naphthyridine (**4**).

Scheme 1[a] Synthetic routes for novel 7-substituted naphthyridine derivatives.



[a]Key: (a) MeONa, 3,4-dimethoxyacetophenone, toluene; (b) MeONa, 3,4-dimethoxy-1-indanone, toluene; (c) pyridine hydrochloride.

The new 1,8-naphthyridines were synthesized via naphthyridine-ring forming reaction with 2,6-diaminopyridine-3-carboxaldehyde (**5**) which was prepared according to literature procedure (Scheme 1).[6] Treatment of **5** with MeONa and 3,4-dimethoxyacetophenone in toluene at reflux for 1 h led to 2-amino-7-(3,4-dimethoxyphenyl)-1,8-naphthyridine (**1**) in 88% yield.[7] Following deprotection of methyl group with pyridine hydrochloride at 200 ºC for 1 h gave water-soluble 2-amino-7-(3,4-dihydroxyphenyl)-1,8-naphthyridine (**2**) in 78% yield.[8] By using of 3,4-dimethoxy-1-indanone instead of 3,4-dimethoxyacetophenone, 2-amino-(5,6-dimethoxy-1*H*-indenyl[2,3-*b*])-1,8-naphthyridine (**3**) and 2-amino-(5,6-dihydroxy-1*H*-indenyl[2,3-*b*])-1,8-naphthyridine (**4**) were prepared in a manner similar to the synthetic procedures described for **1** and **2**.[9] Figures 1A and 1C display absorption spectra (solid line) of the dimethoxy derivatives **1** and **3** which showed absorption maxima at 370 nm and 382 nm with the absorption coefficients of 2.43 x 10^4 and 4.45 x 10^4 $mol^{-1}dm^3cm^{-1}$, respectively, so that these naphthyridines exist as a pale yellow solid. The fluorescence spectra of those exhibited predominant emission around 400 nm in MeCN (dotted line). In the cases of the two dihydroxy derivatives **2** and **4** in phosphate buffer (pH 7.0), an absorption maxima were observed at 361 nm and 388 nm with the absorption coefficients of 1.58 x 10^4 and 1.25 x 10^4 $mol^{-1}dm^3cm^{-1}$, respectively (Figures 1B and 1D), while these fluorescence emissions were negligible.



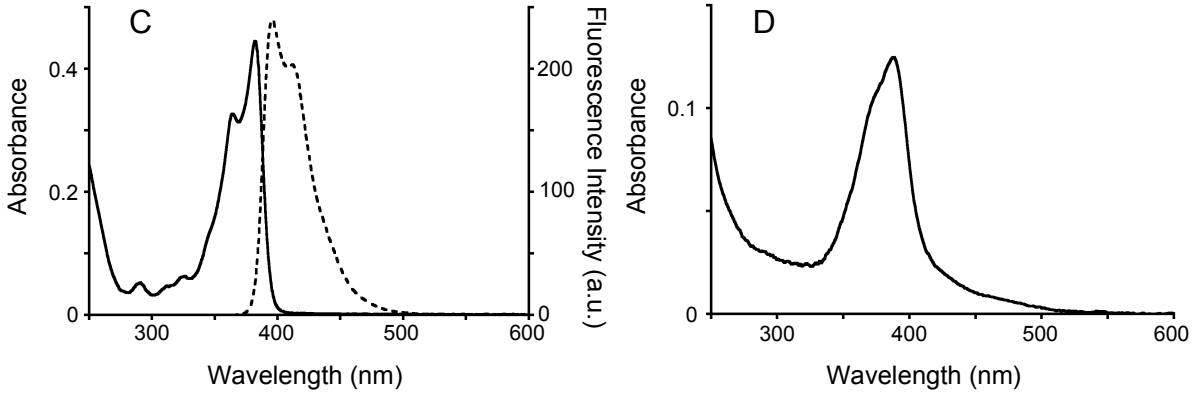


Figure 1. Absorption (solid line) and fluorescence (dotted line) spectra of 10 μM 7-substituted 1,8-naphthyridines at 25 °C. (A) **1** in MeCN (λ_{ex} = 370 nm), (B) **2** in 65 mM phosphate (pH 7.0), (C) **3** in MeCN (λ_{ex} = 382 nm), and (D) **4** in 65 mM phosphate (pH 7.0).

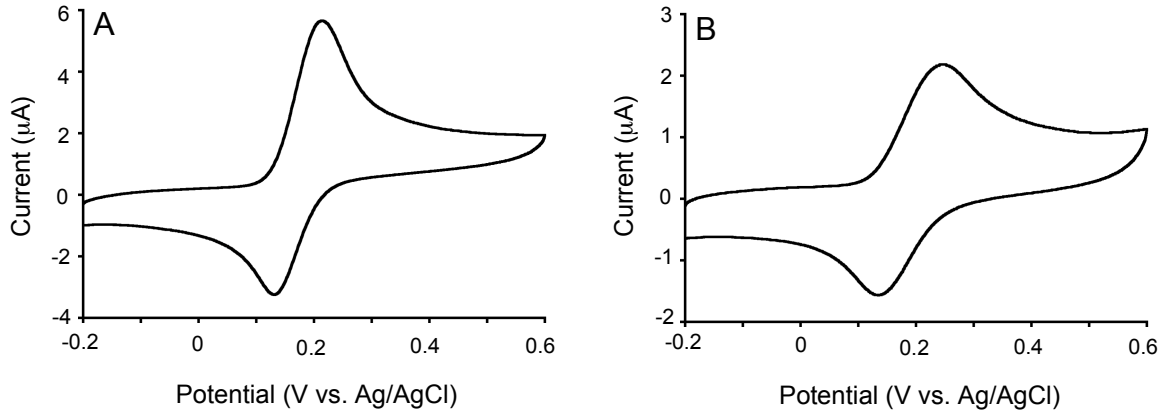


Figure 2. Cyclic voltammograms at 25 °C of (A) **2** (0.5 mM) and (B) **4** (0.5 mM) in 65 mM phosphate (pH 7.0) with a scanning rate of 0.1 V/s, a gold working electrode, a saturated Ag/AgCl reference electrode, and a platinum wire auxiliary electrode.

Electrochemical measurements were carried out for all of the new 1,8-naphthyridines. Used was a normal three-electrode configuration consisting of a commercially available gold working electrode, a saturated Ag/AgCl reference electrode, and a platinum wire auxiliary electrode. Cyclic voltammetry (CV) was performed at 25.0±0.1 °C scanning range from –0.2 to +0.6 V with a scanning rate of 0.1 V/s in appropriate media that had been thoroughly degassed with N_2. Dimethoxy derivatives **1** and **3** showed no electrochemical response within the scanning range (1 mM in MeCN, 100 mM tetrabutylammmonium perchlorate). Figure 2 shows that naphthyridines **2** and **4** have an oxidation potential at 0.21 and 0.25 V and a reduction potential at 0.13 and 0.14 V in 65 mM phosphate, respectively, that fall within a favorable potential range for electrochemical detection of biological targets in aqueous media.

In conclusion, we synthesized novel 7-substituted 1,8-naphtyridines that possess photochemical or electrochemical activities adequate for detecting biomolecules. Development of a simple and efficient detection-system for significant biological targets is now underway by using these naphthyridine derivatives.

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7. To a MeOH (10 mL) solution of Na (168 mg, 7.29 mmol) was added 3,4-dimethoxyacetophenone (1.31 g, 7.29 mmol), and the mixture was stirred for 5 min at rt. To the solution was added **5** (1.00 g, 7.29 mmol) and toluene (10 mL), and then the resulting mixture was refluxed for 1 h. After removal of the solvents, the residue was solidified with water (10 mL), and the precipitate was filtered and washed with water. The obtained solid was dissolved in 2N HCl, and the aqueous solution was then neutralized with K_2CO_3. After filtration, the resulting solid was chromatographed

(SiO_2; eluent, MeOH : CH_2Cl_2 = 5 : 95) to give crude **1** (1.80 g, 88%). Recrystallization from MeOH gave pure **1** as a pale yellow solid. Mp 241~243 ºC; IR (KBr) 3461, 3282, 3116, 1638, 1595, 1503, 1146, 804 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.07 (d, J = 8.5 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 1 H), 7.87 (d, J = 2.0 Hz, 1 H), 7.77 (d, J = 8.5 Hz, 2 H), 7.07 (d, J = 8.5 Hz, 1 H), 6.81 (brs, 2 H), 6.77 (d, J = 8.5 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 161.1, 157.2, 156.7, 150.2, 149.0, 137.3, 137.1, 131.8, 119.8, 115.5, 113.7, 112.6, 111.6, 110.1, 55.6, 55.4; HRMS (ESI) calcd for MH^+, $C_{16}H_{16}N_3O_2$: 282.1243; found 282.1229.

8. A mixture of **1** (300 mg, 1.07 mmol) and pyridine hydrochloride (3.0 g, 26.0 mmol) was heated to 200 ºC for 1 h. After cooled to rt, the residue was solidified with water (100 mL), and the resulting precipitate was filtered, washed with EtOH and Et_2O, and air-dried to give **2** (240 mg, 78%) as a yellow powder. Mp 251~252 ºC (decomp.); IR (KBr) 3328, 3170, 1668, 1613, 1291, 1154 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.72 (brs, 1 H), 9.33 (brs, 1 H), 8.35 (dd, J = 9.0, 2.5 Hz, 2 H), 8.18 (brs, 2 H), 7.97 (d, J = 8.5 Hz, 1 H), 7.68 (d, J = 2.0 Hz, 1 H), 7.57 (dd, J = 8.0, 2.3 Hz, 1 H), 7.07 (d, J = 9.5 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 159.4, 156.6, 148.9, 146.7, 145.9, 142.5, 138.5, 128.1, 119.8, 117.3, 116.1, 114.8, 114.2, 113.4; HRMS (ESI) calcd for MH^+, $C_{14}H_{12}N_3O_2$: 254.0930; found 254.0921.
9. For **3**: To a MeOH (20 mL) solution of Na (352 mg, 15.3 mmol) was added 3,4-dimethoxy-1-indanone (2.94 g, 15.3 mmol), and the mixture was stirred for 5 min at rt. To the solution was added **5** (2.10 g, 15.3 mmol) and toluene (50 mL), and then the resulting mixture was refluxed for 1 h. After removal of the solvents, the residue was solidified with water (50 mL), and the precipitate was filtered and washed with water. The crude solid was dissolved in a small amount of DMF, and then to the solution was added an appropriate amount of Et_2O. The resulting solid was filtered to give pure **3** (2.16 g, 48%) as a pale yellow solid. Mp >248 ºC (decomp.); IR (KBr) 3317, 3139, 1600, 1498, 1365, 1292 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.05 (s, 1 H), 7.91 (d, J = 8.5 Hz, 1 H), 7.53 (s, 1 H), 7.28 (s, 1 H), 6.74 (d, J = 8.5 Hz, 1 H), 6.57 (brs, 2 H), 3.90 (s, 3 H), 3.87 (s, 5 H); ^{13}C NMR (DMSO-d_6) δ 162.6, 160.3, 156.8, 151.1, 149.1, 138.8, 137.7, 132.7, 131.1, 130.4, 114.7, 111.3, 108.7, 103.6, 55.8, 55.6, 33.1; HRMS (ESI) calcd for MH^+, $C_{17}H_{16}N_3O_2$: 294.1243; found 294.1248. For **4**: This compound was obtained from **3** (300 mg, 1.02 mmol) in a manner similar to that described for **2**. **4** (256 mg, 83%) was obtained as a dark yellow powder. Mp >259 ºC (decomp.); IR (KBr) 3461, 3171, 1666, 1477, 1300 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.97 (brs, 1 H), 9.71 (brs, 1 H), 9.18 (brs, 1 H), 8.33–8.14 (m, 3 H), 7.53 (s, 1 H), 7.11 (s, 1 H), 7.05 (d, J = 9.0 Hz, 1 H), 3.86 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 163.4, 156.4, 150.4, 147.3, 146.2, 142.5, 139.6, 134.3, 132.5, 129.0, 113.4, 112.3, 112.0, 108.0, 33.0; HRMS (ESI) calcd for MH^+, $C_{15}H_{12}N_3O_2$: 266.0930; found 266.0922.