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Reactions of Naphthyridines with Aldehydes: Novel Derivatives with Red-Fluorescence Emissions and Two-Photon Absorptions

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Four new 1,8-naphthyridine derivatives were synthesized by reacting the parent molecules with aldehydes and characterized. Two of the compounds have completely new and unusual skeletons, and display red-fluorescence emissions and two-photon absorption. Their structures were determined using MS, 1D and 2D NMR, and density functional theory calculations. The structural investigations of 2-methyl-1,8-naphthyridine hydrochloride and hydrobromide showed that abundant hydrogen-bonds and π-π interactions lead to extended networks.

Keywords naphthyridine derivative, red emission, two-photon absorption, structure, DFT calculation

Introduction

1,8-Naphthyridine derivatives with large conjugated planes are usually biocompatible,[1] their synthesis is relatively simple and they can easily be further modified with specific functional groups to give desired properties. They also provide hydrogen-bond donors or receptors and aromatic rings for π-π stacking, and these non-covalent interactions are useful tools not only in supramolecular chemistry and crystal engineering, but also in multidimensional aggregation to produce properties such as luminescence, and host-guest exchange.[2-4] More importantly, 1,8-naphthyridine derivatives have good fluorescence properties, indicating their potential use as fluorescent markers, especially in molecular biology and related fields, for example, as fluorescent markers of nucleic acids.[5-7] However, the blue-fluorescence emissions of naphthyridine derivatives may limit their applications in some fields. In this paper, we report the synthesis and characterization of four new 1,8-naphthyridine derivatives containing abundant hydrogen-bonds and π-π interactions. Structural studies indicate that 2-methyl-1,8-naphthyridine is a potential co-transporter of H^+/Cl^-, which plays important roles in biological fields. Two of the naphthyridines have completely new skeletons and exhibit red-fluorescence emissions, their two-photon absorption properties (TPA) were also investigated (Figure 1).

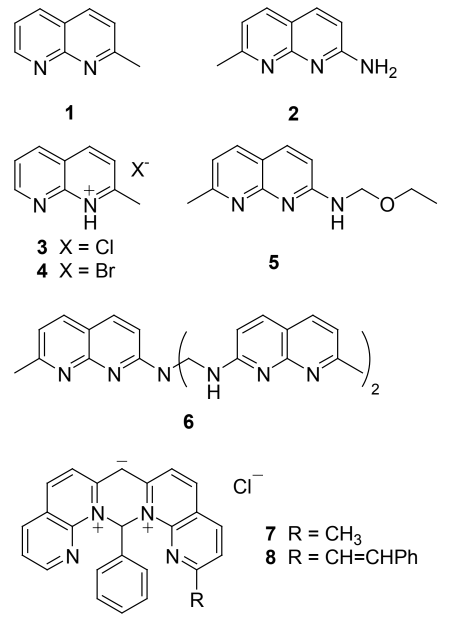

Figure 1 Chemical structures of the compounds **1**—**8**.

Experimental

General methods

Compounds **1** and **2** were synthesized according to a reported procedure,[8] other chemicals and solvents were purchased from commercial sources and used without further purification. The alumina and silica gel used in

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column chromatography were neutral, 200—300 mesh. Spectroscopic measurements were carried out using the following instruments: Bruker BIFLEX III (MS), Bruker Avance II 400 (1D NMR), Bruker Avance 500 (2D NMR), Varian Excalibur 3100 (IR), Elementar Vario EL (elemental analysis), Hitachi U-3010 (UV-vis), Hitachi F-4500 (fluorescence), and Spectra-Physics Tsunami/Spitfire OPA-800C (TPA). Chemical shifts (δ) are referenced to TMS in CD_3OD. Fluorescence quantum efficiencies were measured in methanol solution (1.0×10^{-5} mol•L^{-1}) using quinine sulfate as a reference: $\lambda_{ex}=365$ nm, $\Phi_r=0.55$ (10^{-5} mol•L^{-1} in 1 mol•L^{-1} H_2SO_4). TPA-cross sections were determined by comparing the two-photon excited fluorescences (TPEF) in methanol solution (1.0×10^{-4} mol•L^{-1}) to that of rhodamine B ($\Phi=0.70$).[9]

X-ray data collection and structure determinations

X-ray single-crystal diffraction data for compounds **3** and **4** were collected on a Bruker Smart X-Ray diffractometer using a graphite monochromator with Mo-Kα radiation ($\lambda=0.071073$ nm) at 294 and 298 K, respectively. All structures were solved by direct methods (SHELXL 97) and refined by full-matrix least-squares methods on all F^2 data.[10] The hydrogen atoms of the compounds were generated theoretically onto the specific atoms and refined isotropically with fixed thermal factors.

Computational

The gometries of **7** and **8** were optimized using density functional theory (DFT) at the B3LYP/6-31G(d) level with the Gaussian 03 program.[11] The computed geometries were verified by frequency calculations and by acquiring the atomic polar tensor (APT) charges. Furthermore, the global minima were checked by manually changing the initial geometries and comparing the resulting optimized structures and their energies. NMR chemical shifts were calculated by the gauge ingependent atomic orbital (GIAO) method at the B3LYP/6-311+G(2d,p) level and referenced to TMS calculated at the same level of theory. Calculations were performed using the integral equation formalism polarizable continuum model (IEF-PCM) as if in methanol solution, except for the geometry optimization of **8** because of the molecular volume limit of the software. Instead compound **8** was optimized in the gas-phase with restricted torsional angles of the benzene ring to simulate the situation in the PCM instead. All of the calculations were carried out on a Lenovo DeepComp 6800 computer in the Supercomputing Center of the Chinese Academy of Sciences.

Synthesis

Compounds **5** and **6**: Formaldehyde (0.1 mL, 1.2 mmol) and **2** (80 mg, 0.5 mmol) were refluxed in a 10 mL solution (ethanol for **5** or water for **6**) for 5 h. After cooling to room temperature, the precipitate was filtered and purified by flash column chromatography on a silica gel column, using ethyl acetate as the eluent.

***N*-(Ethoxymethyl)-7-methyl-1,8-naphthyridin-2-amine (5)** 44 mg, 41% yield; ^{1}H NMR (400 MHz, CD_3OD, TMS) δ: 7.83 (d, $J=8.7$ Hz, 1H), 7.82 (d, $J=8.0$ Hz, 1H), 7.07 (d, $J=8.0$ Hz, 1H), 6.85 (d, $J=8.8$ Hz, 1H), 6.36 (br, 1H), 5.09 (d, $J=6.9$ Hz, 2H), 3.63 (q, $J=7.0$ Hz, 2H), 2.69 (s, 3H), 1.18 (t, $J=7.0$ Hz, 3H); ESI-MS *m/z*: 218 $[M+H]^+$. Anal. calcd for $C_{12}H_{15}N_3O$: C 66.34, H 6.96, N 19.34; found C 66.42, H 6.91, N 19.22.

***N,N',N''*-Tris(7-methyl-1,8-naphthyridin-2-yl)-dimethyl enetriamine (6)** 21 mg, 25% yield; ^{1}H NMR (400 MHz, CD_3OD, TMS) δ: 7.79—7.75 (m, 4H), 7.65 (d, $J=8.8$ Hz, 2H), 7.52 (d, $J=9.0$ Hz, 1H), 7.06 (d, $J=8.0$ Hz, 2H), 7.03 (d, $J=8.2$ Hz, 1H), 6.77 (d, $J=8.7$ Hz, 2H), 5.68 (br, 2H), 2.73 (s, 6H), 2.72 (s, 3H), 2.15 (s, 4H); ESI-MS *m/z*: 502 $[M+H]^+$. Anal. calcd for $C_{29}H_{27}N_9$: C 69.44, H 5.43, N 25.13; found C 69.56, H 5.41, N 25.03.

Compounds 7 and 8 To a solution of **3** (1.0 g, 7.0 mmol) in acetic anhydride (50 mL), benzaldehyde (2.1 mL, 21 mmol) was added. The mixture was stirred at 140 ℃ under a N_2 atmosphere for 4 h. The volatiles in the resulting solution were evaporated under a vacuum, and then the residue was redissolved and purified by flash column chromatography. Alumina was used first, eluted with chloroform : ethanol (2 : 1). Most impurities were removed in this step; further purification and separation of compounds **7** and **8** were achieved by repeated gradient elution on a silica-gel column, using chloroform : acetone : ethanol (10 : 1 : 1 to 9 : 3 : 4) as the eluent. The samples for elemental analysis were additionally washed with an aqueous solution of sodium bicarbonate and recrystallized in methanol/water.

2-Methyl-15-phenyl-15*H*-pyrimido[1,6-*a*:3,4-*a*']-bis([1,8]naphthyridine)-14-ium chloride (7) 144 mg, 10% yield; ^{1}H NMR (400 MHz, CD_3OD, TMS) δ: 11.04 (s, 1H), 8.92 (dd, $J=4.7$, 1.7 Hz, 1H), 8.39 (dd, $J=7.8$, 1.7 Hz, 1H), 8.30 (d, $J=8.0$ Hz, 1H), 8.23 (d, $J=9.0$ Hz, 1H), 8.17 (d, $J=9.2$ Hz, 1H), 7.65 (dd, $J=7.8$, 4.7 Hz, 1H), 7.58 (d, $J=8.0$ Hz, 1H), 7.46—7.48 (m, 2H), 7.21—7.32 (m, 3H), 6.91—6.93 (m, 2H), 6.42 (s, 1H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD, TMS) δ: 165.3, 153.7, 150.7, 150.4, 148.3, 147.7, 140.2, 139.6, 139.5, 139.4, 134.6, 130.8, 130.1, 127.3, 124.1, 123.6, 123.0, 122.1, 121.7, 120.1, 96.8, 63.2, 25.4; MALDI-TOF-MS *m/z*: 375 $[C_{25}H1_9N_4]^+$; IR (KBr) ν: 3441, 2361, 1615, 1557, 1520, 1463, 1386, 1275, 1230, 1135, 1053, 867, 697, 620, 533, 484. Anal. calcd for $[C_{25}H_{19}N_4]Cl$•$3H_2O$: C 64.58, H 5.42, N 12.05; found C 64.43, H 5.28, N 11.65.

(*E*)-15-Phenyl-2-styryl-15*H*-pyrimido[1,6-*a*:3,4-*a*']bis([1,8]naphthyridine)-14-ium chloride (8) 264 mg, 15% yield; ^{1}H NMR (400 MHz, CD_3OD, TMS) δ: 11.14 (s, 1H), 8.97 (dd, $J=4.7$, 1.5 Hz, 1H), 8.42 (dd, $J=7.8$, 1.5 Hz, 1H), 8.34 (d, $J=8.2$ Hz, 1H), 8.16—8.24 (m, 2H), 8.04 (d, $J=16.1$ Hz, 1H), 7.81 (d, $J=8.2$

Hz, 1H), 7.66 (dd, J=7.8, 4.7 Hz, 1H), 7.62—7.64 (m, 2H), 7.51 (d, J=9.2 Hz, 1H), 7.41—7.45 (m, 2H), 7.34—7.40 (m, 3H), 7.24—7.32 (m, 3H), 6.99—7.01 (m, 2H), 6.44 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD, TMS) δ: 160.0, 153.7, 150.5, 150.2, 148.2, 147.8, 139.9×2, 139.7, 139.5, 139.1, 136.9, 134.7, 130.9, 130.6, 130.2, 129.9, 128.7, 127.4, 127.3, 123.8, 123.2, 122.7, 122.2, 121.8, 121.3, 97.1, 62.9; MALDI-TOF-MS m/z: 463 $[C_{32}H_{23}N_4]^+$; IR (KBr) v: 3424, 2365, 1611, 1546, 1515, 1462, 1386, 1274, 1204, 1135, 1048, 970, 853, 755, 693, 619, 532. Anal. calcd for $[C_{32}H_{23}N_4]Cl \cdot 3H_2O$: C 69.49, H 5.29, N 10.13; found C 69.19, H 5.29, N 10.07.

Results and Discussion

During our recent synthetic work on naphthyridine compounds, some new unexpected substances were found during reactions of naphthyridines and aldehydes in the case of addition of acid. To understand these reactions with acid, we obtained 2-methyl-1,8-naphthyridine (**1**) hydrohalide, (**3**) and (**4**). X-ray crystal analysis of **3** and **4** revealed that they had totally different supramolecular networks linked through hydrogen bonds and π-π interactions as a result of different halide anions and solvent molecules in their crystal structures (Figure 2). A summary of their crystallographic parameters and data is given in Table 1. Perspective views with a labeling scheme for **3** and **4** are shown in the Supporting Information (SI) Figures S1 and S2, respectively. Structural investigations of **3** and **4** showed that hydrogen ions were associated with the naphthyridine N atom of the adjacent methyl. Figure 2 shows that adjacent naphthyridine moieties are first linked into one-dimensional chains by hydrogen bonds centered on the chloride ion, with C(7)···Cl(1) (x+0.5, $-y$+0.5, z−0.5) and N(1)···Cl(1) (x, $-y$, z−0.5) interaction distances of 3.679 Å and 3.070 Å, and C(7)—H(7)···Cl(1) and N(1)—H(1)···Cl(1) bond angles are 167.5° and 170.8°, respectively. These are connected through solvent water molecules into ladder-like double-chains O(1)···Cl(1) ($-x$, y+1, $-z$+0.5), 3.164 Å; O(1)—H(1D)···Cl(1), 170.8°; C(4)···O(1) [x+0.5, y−0.5, z], 3.384 Å; C(4)—H(4)···O(1) 145.9°. Also, π-π stacking interactions occur between the two ligands linked by water molecule in the chains with a short distance of 3.599 Å. The repeated double-chain units are further interconnected by the same water-involved hydrogen bonds as those among the double-chains into a three-dimensional supramolecular aggregate, in which a dihedral angle of 63.0° between two planar molecules was observed. In the structure of compound **4**, the solvent water molecule is absent (Figure S2), which leads to relatively simple hydrogen-bonding interactions in comparison with those in **3**. We also observed π-π stacking interactions in the two-dimensional supramol-

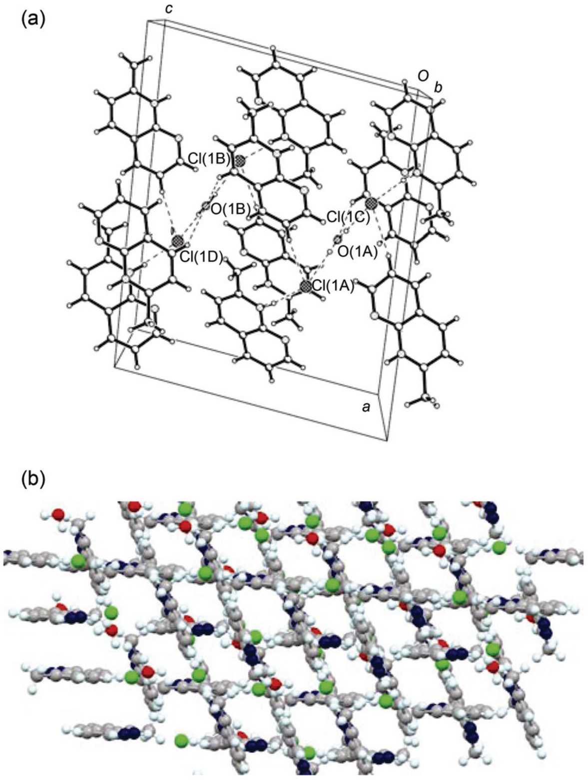


Figure 2 The crystal structure of compound **3**. (a) The structure cell of compound **3**; (b) the 3D net framework.

Table 1 Selected crystallographic data and collection parameters of compounds **3** and **4**[a]

Compound reference	**3**•0.5H$_2$O	**4**
Chemical formula	$C_9H_{10}ClN_2O_{0.50}$	$C_9H_9BrN_2$
Formula mass	189.64	225.09
Crystal system	Monoclinic	Orthorhombic
a/Å	17.134(4)	13.848(5)
b/Å	7.877(2)	7.725(3)
c/Å	14.077(3)	16.782(6)
α/(°)	90.00	90.00
β/(°)	98.851(4)	90.00
γ/(°)	90.00	90.00
Unit cell volume/Å^3	1877.2(7)	1795.2(11)
Temperature/K	294(2)	298(2)
Space group	$C2/c$	$Pbca$
Z	8	8
Radiation type	Mo Kα	Mo Kα
Absorption coefficient, μ/mm^{-1}	0.359	4.523
No. of reflections measured	5113	8620
No. of independent reflections	1916	1579
R_{int}	0.0316	0.0693
Final R_1 values ($I>2\sigma(I)$)	0.0362	0.0347
Final wR_2 (F^2) values ($I>2\sigma(I)$)	0.0867	0.0791
Final R_1 values (all data)	0.0643	0.0693
Final wR_2 (F^2) values (all data)	0.0998	0.0919
Goodness of fit on F^2	1.033	0.996
residual electron density/(e•Å^{-3})	−0.147/0.210	−0.371/0.910

[a] $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$. $wR_2=\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

ecular aggregation between aromatic rings of the naphthyridine moieties, with a mean distance of 3.696 Å, a little longer than that in compound **3**.

N-(Ethoxymethyl)-7-methyl-1,8-naphthyridin-2-amine (**5**) was prepared by the reaction of 7-methyl-1,8-naphthyridin-2-amine (**2**) and formaldehyde in ethanol solution under reflux conditions, *N,N',N''*-tris(7-methyl-1,8-naphthyridin-2-yl)dimethylenetriamine (**6**) was the product of a multistep reaction, and was found during the dehydration reaction of (**2**) and formaldehyde as a by-product along with bis(7-methyl-1,8-naphthyridin-2-ylamino)methane, as reported by our group.[12] 2-Methyl-15-phenyl-15*H*-pyrimido[1,6-*a*:3,4-*a'*]bis([1,8]-naphthyridine)-14-iumchloride (**7**) and (*E*)-15-phenyl-2-styryl-15*H*-pyrimido[1,6-*a*:3,4-*a'*]bis([1,8]-naphthyridin)-14-iumchloride (**8**) were obtained during the dehydration reaction of **1** and benzaldehyde in acetic anhydride, but the yields were very low. After checking all the starting materials and reaction conditions carefully, a high yield was achieved using 1 equiv. of acid and 3 equiv. of aldehyde (Table 2).

Table 2 Optimization of red fluorescent compounds' synthesis[a]

Conditions[a]		Isolated yield	
PhCHO	HCl	**7**	**8**
1 equiv.	—		—
1 equiv.	0.1 equiv.		trace amount
1 equiv.	1 equiv.		trace amount
2 equiv.	0.1 equiv.		trace amount
2 equiv.	1 equiv.	7%	8%
3 equiv.	0.1 equiv.	5%	7%
3 equiv.	1 equiv.	10%	15%

[a] Other reagents and conditions: N_2 atmosphere, Ac_2O as solvent, 140 ℃, 4 h.

Since the structures of **7** and **8** were so unusual, although the MALDI-TOF-MS and NMR spectra were clear enough, DFT calculations with Gaussian 03 software were used to support the structures.[13] The chemical shifts were calculated at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G (d)[14] level by GIAO method using TMS as the reference,[15] with PCM[16] as if in a methanol solution. The details of the optimized structures and APT[17] charges of the atoms in **7** and **8** are listed in Tables S1 and S3, respectively, and the experimental and calculated NMR data are listed in Tables S2 and S4, respectively. By comparing the calculated NMR data with the experimental values, the structures of **7** (Figure 3) and **8** (Figure S3) were finally determined. In compound **7**, two naphthyridine rings form a large conjugated system with a dihedral angle of about 36° between the two ring planes. The benzene ring in the molecule is vertical, with the side C—H bonds directed to the two naphthyridine rings to enable the H-π interactions. Because of the shielding effect of the π-electrons, H(44) and H(48), located about 0.25 nm above the naphthyridine rings, show an upfield NMR shift of about δ 0.3 from the nearby benzene H atoms, even though they are closer to the positively charged center of the molecule. Furthermore, the C_{sp2} atom between the two naphthyridine rings has negative charges (−1.575) and the π-electron number of each side thus complies with $4n+2$, so the NMR signal for H(34) is shifted upfield from normal hydrogen atoms. However, H(35) showed a large downfield shift of over δ 11 in the ^{1}H NMR spectrum, because the central C_{sp3} atom is bound to two quaternary N atoms with obvious positive charges (0.507). The theoretical calculations reproduced all the characteristic NMR signals correctly. The root-mean-square errors (RMSE) were δ 0.22 for the ^{1}H NMR spectrum and δ 1.4 for the ^{13}C NMR spectrum of **7**, and the corresponding values for **8** were δ 0.22 and 1.3. The linear correlations of the theoretical and experimental chemical shifts were also excellent except for the ^{1}H NMR spectrum of **8** (Figure 4). Since ^{1}H NMR is very sensitive to the molecular conformation and the environment, the geometry optimization of **8** was not performed in the PCM because of the limit on the molecular volume in the computer program.

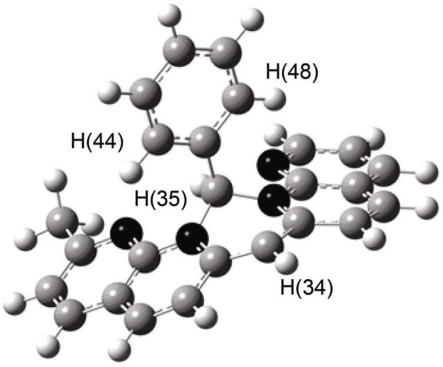


Figure 3 Optimized structure of **7** (dark ball: N, grey ball: C, light ball: H).

To the best of our knowledge, compounds **7** and **8** are novel because of the C_{sp3} bound to two quaternary N atoms in aromatic rings. A reaction mechanism based on the experimental data is proposed and presented in Scheme 1. According to this mechanism, the first step in the reaction is nucleophilic addition of an N atom in 2-methyl-1,8-naphthyridine to a benzaldehyde activated by H^+. The subsequent migration of a proton and dehydration by acetic anhydride results in an intermediate with a C=N double bond on a quaternary N atom. This intermediate can react with 2-methyl-1,8-naphthyridine or the product generated by 2-methyl-1,8-naphthyridine and benzaldehyde, following a nucleophilic addition pattern. After another cyclic nucleophilic addition, oxidation by a second aldehyde leads to the final aromatic products.

The UV-vis absorption and fluorescence emission spectra of **7** and **8** were recorded. Their absorption and emission extend into the long-wavelength region of visible light because of their planar molecular structure and the charge, which enhances the conjugative effect. As shown in Figure 5, **7** and **8** have low-energy absorp-

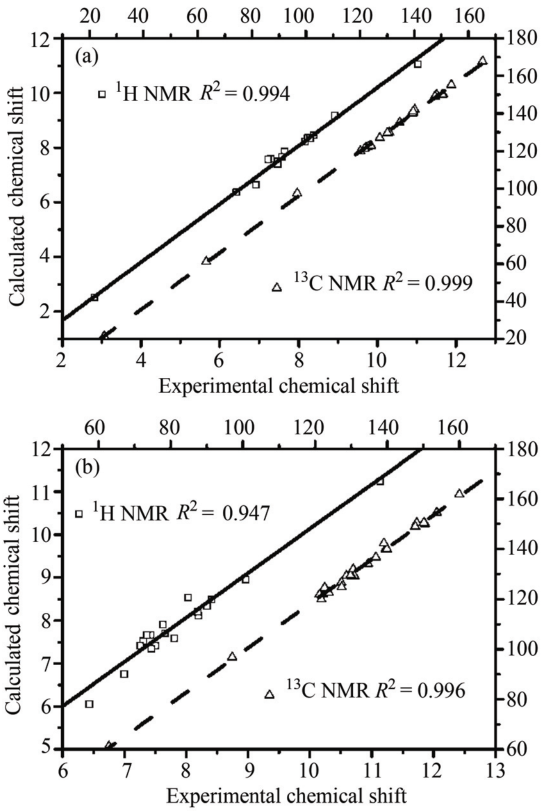
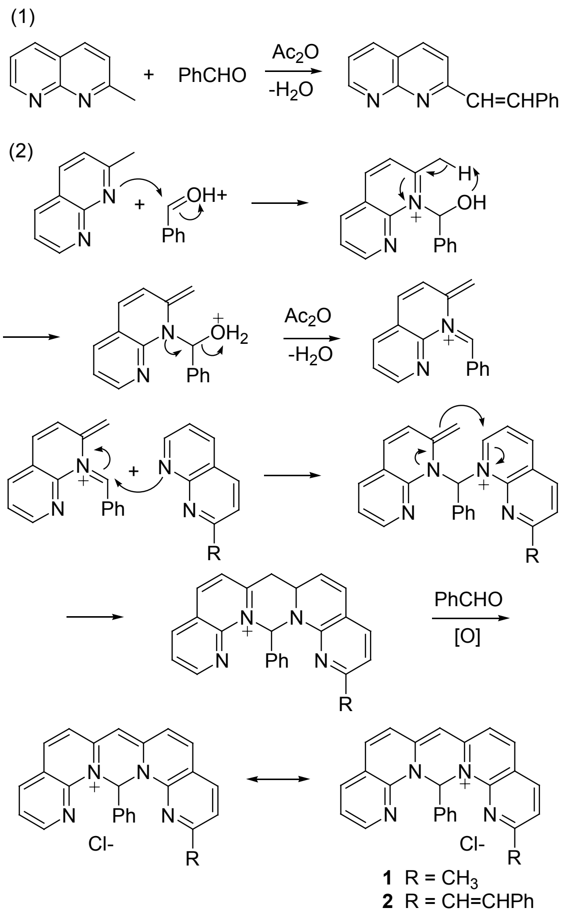


Figure 4 Correlation between theoretical chemical shifts and experiment for (a) compound **7**; (b) compound **8**.

Scheme 1 The suggested mechanism of the synthesis reaction



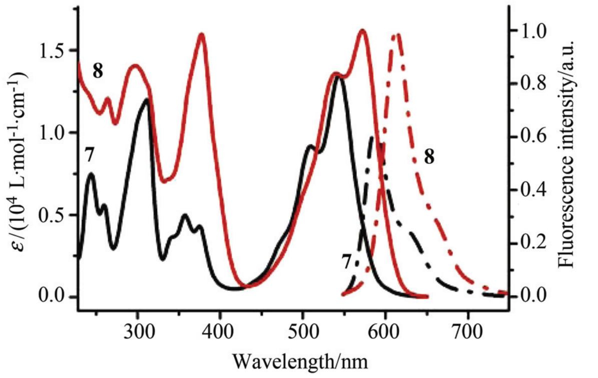


Figure 5 UV-vis absorption (solid line) and fluorescence emission spectra (dash dot line) of **7** and **8** in methanol.

tion peaks at 544 nm ($\varepsilon = 1.35 \times 10^4$ L•mol^{-1}•cm^{-1}) and 572 nm ($\varepsilon = 1.62 \times 10^4$ L•mol^{-1}•cm^{-1}) respectively. Compound **7** has an emission peak with $\lambda_{\max}$ at 590 nm in methanol, whereas that of **8** is red-shifted to 614 nm because of its larger conjugated system (Figure 6). The fluorescence quantum yields of **7** and **8** were measured using quinine sulfate as a reference[18] and were found to be 0.10 and 0.16, respectively, in methanol.

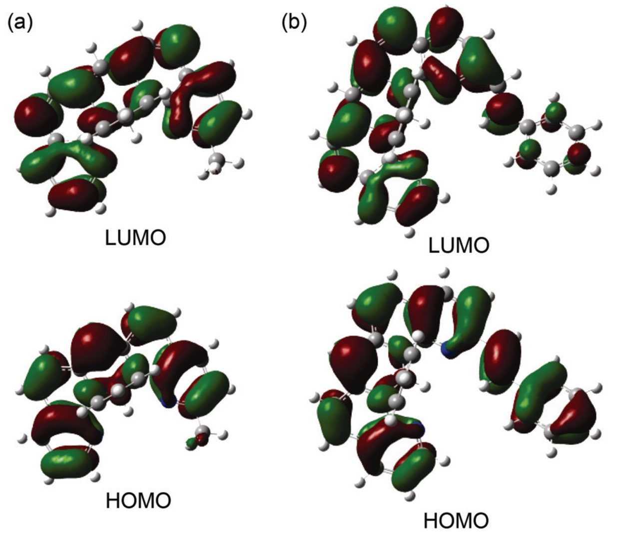


Figure 6 Diagrams showing HOMO and LUMO of compounds (a) **7** and (b) **8**.

The HOMO-LUMO transition in **8** was a charge-transfer transition from the phenyl group to another part of the plane (Figure 6b). Such a large conjugated system with a D-π-A structure may have obvious TPA.[19] As shown in Figure 7, the maximum TPA cross-section value for **7** was only 24 GM (1 GM$=1\times10^{-50}$ cm^4•s•photon^{-1}), but **8** had far better TPA properties, with a maximum cross-section of 287 GM at 740 nm, corresponding to the peak at 377 nm in the single-photon absorption spectrum. The two-photon-excited fluorescence was similar to the single-photon-excited one (Figure S4). The experimental ln(emission intensity)-ln(laser power) fits a linear relation well, with a slope of 1.94, illustrating a two-photon-excited transition process.[20]

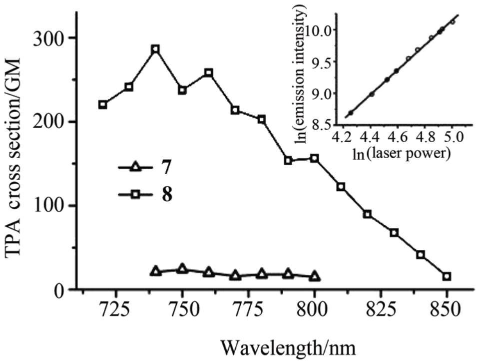


Figure 7 The TPA spectra of **7** and **8** in methanol. The inset shows the linear dependence of ln(emission intensity) on ln(laser power) for **8** upon excitation at 800 nm.

Conclusions

In summary, four novel naphthyridine derivatives were obtained. Compounds **7** and **8**, which have a positive charge and condensed aromatic rings, are the first known naphthyridine derivatives to display low-energy absorptions and red emissions in the visible-light region, and have TPA and TPEF properties. A mechanism for the synthesis reaction is proposed, and the results of optimized experiments showed that the ratio of acid and benzaldehyde is a decisive factor in improving the yields of **7** and **8**. The new compounds could be developed for applications in fields such as *in-situ* fluorescence microscopy because of their TPEF properties and potential biocompatibilities.

Electronic Supplementary Information (ESI) available

The details of the crystallographic data of compounds **3** and **4** (CCDC reference numbers 776818 and 776817), theoretical calculations for compounds **7** and **8**, and other spectra for characterizations of new compounds.

Acknowledgement

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