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Synthesis and characterization of 5-substituted 8-hydroxyquinoline derivatives and their metal complexes

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ABSTRACT

5-Aminomethyl-8-hydroxyquinoline (QN) was synthesized as a scaffold to generate dimers, trimers, and tetramer metalloquinolates. Starting from QN, a series of 5-substituted 8-hydroxyquinoline derivatives conjugated with small bioactive molecules were synthesized. Absorption and emission spectra indicate that these QN derivatives chelate well with metal ions, which may serve as a new platform to explore the applications of metalloquinolates for a variety of potential applications.

1. Introduction

8-Hydroxyquinoline, a monoprotic bidentate chelating agent, has received increased attention recently because its most representative metalloquinolate, aluminum tris(8-hydroxyquinoline) (AlQ_3), has served as the emitting material in organic light emitting diodes (OLEDs).[1] Due to their high thermal stability, excellent electron-transport properties, and unique luminescent properties,[2,3] many derivatives of 8-hydroxyquinoline (for example, substituted at 2, 5, or 7 position, or coordinated with different metal ions) have also attracted considerable interest. The importance of metalloquinolates in analytical chemistry is also well known.[4] In addition, a large number of 8-hydroxyquinoline derivatives have been synthesized and shown to be bioactive. For example, it was reported that some 8-hydroxyquinoline derivatives possess antitumor and antimicrobial activities.[5] Shen and co-workers designed and synthesized 7-morpholinomethyl-8-hydroxyquinoline, which inhibited the DNA synthesis in HepG2 cells at micromolar concentrations. Keppler and co-workers investigated the effect of gallium tris(8-hydroxyquinoline) (GaQ_3) on the viability of A549 human malignant lung adenocarcinoma cells and found that the half-maximal inhibitory concentration (IC_{50}) value of GaQ_3 was 2.5 μM. Recently, Fridkin and co-workers synthesized a series of novel iron chelators that contain the 8-hydroxyquinoline moiety, and these chelators exhibited high antioxidant properties and might serve as potential drug candidates for treating Parkinson's disease.

In order to further explore the biological applications of the metalloquinolates, which combine metal coordination, receptor/ligand interactions, and luminescent properties, we designed and synthesized a series of novel 8-hydroxyquinoline derivatives with substitution at the 5-position (Scheme 1) and examined their spectral properties and chelating abilities with different metal ions. We synthesized 5-aminomethyl-8-hydroxyquinoline (QN, **1**) as the scaffold to generate dimers, trimers, and tetramer metalloquinolates (**2**–**4**). Starting from QN (**1**), we also synthesized (9*H*-fluoren-9-yl)methyl(8-hydroxyquinolin-5-yl) methylcarbamate (QFmoc, **5**) and (*S*)-2-[(*S*)-2-amino-3-phenylpropanamido]-*N*-((8-hydroxyquinolin-5-yl)methyl)-3-phenylpropanamide (QFF, **9**) and studied their chelating properties with bivalent and trivalent metal ions (**7**, **10**, **11**) because they might self-assemble to form fluorescent hydrogels.[6] In addition, we synthesized QN derivatives conjugated with small bioactive molecules (**6**, **8**, **12**–**17**). Absorption and emission spectra indicate that these QN derivatives maintain good abilities to chelate metal ions, which may serve as a new platform to explore the applications of metalloquinolates for various applications.

2. Results and discussion

2.1. Synthesis

Scheme 2 shows the synthesis of 5-aminomethyl-8-hydroxyquinoline (QN, **1**). Derivatization on the 5-position of 8-hydroxyquinoline

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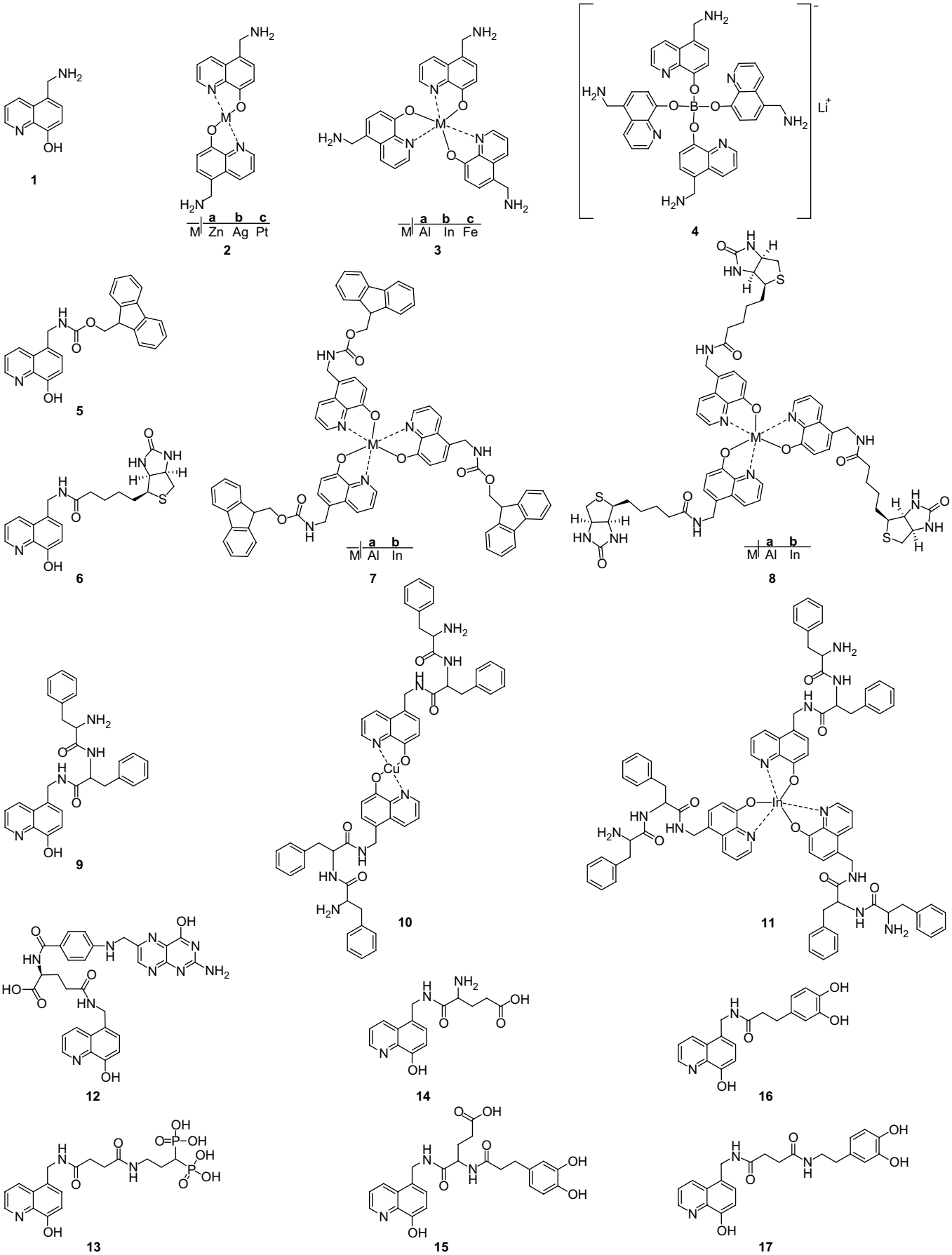
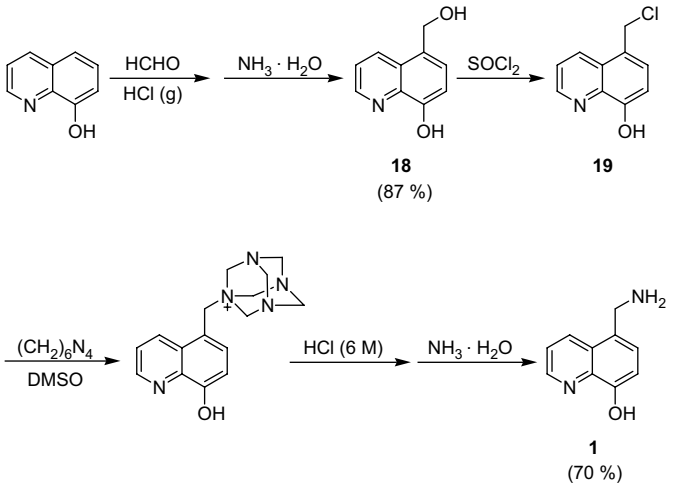


Scheme 1. The structures of the 8-hydroxyquinoline derivatives and their metal chelate complexes.

was based on the method proposed by Buckhalter and Leib.[7] Several papers suggested that the preparation of the free base **19** from its hydrochloride salt could be carried out by treating the hydrochloride salt with sodium hydrogen carbonate ($NaHCO_3$).[8] However, **19** was unstable and readily underwent hydrolysis to form **18**, especially in basic conditions.[7] Hence, **18** was prepared as a precursor for long time storage and converted to **19** by simply reacting with thionyl chloride before the amination reaction. The conversion of the chloromethylation product **19** to the aminomethylation product **1** followed the procedure of amination of benzyl halides by using hexamine as the amination reagent.[9] The reaction of **19** was carried out at room temperature because it would be converted to 5,5′-methylene bis-8-hydroxyquinoline if it was heated under reflux.[7] In the final hydrolysis process, before adjusting the pH value, large amount of HCl was still present in the solution. Therefore, when ammonia was added, the heat generated by acid–base neutralization would cause side reactions. In order to resolve this problem, methanol was used to wash the hydrolysis product before adjusting its pH to get the target product, **1**.



Scheme 2. The synthesis of 5-aminomethyl-8-hydroxyquinoline (QN, **1**).

As shown in Scheme 3, QN (**1**) reacted with (9*H*-fluoren-9-yl)-methyl chloroformate (Fmoc-Cl) in a mixture of dimethylformamide (DMF) and sodium hydrogen carbonate ($NaHCO_3$) aqueous solution at room temperature to give QFmoc (**5**) in 64% yield.

Scheme 4 shows the general synthetic route of coupling of QN (**1**) with several small bioactive molecules using 2-(1-hydroxybenzotriazol-1-yl)-l,l,3,3-tetramethyluronium hexafluorophosphate (HBTU) as the coupling reagent. Compounds **6** (QB, the conjugate of QN with biotin), **12** (QFA, the conjugate of QN with folic acid), and **16** (QN–Dopa, the conjugate of QN with a carboxylic acid analogue of dopamine) were obtained directly via HBTU mediated condensation reactions. Compound **9** (QFF, the conjugate of QN with L-Phe–L-Phe) was obtained after deprotecting the Fmoc group from the condensation product (**20**). Compound **13** (QN–bisP, the conjugate of QN with a bisphosphonate derivative) was obtained after deprotecting the ethyl groups from the condensation product (**21**). All these compounds were purified using reversed-phase HPLC.

Scheme 5 shows the general synthetic route of the coupling of QN (**1**) with small bioactive molecules by reacting with the *N*-hydroxysuccinimide (NHS) activated esters of the corresponding carboxylic acids. Compound **17** (QN–Su-Dopa, the conjugate of QN with the succinic acid derivative of dopamine) was obtained after deprotecting the benzyl groups from the condensation product **23**. Compound **24** was obtained after deprotecting the Fmoc group from the condensation product **22**. Deprotecting the Boc group from **24** afforded compound **14** (QG, the conjugate of QN with glutamate). Reacting **24** with the carboxylic acid analogue of dopamine then deprotecting the Boc group yielded QG-Dopa (**15**). All of the compounds were purified using reversed-phase HPLC.

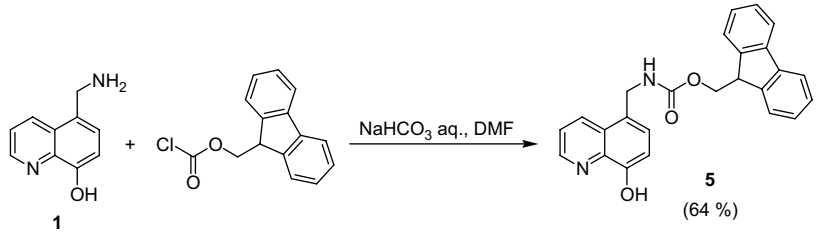
The target compounds were characterized by ^{1}H NMR spectroscopy, mass spectrometry (MS), UV–vis spectroscopy, and fluorescence spectroscopy. After the conjugates formed, the amino group of QN (**1**) was converted to the amide bond, as a result, the chemical shift of the protons on the methylene group of **1** (δ=4.1 ppm) moved to down field (δ=4.6–4.7 ppm), which was a characteristic property in their ^{1}H NMR spectra.

2.2. Formation of metalloquinolates and their spectral properties

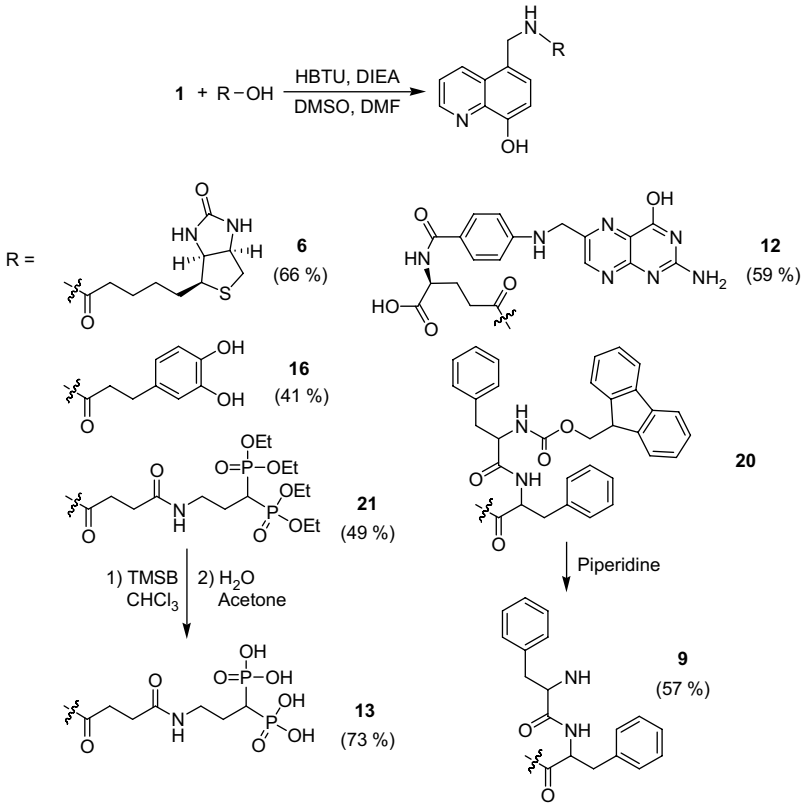
By modifying the typical procedures,[10,11] we used UV–vis and fluorescence spectra to examine the formation of the metalloquinolates. The photophysical properties of 8-hydroxyquinoline derivatives have been extensively studied.[12] Their absorption spectra share a common feature: a very intense band lies around the 250 nm region, which is attributed to a π–π^* transition, while a less intense and broader band lies at lower energy (above 300 nm). After metal coordination, the peaks usually show red-shift. The fluorescence properties of metalloquinolates also have long been known.[13] In their fluorescence spectra, hydroxyquinoline derivatives exhibit a fluorescence band in the 360–520 nm region.

Figure 1 shows the absorption spectra of QN (**1**) and M(QN)s (**2a**, **3a**–**c**) obtained in methanol. After **1** chelated with metal ions, the higher energy transition bands of QN (**1**) red-shifted from 245 nm to 259 nm; the lower energy bands red-shifted to a longer wavelength from the 325 nm of **1**. Such red-shifts are characteristic for metalloquinolates,[10,11,14,15] which are 390, 380, 386 nm for $Zn(QN)_2$ (**2a**),[10] $Al(QN)_3$ (**3a**),[10,14,15] and $In(QN)_3$ (**3b**),[10,14] respectively. For $Fe(QN)_3$ (**3c**), three bands appear at 375, 460, and 590 nm, which are characteristic for iron quinolate.[15]

Figure 2 shows the fluorescent spectra of QN (**1**), $Zn(QN)_2$ (**2a**), $Al(QN)_3$ (**3a**), and $In(QN)_3$ (**3b**) in methanol at the similar concentration based on [QN]. The typical shifts of the emission peaks of metalloquinolates[10,13,16] were observed. As the covalent nature of the metal–ligand bonds increases, the emission shifts to longer wavelength relative to the emission of QN (**1**) at 435 nm. As a result, $Al(QN)_3$ (**3a**) emits at 511 nm, $In(QN)_3$ (**3b**) at 542 nm, and $Zn(QN)_2$ (**2a**) at 558 nm (**2a**). Although the concentrations of these compounds are similarly based on [QN], metalloquinolates exhibit obviously enhancement of the fluorescent intensity comparing



Scheme 3. The synthesis of (9*H*-fluoren-9-yl)methyl(8-hydroxyquinolin-5-yl) methylcarbamate (QFmoc, **5**).



Scheme 4. The general synthetic route of coupling of QN (**1**) with small bioactive molecules using HBTU as the coupling reagent.

with that of the monomer **1**, and the complexes of trivalent metal ions (**3a** and **3b**) show higher enhancement than that of divalent metal ions (**2a**). As the same group of metal ions, fluorescence intensity decreases with the increase of atomic number. For example, the emission of $Al(QN)_3$ (**3a**) has higher intensity than that of $In(QN)_3$ (**3b**). Figure 3 shows the fluorescent spectra of QN (**1**) at different Al^{3+} concentrations. A significant enhancement of the fluorescence is observed with the increase of the Al^{3+} concentrations.

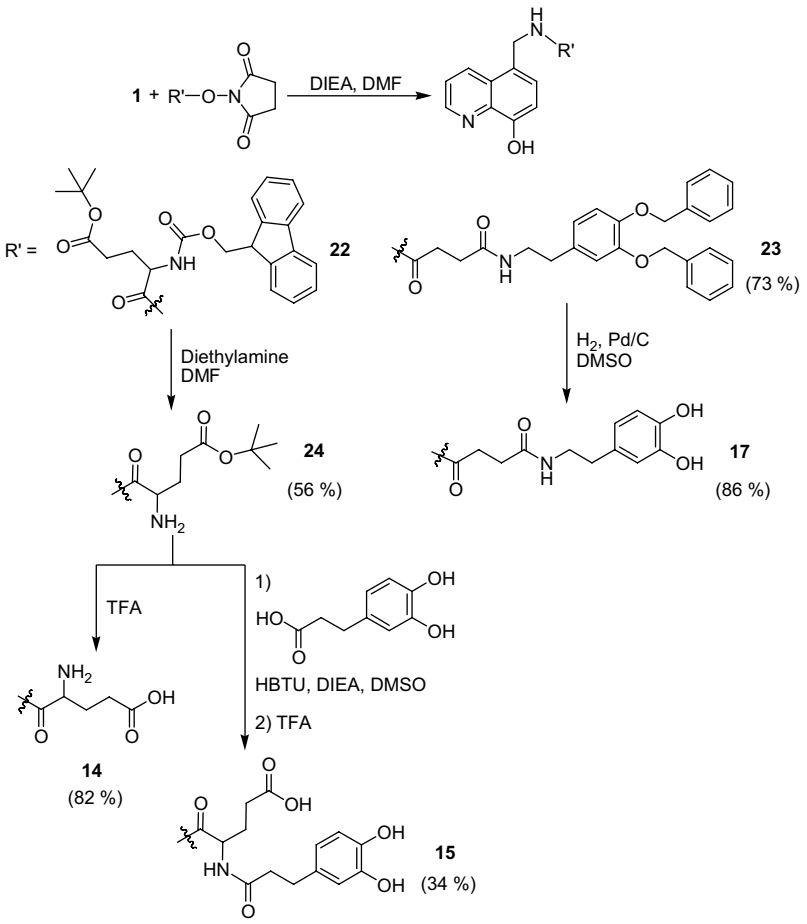
Besides using Zn, Al, In, and Fe as the metal centers to generate metalloquinolates, we also studied other metal ions, such as Ag and Pt. Silver/platinum-containing antibiotics were widely studied for decades.[17] The self-assembly of a silver(I) polymer based on derivatives of 8-hydroxyquinoline[18] and an organogelator constructed using an 8-hydroxyquinoline/platinum(II) chelate[3,19] have been reported recently. In order to explore the self-assembly of 8-hydroxyquinoline derivatives in water for generating novel antibiotics, we designed silver–QN and platinum–QN templates. It is known that the peaks of metalloquinolates at lower energy (above 300 nm) usually show red-shifts after metal coordination.[10,11,14,15,20] Based on this property, the synthesis can be monitored using UV–vis absorption spectra.

Using silver acetate as the source of silver, $Ag(QN)_2$ (**2b**) was produced in DMF. UV–vis spectra of the reaction process indicated a high conversion of QN (**1**) to **2b**, which was stable in basic condition (Fig. 4). According to the reported procedure,[3] synthesis of $Pt(QN)_2$ (**2c**) was carried out in a basic solution containing K_2PtCl_4. UV–vis spectra indicated a modest conversion (Fig. 5).

Besides generating the dimers and trimers, we also synthesized a tetramer of QN. According to a reported tetramerization of 8-hydroxyquinoline derivative constructed with boron, which was a blue electroluminescence material,[21] we synthesized $LiB(QN)_4$ (**4**), in which only oxygen atoms of QN coordinated to the central boron atom. The emission peak of **4** (451 nm) is about 60 nm blue shifted comparing with that of $Al(QN)_3$ (**3a**) (511 nm) (Fig. 6), as the similar trend as the results reported by Tao.[21] However, **4** is unstable in water. As shown in Figure 7, after treating **4** with water, the absorption peak of **4** was just the same as that of QN (**1**), indicating a decomposition of **4** to its precursor **1** in water.

In our research on the small molecule hydrogels, we have successfully demonstrated hydrogelators based on Fmoc,[22] Nap,[23] and Phe–Phe.[24] In order to explore the hydrogelation generated via the interactions of metalloquinolates for searching potential hydrogelator moieties, we synthesized QFmoc (**5**) and QFF (**9**), and studied their chelating properties with bivalent and trivalent metal ions. Figure 8 shows the fluorescent spectra of QN (**1**), QFmoc (**5**), and $Al(QFmoc)_3$ (**7a**). Compound **5**, the Fmoc derivative of **1**, exhibits the same emission peak (434 nm) as **1** (435 nm), and the typical shift of the emission peaks of metalloquinolates[10,13,16] also shows on the aluminum chelate complex **7a** (538 nm). Figures 9 and 10 show the UV–vis spectra of the chelating process of Cu(II) and In(III) with QFF (**9**). The characteristic absorption peaks completely red-shifted from the 321 nm of **9** to 400 and 390 nm for $Cu(QFF)_2$ (**10**) and $In(QFF)_3$ (**11**), respectively, after 2 h, indicating a fast and complete conversion.

Unfortunately, both **5** and **9** could not form hydrogels before or after chelating with the metal ions (Cu^{2+} and In^{3+}). The possible reasons could be: (i) the 8-hydroxyquinoline platform contains a nitrogen and a hydroxyl moiety on the 8-hydroxyquinoline ring that might disfavor efficient π–π interactions between the rings; (ii) in the complexes of trivalent metal ions, the three 8-hydroxyquinoline rings around the central metal result in nonplanar arrangment,[25] which disfavors the packing of the QN to form nanofibers; (iii) in the complexes of divalent metal ions, their



Scheme 5. The general synthetic route of coupling of QN (**1**) with small bioactive molecules by reacting with the NHS activated esters of corresponding carboxylic acids.

square-planar chelate structures would favor gel formation. However, the 8-hydroxyquinoline moiety might be too hydrophilic to form a hydrogel.

In order to explore the potential applications of 8-hydroxyquinoline systems, we also synthesized QN derivatives conjugated with small bioactive molecules, such as biotin,[26] folic acid,[27] bisphosphonates,[28] and glutamate.[29] Spectral properties of those conjugates were studied as the preliminary information for further exploration. Figure 11 shows the fluorescent spectra of these QN derivatives. These conjugates exhibit similar emission peaks as QN (435 nm). QB (**6**) emits peak at 430 nm, QFA (**12**) at 455 nm, QN–bisP (**13**) at 446 nm, and QG (**14**) at 441 nm. The fluorescent spectrum of Al(QB)$_3$ (**8a**) (Fig. 12) and the UV–vis spectra of the chelating process

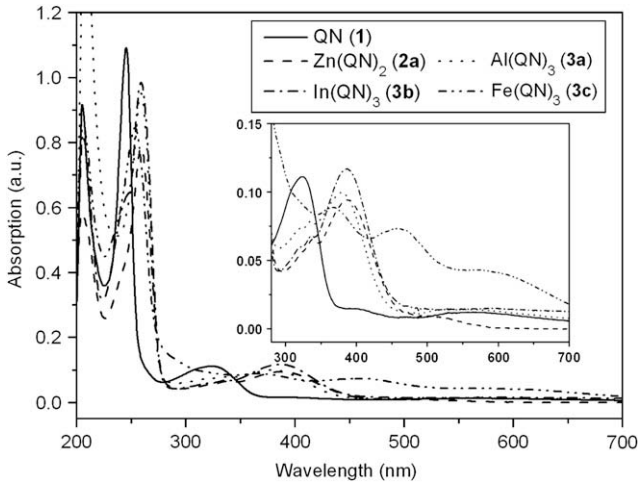


Figure 1. The absorption spectra of QN (**1**) and M(QN)s (**2a**, **3a**–**b**) in methanol at room temperature.

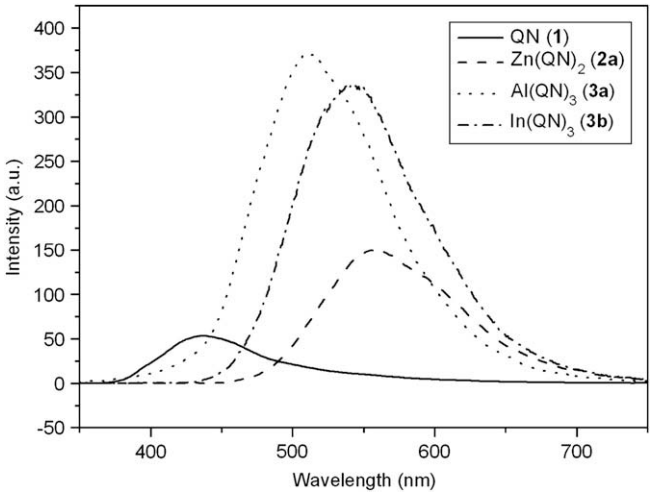


Figure 2. The fluorescent spectra (λ_{ex}=325 nm) of QN (**1**), Zn(QN)$_2$ (**2a**), Al(QN)$_3$ (**3a**), and In(QN)$_3$ (**3b**) in methanol at room temperature and at the concentration (based on QN) of 1.149, 1.161, 0.928, and 1.079 mM for **1**, **2a**, **3a**, and **3b**, respectively.

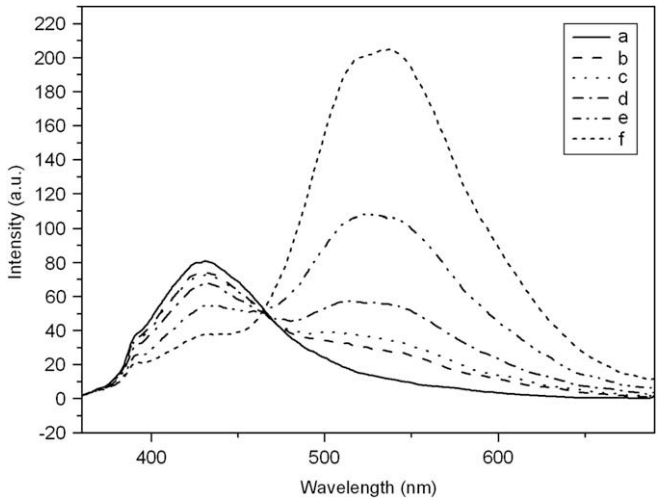


Figure 3. The fluorescent spectra (λ_{ex}=350 nm) of QN (**1**) in ethanol (0.200 μM) at room temperature upon addition of increasing amounts of Al^{3+} ions. The ratio of Al^{3+} to QN (**1**) is (a) 0, (b) 0.03, (c) 0.04, (d) 0.08, (e) 0.17, and (f) 0.33.

of In(QB)$_3$ (**8b**) (Fig. 13) exhibit the typical shift of the emission[10,13,16] and absorption[10,11,14,15,20] peaks of metalloquinolates.

3. Conclusion

In summary, starting from 5-aminomethyl-8-hydroxyquinoline (QN, **1**), we have synthesized a series of 8-hydroxyquinoline derivatives that can chelate with different metal ions and conjugate covalently with various small molecules for the further exploration of their potential applications. According to their absorption and emission spectra, these conjugates maintain good abilities to chelate metal ions, suggesting that QN would potentially serve as a useful scaffold to construct multivalent receptors, a subject is being investigated.

4. Experimental

4.1. General

Chemical reagents and solvents were used as received from commercial sources unless otherwise stated. Reversed-Phase HPLC (RP-HPLC) was carried out with Waters 600 Controller and 996 photodiode Array Detector, using XTerra RP18 C18 7 μm columns for both analytical and preparative purposes. HPLC elution employed linear gradients of [0.1% trifluoroacetic acid (TFA) in water] and [0.1% TFA in acetonitrile]. ^{1}H NMR and ^{31}P NMR spectra were obtained on a 300 MHz Bruker ARX 300 in DMSO-d_6 or D_2O. Mass spectra were obtained on a Finnigan TSQ7000 System. UV–vis spectra were obtained on a Varian Cary 50 Scan UV–Visible spectrophotometer. Fluorescent spectra were taken on a Perkin–Elmer LS-55 luminance spectrometer. Transmission electron micrograph (TEM) was done on a JEOL 2010 transmission electron microscope, operating at 200 kV.

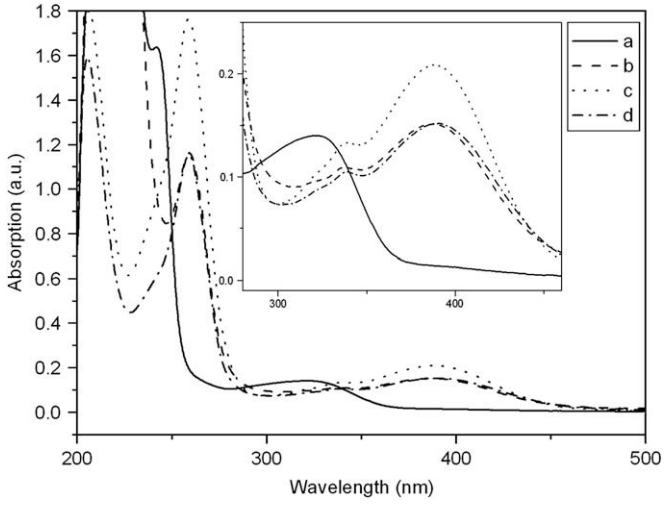


Figure 4. The absorption spectra for monitoring the synthesis of Ag(QN)$_2$ (**2b**). (a) Before adding silver acetate; (b) 4 h after adding silver acetate; (c) after adjusting pH to 8; (d) after adjusting pH to 10.

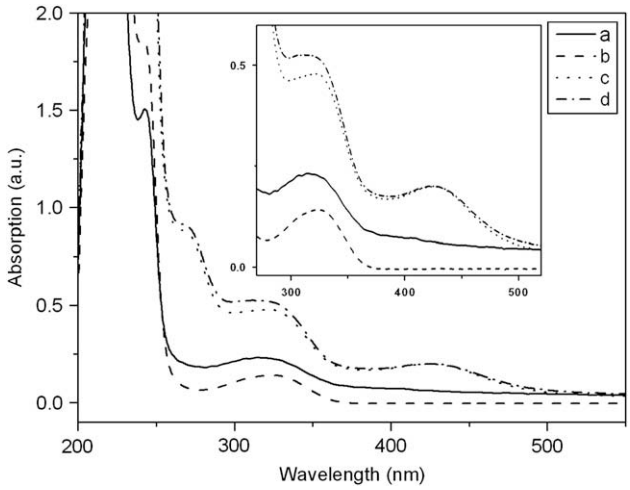


Figure 5. The absorption spectra for monitoring the synthesis of Pt(QN)$_2$ (**2c**). (a) Before adding K_2PtCl_4; (b) 5 h after adding K_2PtCl_4, rt; (c) 22 h, 80 °C; (d) 24 h, 80 °C.

4.2. Synthesis

*4.2.1. 5-Hydroxymethyl-8-hydroxyquinoline (**18**)*

A mixture of 7.37 g (0.0508 mol) of 8-hydroxyquinoline, 16 mL (0.526 mol) of concentrated hydrochloric acid, and 8 mL (0.290 mol) of 37% formaldehyde was treated with hydrogen chloride gas and stirred overnight. The solvent was stripped off and then treated with 15 mL of water. The pH value was adjusted to 10 by using ammonia. The mixture was filtered and dried to give the title compound **18** (7.71 g, 87%) as a white solid; mp 138–140 °C. IR

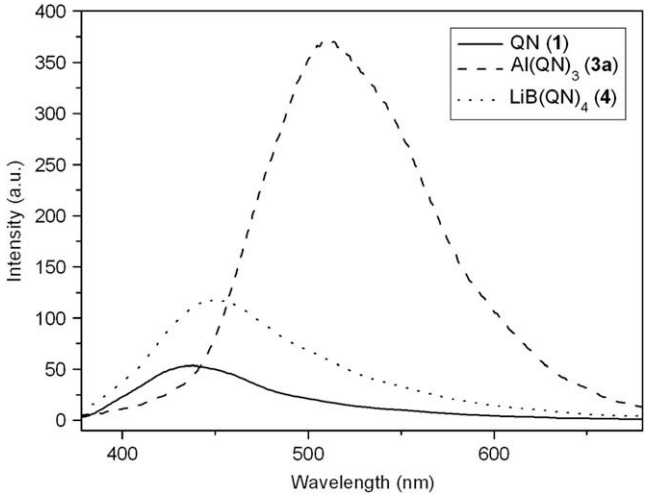


Figure 6. The fluorescent spectra (λ_{ex}=325 nm) of QN (**1**), Al(QN)$_3$ (**3a**), and LiB(QN)$_4$ (**4**) in methanol at room temperature.

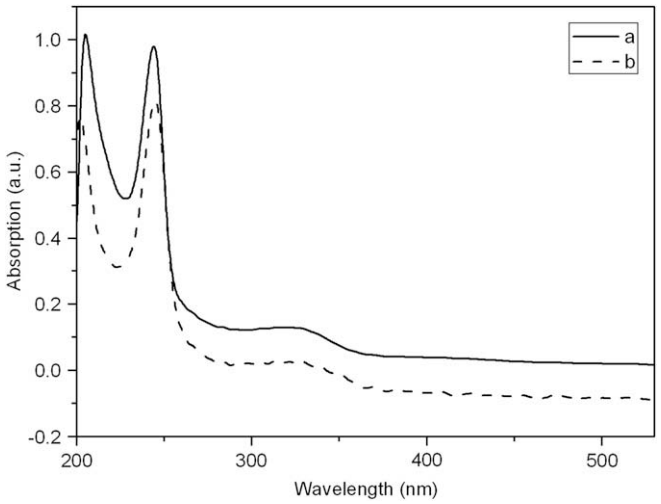


Figure 7. The absorption spectra of (a) QN (**1**) and (b) water treated $LiB(QN)_4$ (**4**) in methanol at room temperature.

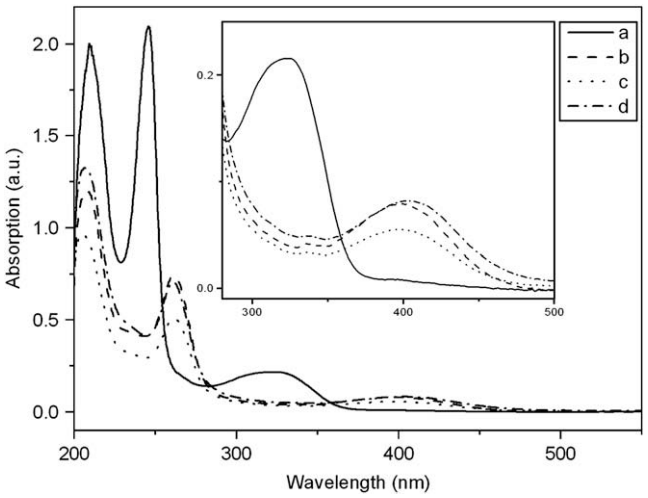


Figure 9. The absorption spectra for monitoring the synthesis of $Cu(QFF)_2$ (**10**). (a) Before adding $CuCl_2$ (pH=5.6); (b) 2 h after adding $CuCl_2$; (c) 20 h after adding $CuCl_2$; (d) after adjusting pH to 10.

(cm^{-1}): 3031, 2726, 1578, 1522, 1430, 1338, 1000. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.85 (1H, d, J=4.1 Hz, Ar–*H*), 8.51 (1H, d, J=8.5 Hz, Ar–*H*), 7.57 (1H, dd, J=8.5, 4.1 Hz, Ar–*H*), 7.40 (1H, d, J=7.8 Hz, Ar–*H*), 7.00 (1H, d, J=7.8 Hz, Ar–*H*), 4.82 (2H, s, ArCH_2OH). HRMS: $[M+H]^+$ calcd for $C_{10}H_{10}NO_2$: 176.0712, found: 176.0699.

4.2.2. 5-Aminomethyl-8-hydroxyquinoline (QN, *1*)

Compound **18** (1.03 g, 5.87 mmol) was treated by 30 mL of thionyl chloride. The mixture was stirred at room temperature for 6 h. The solvent was stripped off to give 5-chloromethyl-8-hydroxyquinoline (**19**) as a yellow solid. Compound **19** (1.13 g, 5.87 mmol) was dissolved in 45 mL of DMSO (dried). Hexamine (1.60 g, 11.4 mmol) was added into the yellow solution. The mixture was stirred at room temperature overnight, then filtered to remove the white solid (hexamine). The yellowish green filtrate was dried to give a green solid, then was dissolved into 25 mL of 6 M HCl. The yellow solution was stirred at room temperature for about two days. The solvent was stripped off and the yellow solid was washed by 12 mL of methanol and then filtered. The filtrate was evaporated and washed by 8 mL of methanol again. The combined solid was dissolved in 20 mL of water. The pH value was adjusted from 4 to 10 using ammonia. The mixture was filtered and dried to give the title compound **1** (710 mg, 70%) as a yellow solid; mp 98–99 °C. IR (cm^{-1}): 3292, 3018, 2653, 1560, 1508, 1457, 1298, 1077. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.84 (1H, d, J=4.1 Hz, Ar–*H*), 8.55 (1H, d, J=8.5 Hz), 7.57 (1H, dd, J=8.5, 4.1 Hz, Ar–*H*), 7.42 (1H, d, J=7.8 Hz, Ar–*H*), 7.01 (1H, d, J=7.8 Hz, Ar–*H*), 4.10 (2H, s, ArCH_2NH_2). HRMS: $[M+H]^+$ calcd for $C_{10}H_{11}N_2O$: 175.0871, found: 175.0955.

4.2.3. (9H-Fluoren-9-yl)methyl(8-hydroxyquinolin-5-yl)-methylcarbamate (QFmoc, *5*)

QN (**1**) (209 mg, 1.19 mmol) was dissolved in 15 mL DMF, followed by the addition of $NaHCO_3$ (150 mg, 1.79 mmol) aqueous solution. (9*H*-Fluoren-9-yl)methyl chloroformate (333 mg, 1.29 mmol) was dissolved in 4 mL of DMF, then was added dropwise to the reaction solution. The reaction was stirred overnight; 20 mL of water was added. A yellow solid was precipitated and filtered out; 10 mL of methanol and 10 mL of diethyl ether were used to wash it to give the title compound **5** (301 mg, 64%) as a yellow solid; mp 124–126 °C. IR (cm^{-1}): 3286, 3083, 2780, 1701, 1599, 1512, 1397, 1314, 1185, 1017. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.85 (1H, d, J=3.3 Hz, Ar–*H*), 8.49 (1H, d, J=8.3 Hz, Ar–*H*),

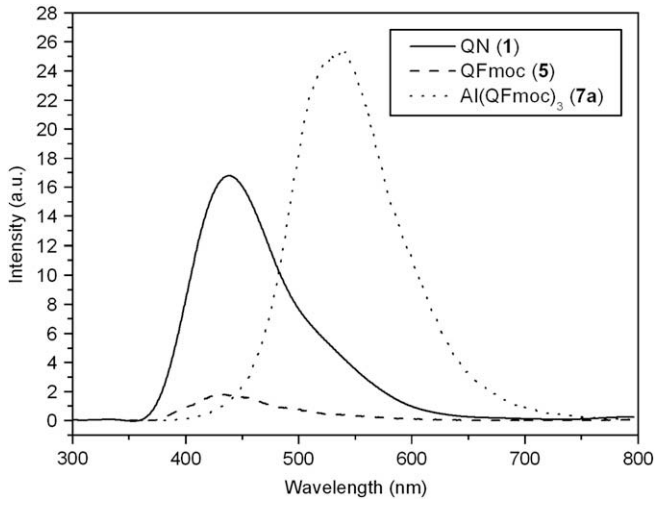


Figure 8. The fluorescent spectra (λ_{ex}=325 nm) of QN (**1**), QFmoc (**5**), and $Al(QFmoc)_3$ (**7a**) in methanol at room temperature.

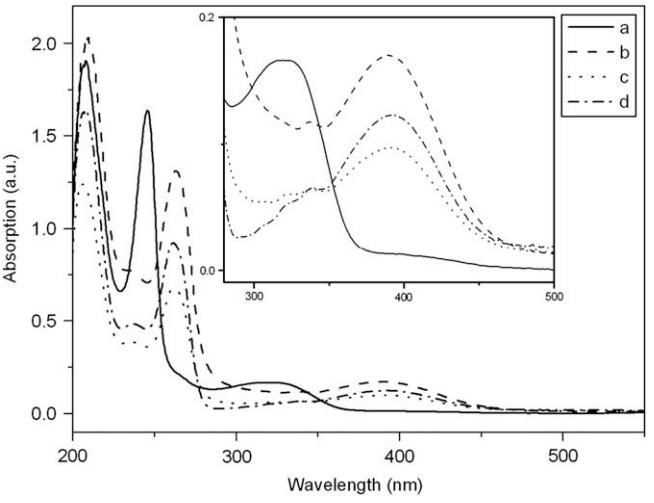


Figure 10. The absorption spectra for monitoring the synthesis of $In(QFF)_3$ (**11**). (a) Before adding $InCl_3$ (pH=5.6); (b) 2 h after adding $InCl_3$; (c) 24 h after adding $InCl_3$; (d) after adjusting pH to 10.

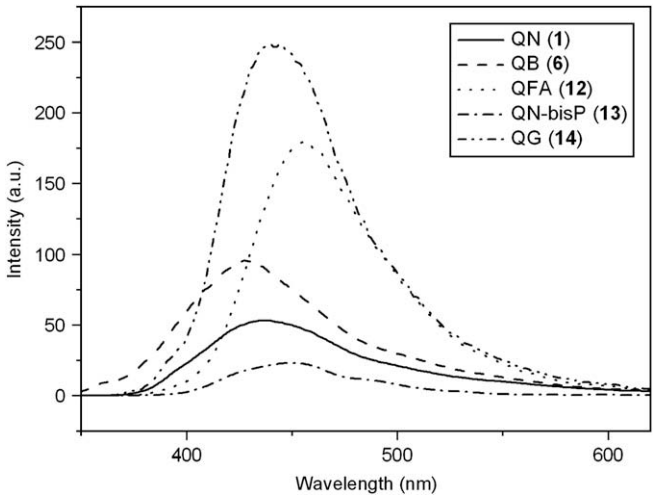


Figure 11. The fluorescent spectra (λ_{ex}=325 nm) of QN (**1**), QB (**6**), QFA (**12**), QN–bisP (**13**), and QG (**14**) in methanol at room temperature.

7.87 (2H, d, *J*=7.4 Hz, Ph), 7.66 (2H, d, *J*=7.3 Hz, Ph), 7.58 (1H, dd, *J*=8.3, 3.3 Hz, Ar–*H*), 7.41–7.25 (5H, m, Ph, Ar–*H*), 7.01 (1H, d, *J*=7.7 Hz, Ar–*H*), 4.53 (2H, s, ArCH_2), 4.33 (2H, d, *J*=6.3 Hz, CHCH_2CO), 4.20 (1H, t, *J*=6.3 Hz, C*H*CH$_2$CO). HRMS: $[M+H]^+$ calcd for $C_{25}H_{21}N_2O_3$: 397.1552, found: 397.1465.

*4.2.4. QN–biotin conjugate (QB, **6**)*

QN (**1**) (87.4 mg, 0.502 mmol) and D-(+)-biotin (123 mg, 0.504 mmol) were dissolved in 5 mL of DMSO (dried). The mixture was cooled to 0 °C and HBTU (252 mg, 0.664 mmol) in 2 mL of DMF (dried) was added, followed by *N*,*N*-diisopropylethylamine (DIEA) (0.41 mL, 2.4 mmol). The mixture was allowed to rise to room temperature and stirred overnight. The reaction was quenched by adding dropwise 30 mL of acetone. A yellow solid was precipitated and filtered out; 10 mL of acetone was used to wash it once. The crude product was purified by RP-HPLC to give the title compound **6** (133 mg, 66%) as a yellow solid; mp 199–201 °C; $[\alpha]_D^{25}$ +46 (*c* 0.3, MeOH). IR (cm^{-1}): 3282, 3075, 2933, 2863, 1670, 1560, 1399, 1313, 1191, 1127. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.85 (1H, d, *J*=4.1 Hz, Ar–*H*), 8.44 (1H, d, *J*=8.5 Hz, Ar–*H*), 8.24 (1H, t, *J*=5.3 Hz, ArCH$_2$N*H*CO), 7.58 (1H, dd, *J*=8.5, 4.1 Hz, Ar–*H*), 7.36 (1H, d, *J*=7.8 Hz, Ar–*H*), 7.01 (1H, d, *J*=7.8 Hz, Ar–*H*), 6.37 (2H, d, *J*=15.6 Hz, CHN*H*CO), 4.59 (2H, d, *J*=5.3 Hz, ArCH_2NHCO), 4.30–4.26 (1H, m, (CH)$_2$C*H*NH), 4.08–4.05 (1H, m, (CH)$_2$C*H*NH), 3.05–2.99 (1H, m, CH$_2$C*H*CH), 2.80 (1H, dd, *J*=12.5, 4.9 Hz, SCH_aH$_b$CH), 2.56 (1H, d, *J*=12.5 Hz, SCH$_a$CH_bCH), 2.09 (2H, t, *J*=7.2 Hz, COCH_2CH$_2$), 1.54–1.24 (6H, m, COCH$_2$CH_2CH_2CH_2CHS). HRMS: $[M+H]^+$ calcd for $C_{20}H_{25}N_4O_3S$: 401.1647, found: 401.1694.

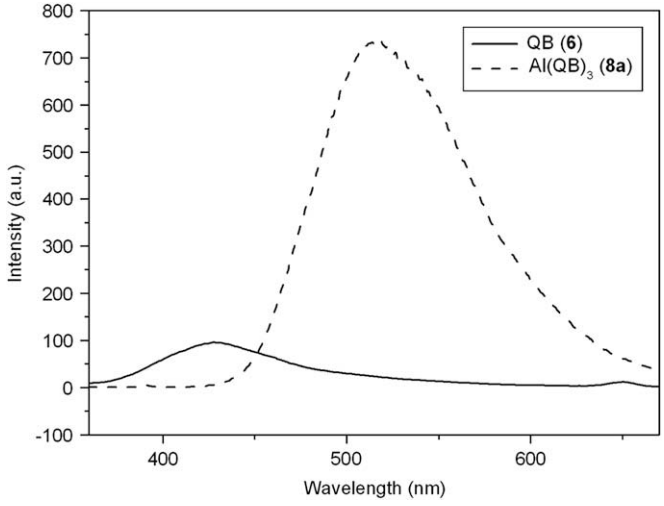


Figure 12. The fluorescent spectra (λ_{ex}=325 nm) of QB (**6**) and Al(QB)$_3$ (**8a**) in methanol at room temperature.

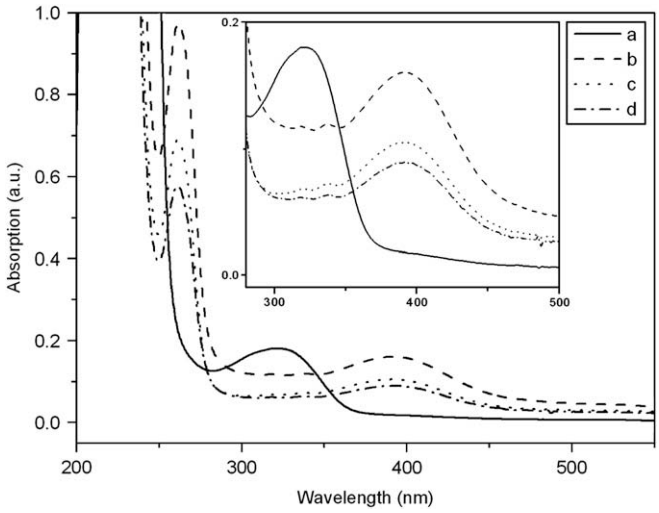


Figure 13. The absorption spectra for monitoring the synthesis of In(QB)$_3$ (**8b**). (a) Before adding InCl$_3$ (pH=5.6); (b) 2 h after adding InCl$_3$; (c) 18 h after adding InCl$_3$; (d) after adjusting pH to 10.

*4.2.5. (S)-2-[(S)-2-Amino-3-phenylpropanamido]-N-((8-hydroxyquinolin-5-yl)methyl)-3-phenylpropanamide (QFF, **9**)*

QN (**1**) (69.8 mg, 0.401 mmol) and Fmoc-L-Phe-L-Phe-OH (215 mg, 0.403 mmol) were dissolved in 5 mL of DMSO. HBTU (226 mg, 0.595 mmol) in 1 mL of DMF was added to the solution, followed by 0.30 mL (1.7 mmol) of DIEA. After stirring overnight, 8 mL of piperidine was added and stirred for another 6 h. The solvent was stripped off, and the crude product was purified using RP-HPLC to give the title compound **9** (107 mg, 57%) as a yellow solid; mp 185–188 °C; $[\alpha]_D^{25}$ +6.8 (*c* 0.5, MeOH). IR (cm^{-1}): 3282, 3052, 2963, 2667, 1636, 1560, 1508, 1455, 1374, 1240, 1077. ^{1}H NMR (300 MHz, D$_2$O) δ (ppm): 8.87 (1H, d, *J*=4.0 Hz, Ar–*H*), 8.29 (1H, d, *J*=8.6 Hz, Ar–*H*), 7.60 (1H, dd, *J*=8.6, 4.0 Hz, Ar–*H*), 7.41–7.28 (5H, m, Ph, Ar–*H*), 7.19–7.09 (6H, m, Ph), 6.91 (1H, d, *J*=7.6 Hz, Ar–*H*), 4.47 (2H, s, ArCH_2), 4.36 (1H, t, *J*=5.7 Hz, CH$_2$C*H*), 4.22 (1H, t, *J*=5.8 Hz, CH$_2$C*H*), 3.14–3.08 (2H, m, PhCH_2CH), 2.73–2.65 (2H, m, PhCH_2CH). HRMS: $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_3$: 469.2240, found: 469.2162.

*4.2.6. QN–folic acid conjugate (QFA, **12**)*

QN (**1**) (29.8 mg, 0.171 mmol) and folic acid (77.1 mg, 0.175 mmol) were dissolved by ultrasonic in 8 mL of DMSO to get a deep yellow solution. HBTU (87.7 mg, 0.231 mmol) in 1 mL of DMF was added to the solution, followed by 0.12 mL (0.69 mmol) of DIEA. The resultant clear yellow solution was stirred overnight and concentrated. The crude product was purified by RP-HPLC to give the title compound **12** (60.2 mg, 59%) as a yellow solid; mp 223–225 °C; $[\alpha]_D^{25}$ +14 (*c* 0.1, MeOH). IR (cm^{-1}): 3254, 3065, 2780, 1701, 1605, 1508, 1406, 1298, 1185. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.83 (1H, d, *J*=4.0 Hz, Ar–*H*), 8.62 (1H, s, Ar–*H*), 8.41 (1H, d, *J*=8.6 Hz, Ar–*H*), 8.29 (1H, t, *J*=5.6 Hz, ArCH$_2$N*H*CO), 8.04 (1H, d, *J*=6.9 Hz, CHN*H*CO), 7.63 (2H, d, *J*=7.9 Hz, Ph), 7.53 (1H, dd, *J*=8.6, 4.0 Hz, Ar–*H*), 7.37 (1H, d, *J*=7.7 Hz, Ar–*H*), 6.99 (1H, d, *J*=7.7 Hz, Ar–*H*), 6.92 (1H, t, *J*=5.7 Hz, PhN*H*CH$_2$Ar), 6.62 (2H, d, *J*=7.9 Hz, Ph), 4.59 (2H, d, *J*=5.6 Hz, ArCH_2NHCO), 4.47 (2H, d, *J*=5.7 Hz, PhNHCH_2Ar), 4.38–4.32 (1H, m, CH$_2$C*H*NHCO), 2.22 (2H, t, *J*=6.9 Hz, COCH_2CH$_2$), 1.95–1.89 (2H, m, COCH$_2$CH_2CH). HRMS: $[M+H]^+$ calcd for $C_{29}H_{28}N_9O_6$: 598.2163, found: 598.2190.

4.2.7. N^1-((8-Hydroxyquinolin-5-yl)methyl)-N^4-(3,3-di(ethoxyphosphono)propyl)succinamide (**21**)

QN (**1**) (23.6 mg, 0.136 mmol) and 3-(3,3-di(ethoxyphosphono)propylcarbamoyl)propanoic acid (57.4 mg, 0.133 mmol) were dissolved in 5 mL of DMSO to get a yellow solution. HBTU (72.9 mg, 0.192 mmol) in 1 mL of DMF was added to the solution, followed by 0.12 mL (0.69 mmol) of DIEA. The reaction was stirred overnight and concentrated. The crude product was purified by RP-HPLC to give the title compound **21** (38.3 mg, 49%) as a yellow solid; mp 280 °C (decomp.). IR (cm^{-1}): 3313, 3022, 2906, 2740, 1684, 1654, 1508, 1474, 1299, 1240, 1084, 1006. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.94 (1H, d, J=4.1 Hz, Ar–*H*), 8.74 (1H, d, J=8.4 Hz, Ar–*H*), 8.35 (1H, t, J=5.0 Hz, ArCH$_2$N*H*CO), 7.89 (1H, t, J=5.5 Hz, CH$_2$N*H*CO), 7.77 (1H, dd, J=8.4, 4.1 Hz, Ar–*H*), 7.48 (1H, d, J=7.8 Hz, Ar–*H*), 7.16 (1H, d, J=7.8 Hz, Ar–*H*), 4.63 (2H, d, J=5.0 Hz, ArC*H*$_2$-NHCO), 4.03 (8H, q, J=6.7 Hz, C*H*$_2$Me), 3.20–3.16 (2H, m, NHC*H*$_2$CH$_2$), 2.27 (4H, s, COC*H*$_2$C*H*$_2$CO), 1.89–1.79 (3H, m, CH$_2$C*H*$_2$C*H*), 1.22 (12H, t, J=6.7 Hz, Me). ^{31}P NMR (300 MHz, DMSO-d_6) δ (ppm): 23.5 (s). HRMS: $[M+H]^+$ calcd for $C_{25}H_{40}N_3O_9P_2$: 588.2240, found: 588.2247.

4.2.8. N^1-((8-Hydroxyquinolin-5-yl)methyl)-N^4-(3,3-bisphosphono propyl)succinamide (QN–bisP, **13**)

Compound **21** (19.2 mg, 0.0327 mmol) was dissolved in 4 mL of chloroform, followed by adding 0.07 mL (0.5 mmol) of trimethylsilyl bromide (TMSB). The reaction was stirred overnight and the solvent was evaporated under vacuum. Then, acetone with a small amount of water was added and stirred for another 30 min. After removing the organic solvent, hexane and chloroform were used to wash it and separated by extraction. The aqueous layer was collected and dried. The crude product was purified by RP-HPLC to give the title compound **13** (11.4 mg, 73%) as a yellow solid; mp 300 °C (decomp.). IR (cm^{-1}): 3345, 3040, 2898, 2836, 2726, 2645, 1684, 1618, 1578, 1522, 1430, 1372, 1280, 1246, 1162, 1083, 1000. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.93 (1H, d, J=3.9 Hz, Ar–*H*), 8.68 (1H, d, J=7.9 Hz, Ar–*H*), 8.44 (1H, t, J=5.2 Hz, ArCH$_2$N*H*CO), 7.92 (1H, t, J=5.7 Hz, CH$_2$N*H*CO), 7.72 (1H, dd, J=7.9, 3.9 Hz, Ar–*H*), 7.59 (1H, d, J=7.6 Hz, Ar–*H*), 7.30 (1H, d, J=7.6 Hz, Ar–*H*), 4.67 (2H, d, J=5.2 Hz, ArC*H*$_2$NHCO), 3.22–3.18 (2H, m, NHC*H*$_2$CH$_2$), 2.26 (4H, s, COC*H*$_2$C*H*$_2$CO), 1.91–1.74 (3H, m, CH$_2$C*H*$_2$C*H*). ^{31}P NMR (300 MHz, DMSO-d_6) δ (ppm): 20.6 (s). MS: $[M+H]^+$ calcd for $C_{17}H_{24}N_3O_9P_2$: 476.0988, found: 476.1002.

4.2.9. tert-Butyl 4-((8-hydroxyquinolin-5-yl)methylcarbamoyl)-4-aminobutanoate (**24**)

QN (**1**) (71.0 mg, 0.408 mmol) and Fmoc–Glu(O^{t}Bu)–NHS (209 mg, 0.401 mmol) were dissolved in 10 mL of DMF, followed by adding 0.30 mL (1.7 mmol) of DIEA. After stirring overnight, 10 mL of diethyl amine was added and stirred for another 4 h. The solvent was stripped off, and the crude product was purified using RP-HPLC to give the title compound **24** (80.5 mg, 56%) as a yellow solid; mp 127–130 °C; $[\alpha]_D^{25}$ −8.6 (c 0.5, MeOH). IR (cm^{-1}): 3398, 2978, 1727, 1698, 1541, 1450, 1367, 1292, 1153, 1062. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.92 (1H, d, J=4.3 Hz, Ar–*H*), 8.61 (1H, d, J=7.8 Hz, Ar–*H*), 8.16 (1H, t, J=5.6 Hz, ArCH$_2$N*H*CO), 7.71 (1H, dd, J=7.8, 4.3 Hz, Ar–*H*), 7.50 (1H, d, J=7.6 Hz, Ar–*H*), 7.12 (1H, d, J=7.6 Hz, Ar–*H*), 4.69 (2H, d, J=5.6 Hz, ArC*H*$_2$NHCO), 3.76 (1H, t, J=4.8 Hz, COC*H*CH$_2$), 2.18 (2H, t, J=5.2 Hz, CH$_2$C*H*$_2$CO), 1.95–1.87 (2H, m, CHC*H*$_2$CH$_2$), 1.35 (9H, s, Me). HRMS: $[M+H]^+$ calcd for $C_{19}H_{26}N_3O_4$: 360.1923, found: 360.1838.

4.2.10. 4-((8-Hydroxyquinolin-5-yl)methylcarbamoyl)-4-aminobutanoic acid (QG, **14**)

Compound **24** (52.0 mg, 0.145 mmol) was dissolved in 5 mL of methanol, followed by adding 10 mL of trifluoroacetic acid (TFA). After stirring overnight, the solvent was stripped off, and the crude product was purified using RP-HPLC to give the title compound **14** (36.1 mg, 82%) as a yellow solid; mp 153–155 °C; $[\alpha]_D^{25}$ +7.5 (c 0.2, MeOH). IR (cm^{-1}): 3246, 3076, 2938, 1718, 1684, 1560, 1458, 1399, 1202. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.93 (1H, d, J=4.2 Hz, Ar–*H*), 8.59 (1H, d, J=8.4 Hz, Ar–*H*), 8.20 (1H, t, J=5.3 Hz, ArCH$_2$-N*H*CO), 7.69 (1H, dd, J=8.4, 4.2 Hz, Ar–*H*), 7.49 (1H, d, J=7.8 Hz, Ar–*H*), 7.11 (1H, d, J=7.8 Hz, Ar–*H*), 4.65 (2H, d, J=5.3 Hz, ArC*H*$_2$NHCO), 3.77 (1H, t, J=4.7 Hz, COC*H*CH$_2$), 2.24 (2H, t, J=4.7 Hz, CH$_2$C*H*$_2$COOH), 1.95–1.88 (2H, m, CHC*H*$_2$CH$_2$). HRMS: $[M+H]^+$ calcd for $C_{15}H_{18}N_3O_4$: 304.1297, found: 304.1213.

4.2.11. 4-((8-Hydroxyquinolin-5-yl)methylcarbamoyl)-4-(3-(3,4-dihydroxyphenyl)propanamido)butanoic acid (QG–Dopa, **15**)

Compound **24** (27.2 mg, 0.0758 mmol) and 15.6 mg of 3-(3,4-dihydroxyphenyl)propionic acid (0.0856 mmol) were dissolved in 5 mL of DMSO to get a yellow solution. HBTU (40.0 mg, 0.106 mmol) in 1 mL of DMF was added to the solution, followed by 0.06 mL (0.3 mmol) of DIEA. The reaction was stirred overnight and concentrated. Acetone was added and then filtered. The solid was dissolved in 2 mL of DMSO, followed by adding 10 mL of TFA. After stirring overnight, the solvent was stripped off, and the crude product was purified using RP-HPLC to give the title compound **15** (11.9 mg, 34%) as a yellow solid; mp 182–184 °C; $[\alpha]_D^{25}$ +7.0 (c 0.2, MeOH). IR (cm^{-1}): 3311, 3068, 2928, 2870, 1718, 1654, 1508, 1458, 1264, 1136, 1021. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.89 (1H, d, J=4.1 Hz, Ar–*H*), 8.57 (1H, d, J=8.5 Hz, Ar–*H*), 8.34 (1H, t, J=5.3 Hz, ArCH$_2$N*H*CO), 7.97 (1H, d, J=5.7 Hz, CHN*H*CO), 7.65 (1H, dd, J=8.5, 4.1 Hz, Ar–*H*), 7.42 (1H, d, J=7.8 Hz, Ar–*H*), 7.08 (1H, d, J=7.8 Hz, Ar–*H*), 6.61–6.55 (2H, m, Ph), 6.42 (1H, d, J=7.9 Hz, Ph), 4.62 (2H, d, J=5.3 Hz, ArC*H*$_2$NHCO), 4.23–4.18 (1H, m, NHC*H*CH$_2$), 2.71–2.59 (4H, m, PhC*H*$_2$C*H*$_2$CO), 2.34–2.14 (4H, m, CHC*H*$_2$C*H*$_2$COOH). HRMS: $[M-H]^+$ calcd for $C_{24}H_{24}N_3O_7$: 466.1614, found: 466.1484.

4.2.12. 3-(3,4-Dihydroxyphenyl)-N-((8-hydroxyquinolin-5-yl)methyl)propanamide (QN–Dopa, **16**)

QN (**1**) (26.5 mg, 0.152 mmol) and 3-(3,4-dihydroxyphenyl)propionic acid (27.1 mg, 0.149 mmol) were dissolved in 4 mL of DMSO to get a yellow solution. HBTU (75.5 mg, 0.199 mmol) in 1 mL of DMF was added to the solution, followed by 0.10 mL (0.57 mmol) of DIEA. The reaction was stirred overnight and concentrated. The crude product was purified using RP-HPLC to give the title compound **16** (20.4 mg, 41%) as a yellow solid; mp 117–118 °C. IR (cm^{-1}): 3309, 3068, 2930, 2863, 1654, 1560, 1508, 1458, 1264, 1136, 1021. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.93 (1H, d, J=4.0 Hz, Ar–*H*), 8.66 (1H, d, J=7.5 Hz, Ar–*H*), 8.28 (1H, t, J=5.5 Hz, ArCH$_2$N*H*CO), 7.79 (1H, dd, J=7.5, 4.0 Hz, Ar–*H*), 7.35 (1H, d, J=7.8 Hz, Ar–*H*), 7.12 (1H, d, J=7.8 Hz, Ar–*H*), 6.58–6.53 (2H, m, Ph), 6.38 (1H, d, J=8.1 Hz, Ph), 4.61 (2H, d, J=5.5 Hz, ArC*H*$_2$NHCO), 2.64 (2H, t, J=7.2 Hz, COC*H*$_2$CH$_2$), 2.32 (2H, t, J=7.2 Hz, CH$_2$C*H*$_2$Ph). MS: $[M+H]^+$ calcd for $C_{19}H_{19}N_2O_4$: 339.1345, found: 339.1321.

4.2.13. N^1-(3,4-Bis(benzyloxy)phenethyl)-N^4-((8-hydroxyquinolin-5-yl)methyl)succinamide (**23**)

3-(3,4-Bis(benzyloxy) phenethylcarbamoyl)propanoic acid (99.1 mg, 0.229 mmol) and 27.0 mg (0.235 mmol) of NHS were dissolved in 3 mL of DMF, followed by adding 54.5 mg (0.264 mmol) of DCC. After stirring overnight, DCU was filtered out and the filtrate containing the NHS ester was used for the next step without further purification. QN (**1**) (39.4 mg, 0.226 mmol) was added to the solution, followed by adding 0.2 mL of DIEA. The reaction was stirred overnight and concentrated. The crude product was purified using RP-HPLC to give the title compound **23** (98.6 mg, 73%) as a yellow solid; mp 154–157 °C. IR (cm^{-1}): 3302, 3065, 2929, 1636, 1509, 1426, 1382, 1270, 1131, 1025. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.84 (1H, d, J=3.2 Hz, Ar–*H*), 8.43 (1H, d, J=7.6 Hz, Ar–*H*), 8.30 (1H, t, J=5.4 Hz, ArCH$_2$N*H*CO), 7.87 (1H, t, J=5.5 Hz, CH$_2$N*H*CO), 7.56 (1H, dd, J=7.6, 3.2 Hz, Ar–*H*), 7.44–7.29 (11H, m,

Ar–*H*, Ph), 7.00 (1H, d, *J*=7.8 Hz, Ar–*H*), 6.96–6.93 (2H, m, Ph), 6.70 (1H, d, *J*=7.5 Hz, Ph), 5.06 (4H, s, PhCH_2O), 4.58 (2H, d, *J*=5.4 Hz, ArCH_2NHCO), 3.21–3.14 (2H, m, NHCH_2CH_2), 2.57 (2H, t, *J*=7.3 Hz, CH_2CH_2Ph), 2.31 (4H, s, COCH_2CH_2CO). HRMS: $[M+H]^+$ calcd for $C_{36}H_{36}N_3O_5$: 590.2655, found: 590.2501.

4.2.14. N^1-(3,4-Dihydroxyphenethyl)-N^4-((8-hydroxyquinolin-5-yl)methyl)succinamide (QN–Su-Dopa, **17**)

Compound **23** (57.3 mg, 0.0973 mmol) was dissolved in 10 mL of DMSO, and 50 mg of the catalyst (10% Pd on charcoal) was added under nitrogen atmosphere. The reaction proceeded at room temperature under hydrogen atmosphere overnight. After removing the catalyst by filtration, the solution was concentrated to dryness. The crude product was purified by RP-HPLC to give the title compound **17** (34.1 mg, 86%) as a yellow solid; mp 185–187 °C. IR (cm^{-1}): 3297, 3068, 2930, 1654, 1554, 1516, 1431, 1212, 1130, 1041. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.85 (1H, d, *J*=4.2 Hz, Ar–*H*), 8.40 (1H, d, *J*=7.2 Hz, Ar–*H*), 7.56 (1H, dd, *J*=7.2, 4.2 Hz, Ar–*H*), 7.34 (1H, d, *J*=7.8 Hz, Ar–*H*), 7.03 (1H, d, *J*=7.8 Hz, Ar–*H*), 6.62–6.56 (2H, m, Ph), 6.37 (1H, d, *J*=7.6 Hz, Ph), 4.55 (2H, s, ArCH_2), 3.14 (2H, t, *J*=5.8 Hz, CH_2CH$_2$Ph), 2.56 (2H, t, *J*=5.8 Hz, CH$_2$CH_2Ph), 2.30 (4H, s, COCH_2CH_2CO). MS: $[M+H]^+$ calcd for $C_{22}H_{24}N_3O_5$: 410.1716, found: 410.1739.

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