Supporting Information

Rational Design of a Highly Selective Fluorescent Sensor for L-Histidine Detection in Aqueous Solution

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1. Computational Details

All of the calculations were performed with the Gaussian 09 program suite. In previous theoretical studies, it was reported that Ni^{2+} complexes have high-spin (triplet) ground state and octahedral coordination geometry is most favorable.[1] In the present work, similar results were obtained (data not shown). Thus, all the considered complexes in this work were assumed to have high-spin ground states.

The computational schemes are according to the relevant reference 1 and comprise three steps:

First, the optimization of molecular geometries of the selected five systems including $Ni(H_2O)_6$, Ni-2His, Ni-His-**H3**, Ni-His-Asp, and Ni-His-Glu were carried out with M06-L functional in combination with 6-31+G* basis set for light atoms and def2-TZVP basis set for the metal ion. Solvation effects were also taken into account by employment of SMD solvation model with water as solvent.

Second, the single-point energy calculations of all the studied structures were performed employing M06-L functional with a combination of 6-311++G** basis set for light atoms and def2-TZVP basis set for the metal ion.

Third, the metal ion at the optimized geometry was replaced by the corresponding ghost atom Bq and single-point energy was calculated for BqX and $Bq(H_2O)_6$ systems.

Interaction energies and Gibbs Energies. The interaction energy of a given system with the metal ion Ni^{2+} is defined as:

$$E_{\mathrm{int}}(Ni, X) = E(NiX) - E(BqX) - (E([Ni(H_2O)_6]^{2+}) - E(Bq(H_2O)_6)) \qquad \text{(Eq 1)}$$

According to this formula, the computed interaction energy has been corrected for the non-bond interactions between neighboring ligands and for a part of basis set superposition error (BSSE).

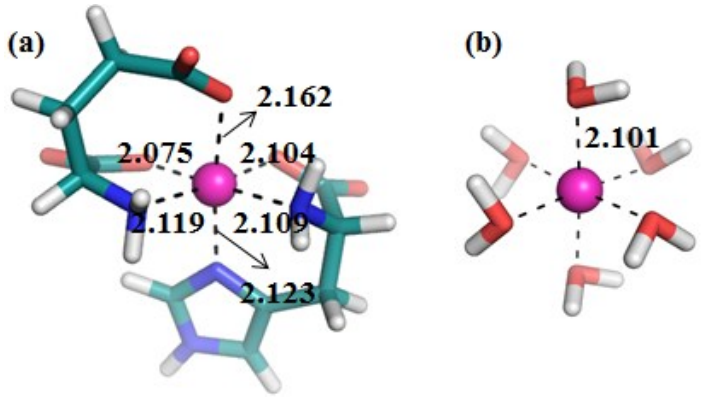
Table S1. The ZPE, δG, E+ZPE, and G of SP (stationary points) at the M06-L/(6-31+G*:def2-TZVP) level in water using SMD model, and single-point energy E1 at M06-L/(6-311++G**:def2-TZVP) level in water using SMD model (unit: a.u.)

SP	δE	δG	E+ZPE	G	E1
$Ni(H_2O)_6$	0.151211	0.109114	-1966.513484	-1966.555580	-1966.84623656
Ni-2His	0.304340	0.254142	-2604.451864	-2604.502062	-2605.02996352
Ni-His-H3	0.472847	0.407687	-3253.886431	-3253.951590	-3254.78408482
Ni-His-Asp	0.253862	0.204229	-2567.599007	-2567.648640	-2568.12031119
Ni-His-Glu	0.283046	0.231943	-2606.872299	-2606.923402	-2607.43441391
$Bq(H_2O)_6$	—	—	—	—	-458.693009331
Bq-2His	—	—	—	—	-1096.76290208
Bq-His-H3	—	—	—	—	-1746.51851973
Bq-His-Asp	—	—	—	—	-1059.85904413
Bq-His-Glu	—	—	—	—	-1099.17736593

Table S2. Interaction energies, E_{int}(Ni, X), of X with Ni^{2+} in octahedral coordination geometry, defined by Eq 1. (All values in kcal/mol)

Complexes	Ni-2His	Ni-His-**H3**	Ni-His-Asp	Ni-His-Glu
E_{int}	-71.4	-70.5	-67.8	-65.1

Figure S1. The optimized geometries for Ni-His-Glu and $Ni(H_2O)_6$ complexes. All the distances are shown in Å.



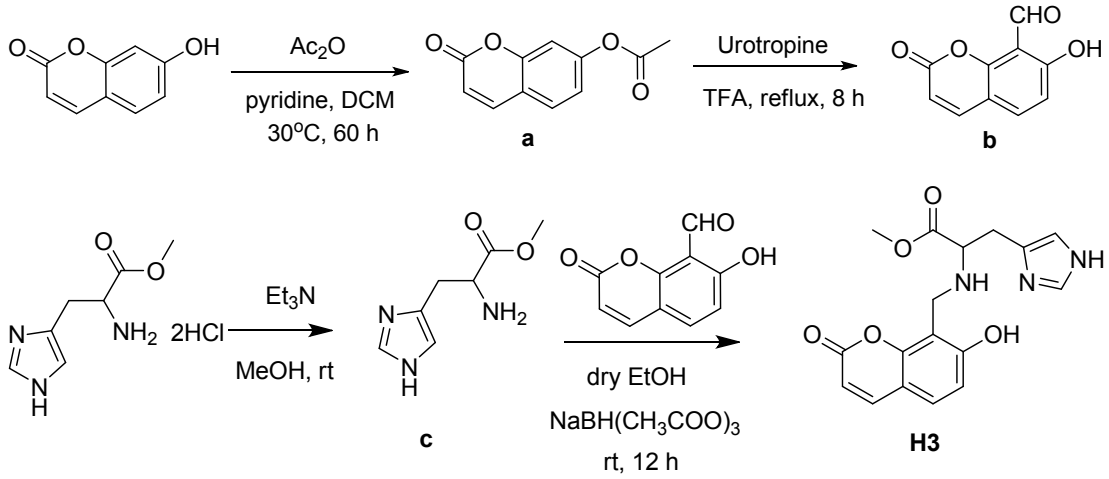
2. General Experimental Procedure

All reagents were purchased from commercial sources and used without further purification. NMR spectra for the synthetic components were recorded using a Avance 400 MHz (Bruker) for ^1H and 100 MHz for ^{13}C, and processed using MestRe-

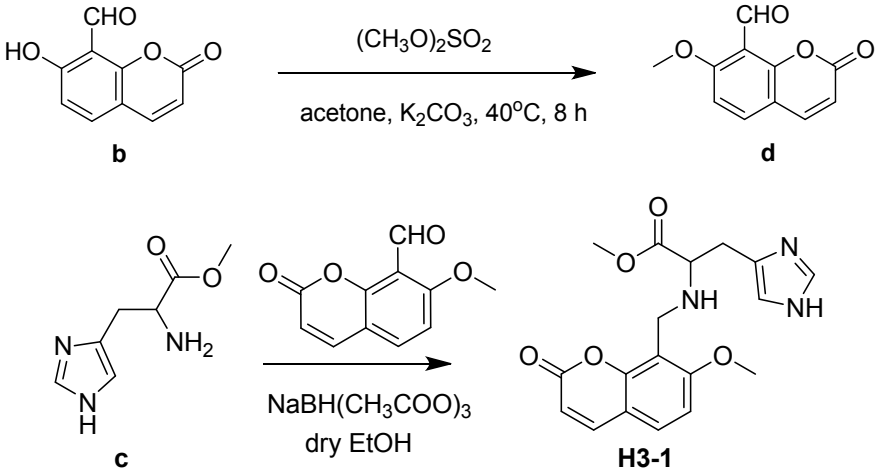
C 6.1.1. software. Mass spectroscopy data were recorded by the Analysis & Research Center ECUST. Fluorescence emission spectra were conducted on a Varian Cary Eclipse fluorescence spectrofluorometer and processed using OriginPro 8.0 software. Solvents for spectroscopic measurements (methanol, ethanol, acetonitrile, DMSO, etc) were of analytical grade and were used as received. Metal ions were purchased from analytical grade perchlorate salts and were dissolved in doubly distilled water. The test temperature was 22-25 ^{o}C.

3. Experimental Procedures

Probe **H3** and reference compound **H3-1** were synthesized according to the following Scheme.



Scheme S1 Synthesis route of **H3**



Scheme S2 Synthesis route of **H3-1**

Synthesis of compound a.

A suspension of 7-hydroxycoumarin (6 g, 37.00 mmol) and acetic anhydride (4.2 mL, 44.41 mmol) in DCM was added several drops of pyridine. The mixture was stirred for 60 hours at 30 ^{o}C and monitored by TLC. The resulting solution was then added

100 mL water and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried with anhydrous Na_2SO_4, and evaporated. The product was then recrystallized by EtOH as a white solid (6.3 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 9.6 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.41 (d, J = 9.6 Hz, 1H), 2.35 (s, 3H).

Synthesis of compound b.

TFA (trifluoroacetic acid) under ice-bath was added (**a**) (2.0 g, 9.8 mmol) and urotropine (2.06 g, 14.69 mmol) slowly. The reaction mixture was warming to room temperature, and then was heated to reflux for 8 h with stirring and monitored by TLC. After evaporation of the solvent, 30 mL water was added and stirred at 50 ^{o}C for 0.5 h. Then under ice-bath, the yellow precipitate was collected by filtration, washed with water and dried. The residue was purified by recrystallization and chromatography (DCM/PE = 5:1,v/v) to yield (**b**) as a light yellow powder (0.68 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.22 (s, 1H), 10.61 (s, 1H), 7.66 (d, J = 9.6 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 9.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 192.93. 165.50, 159.10, 156.76, 143.37, 136.01, 114.70, 113.42, 110.87, 108.69. ESI: Calcd for $C_{10}H_6O_4$ $[M-H]^-$ 189.0; Found, 189.0.

Synthesis of Compound **H3**

Histidine methyl ester-dihydrochloride (100 mg, 0.59 mmol) was dissolved in 5 ml MeOH, to which was added triethylamine (165 μL, 1.18 mmol) and stirred. After 20 min triethylamine hydrochloride was precipitated and filtered. The filtrate was evaporated to give histidine methyl ester (**c**). Then under argon, a solution of (**c**) in 20 ml dry EtOH was added (**b**) (80 mg, 0.42 mmol) which was stirred at room temperature for 2 h monitored by TLC. Sodium triacetoxyborohydride (240 mg, 1.13 mmol) was added to the above reaction solution and left to react for another 8 h. After that, the suspension was filtered. The filtrate was concentrated and the residue was purified by chromatography (DCM/MeOH = 15:1, v/v) to yield **H3** as a white solid (30 mg, 21%).^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J = 9.2 Hz, 1H), 7.51 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.79 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.19 (d, J = 9.2 Hz, 1H), 4.03-3.90 (m, 2H), 3.57 (t, J = 7.2 Hz, 1H), 3.55 (s, 3H), 2.88-2.80 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.40, 172.00, 161.01, 160.26, 152.98, 144.96, 134.71, 128.12, 112.90, 111.05, 110.83, 60.18, 51.50, 45.31, 29.82, 21.06, 8.43. HRMS (ESI): Calcd for $C_{17}H_{17}N_3O_5$ $[M+H]^+$ 344.1236; Found, 344.1236.

Synthesis of compound d

A solution of (**b**) (100 mg, 0.53 mmol) in anhydrous acetone was added potassium carbonate (360 mg, 2.63 mmol) with stirring at 40 ^{o}C for 30 min. Then dimethyl sulfate (165 μL, 1.31 mmol) was added carefully and stirred for 8 h at the same temperature monitored by TLC. When the reaction was completed, 12 ml ice-water was poured into the above solution to quench the reaction. Cooling under the ice-bath, light yellow solid was precipitate and filtered. The product was purified by chromatography (DCM/MeOH = 30:1, v/v) to give (**d**) (80 mg, 70%). ^{1}H NMR (400

MHz, $CDCl_3$): δ 10.67 (s, 1H), 7.65 (t, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 8.8 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 186.94, 163.25, 159.53, 156.12, 143.11, 134.25, 114.04, 112.68, 112.58, 108.23, 56.76, 18.44. ESI: Calcd for $C_{11}H_8O_4$ $[M+H]^+$ 205.0; Found, 205.0.

Synthesis of compound H3-1.

Following the same procedure (**H3**) described above, histidine methyl ester (**c**) was allowed to react with (**d**) to give (**H3-1**) as a white solid (25 mg, 18%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 9.6 Hz, 1H), 7.58 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.81 (s, 1H), 6.24 (d, J = 9.6 Hz, 1H), 4.06-4.03 (m, 2H), 3.91 (s, 3H), 3.65 (s, 3H), 3.55 (t, J = 4.8 Hz, 1H), 3.06-3.01 (m, 1H), 2.90-2.84 (m, 1H)。 ^{13}C NMR (100 MHz, $CDCl_3$): 173.63, 160.93, 160.83, 153.37, 146.43, 144.03, 129.22, 128.50, 118.41, 115.08, 114.25, 112.97, 107.59, 59.95, 56.28, 52.19, 39.08, 29.65. HRMS (ESI): Calcd for $C_{18}H_{20}N_3O_5$ $[M+H]^+$ 358.1403; Found, 358.1411.

4. Spectroscopic Properties

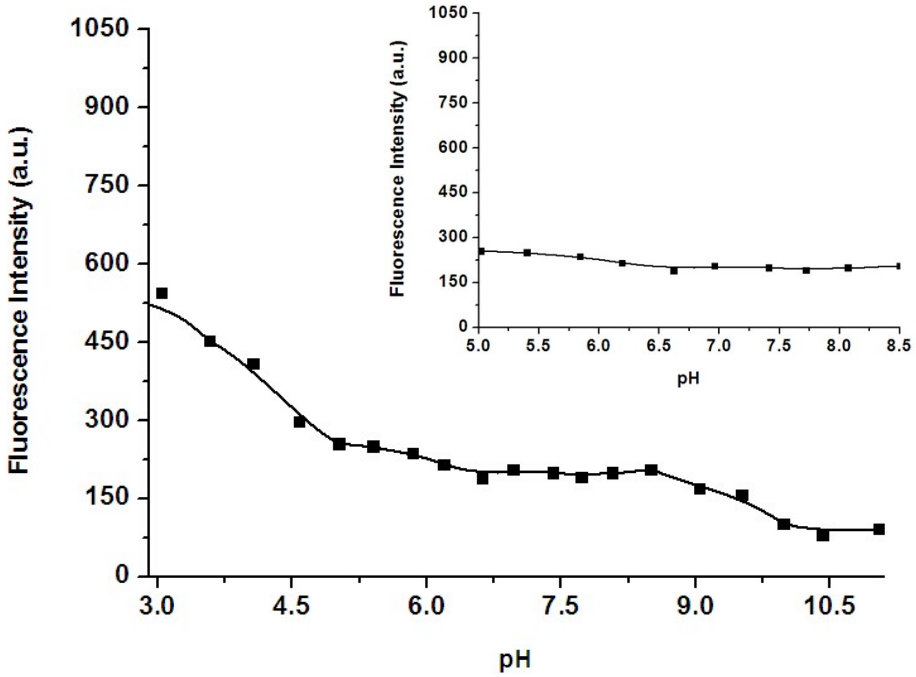


Figure S2. The pH titration of fluorescent probe **H3**. The fluorescent curve of **H3** in response to pH 3.0-11.0. Inset shows the fluorescent curve in response to pH 5.0-8.5. Probe concentration was 5 μM. Ex= 324 nm, Em= 451 nm, slit: 2.5 nm- 5 nm.

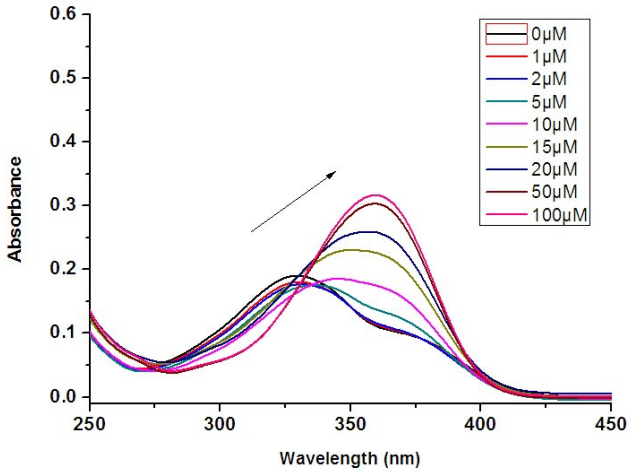


Figure S3. The absorption spectra of **H3** in the presence of increasing concentrations of Ni^{2+} in MOPS (50 mM, pH 7.2) buffer. Probe concentration was 10 μM. $Ni(ClO)_2$ was 10 μM.

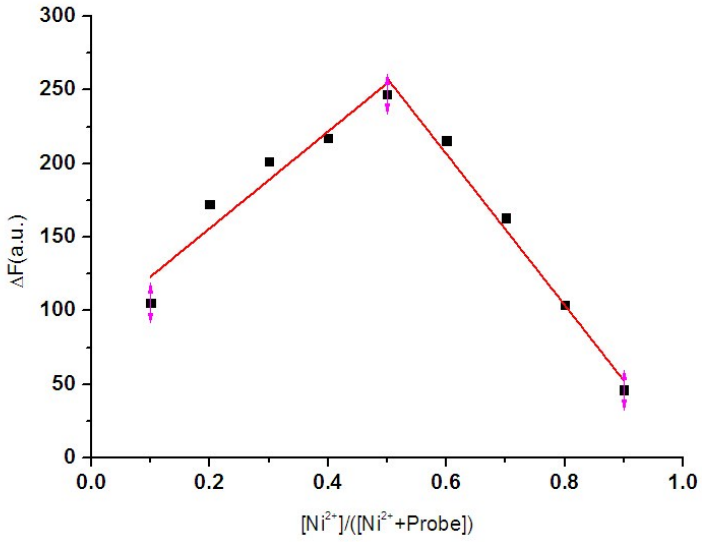


Figure S4. Job's plot of probe **H3** in in MOPS (50 mM, pH 7.2) buffer solution. The total concentration of probe and Ni^{2+} ion was 10 μM.

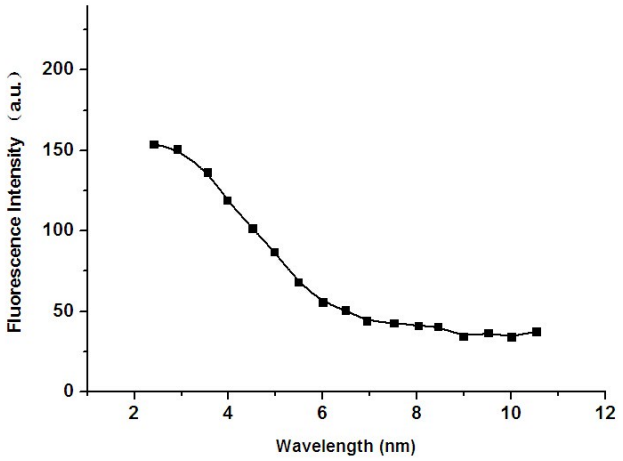


Figure S5. The fluorescence titration at 455 nm of complex [**H3**+Ni^{2+}] (5 μM) in response to different pH in water.

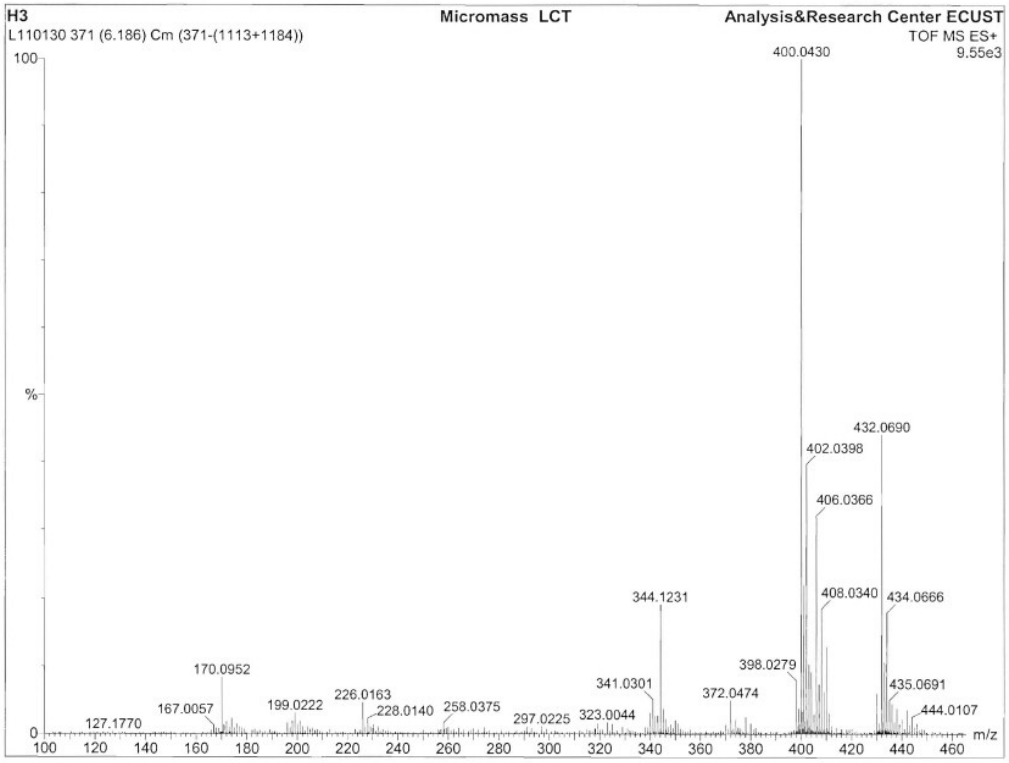


Figure S6. ESI Mass of complex [**H3**+Ni^{2+}-H^{+}]$^{+}$.

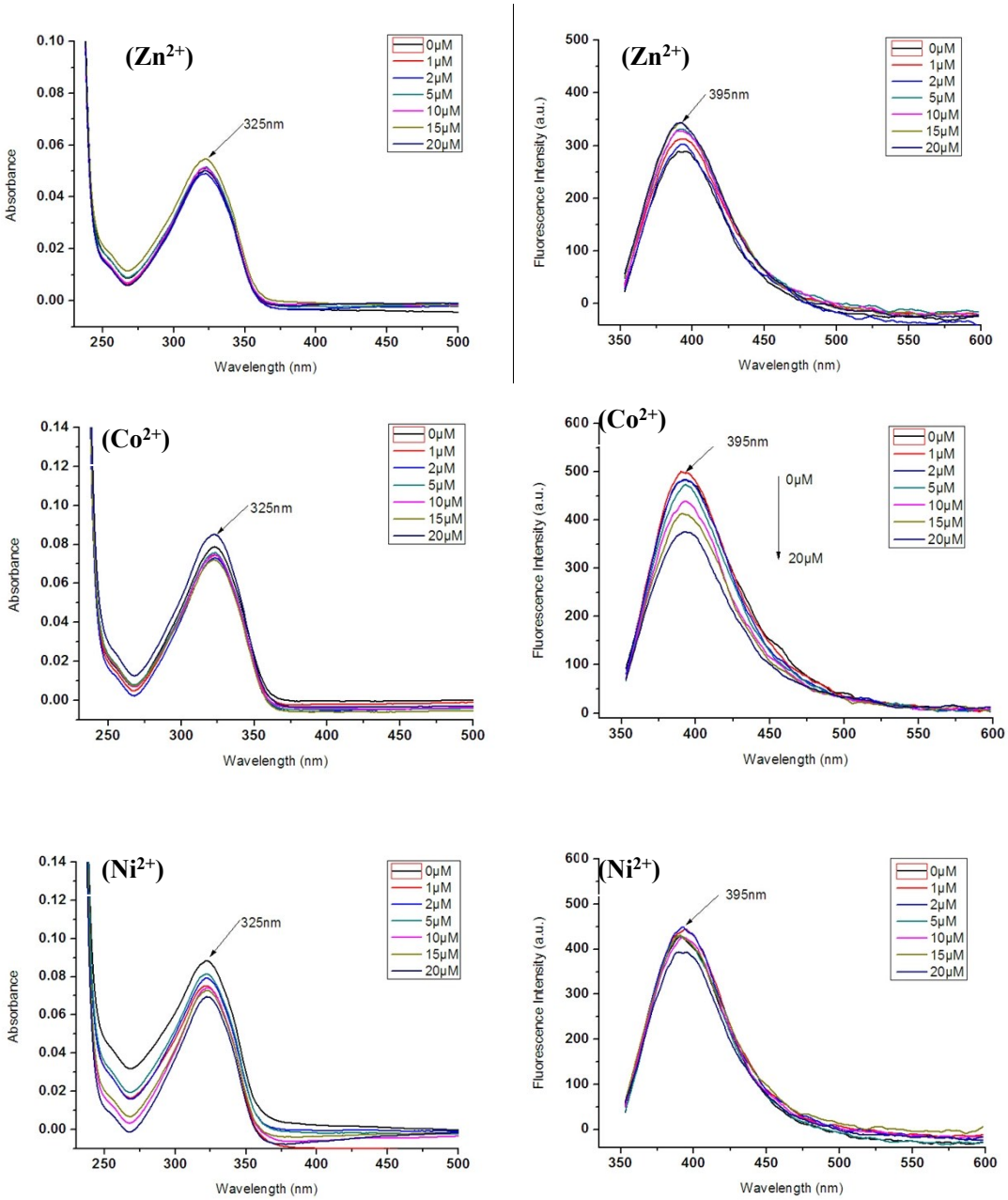
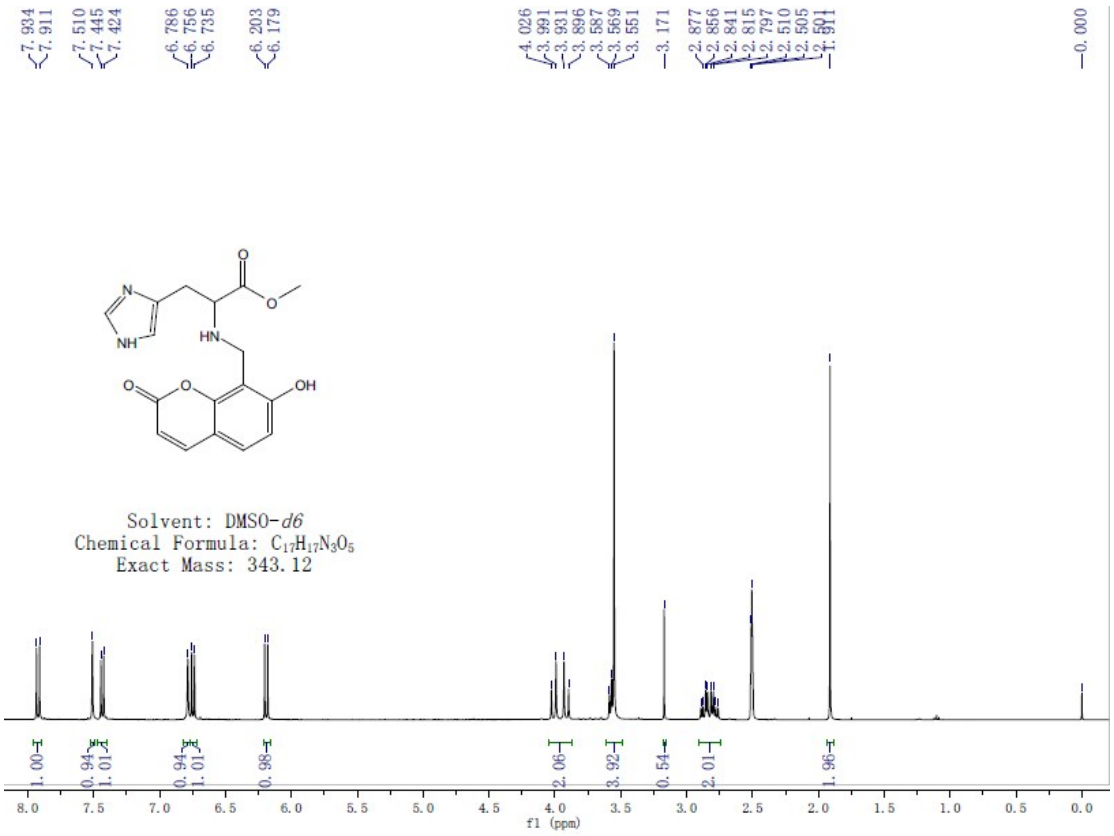


Figure S7. Absorbtion and fluorescence emission spectra of compound H3-1 in response to Zn^{2+}, Co^{2+} and Ni^{2+} ions in MOPS (50 mM, pH 7.2) buffer solution. Ex= 325 nm, Em= 395 nm, slit: 10 nm- 10 nm.

5. ^{1}H NMR, ^{13}C NMR and HRMS of compounds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7.424
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6.735
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3.991
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3.896
3.587
3.569
3.551
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2.510
2.505
1.911
0.000
Solvent: DMSO-d6
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0.94
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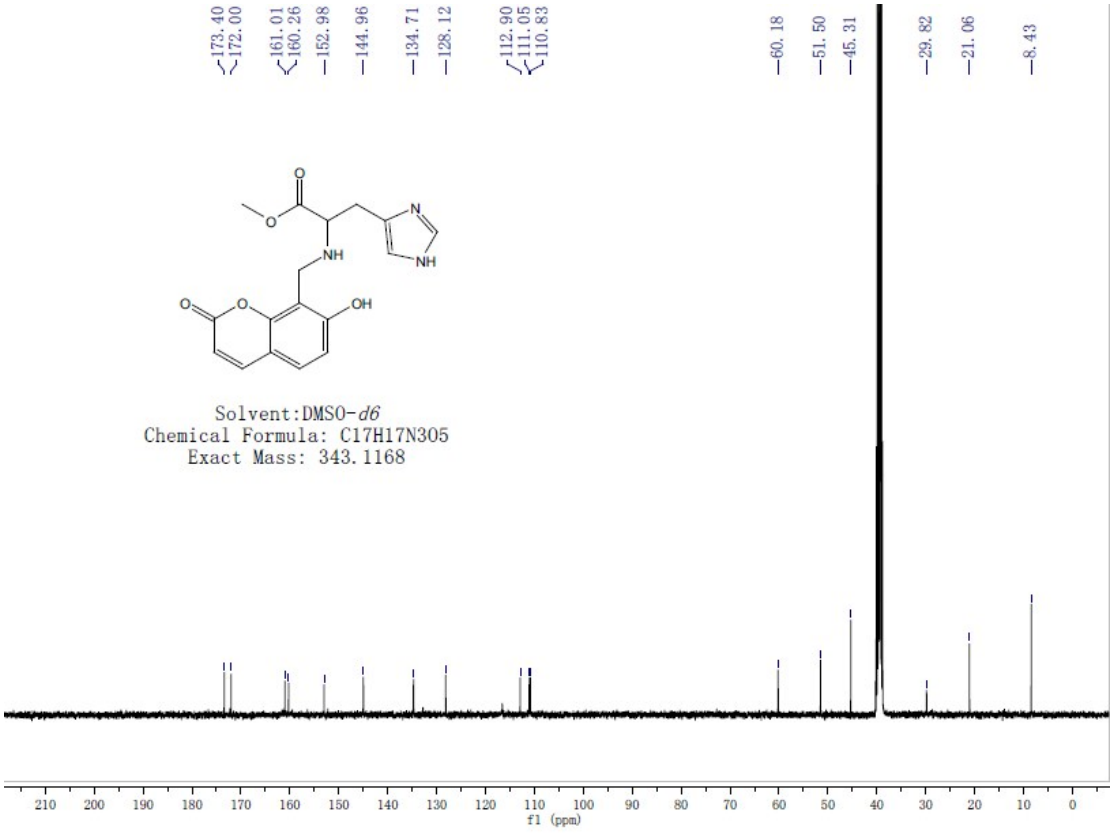
2.01
1.96
f1 (ppm)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172.00
161.01
160.26
152.98
144.96
134.71
128.12
112.90
111.05
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51.50
45.31
29.82
21.06
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Solvent:DMSO-d6
Chemical Formula: C17H17N3O5
Exact Mass: 343.1168
f1 (ppm)

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
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Elements Used:
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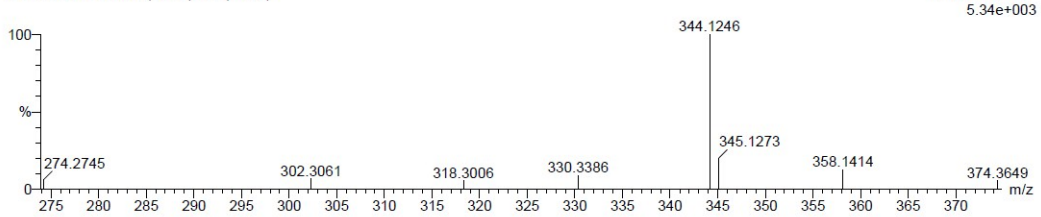

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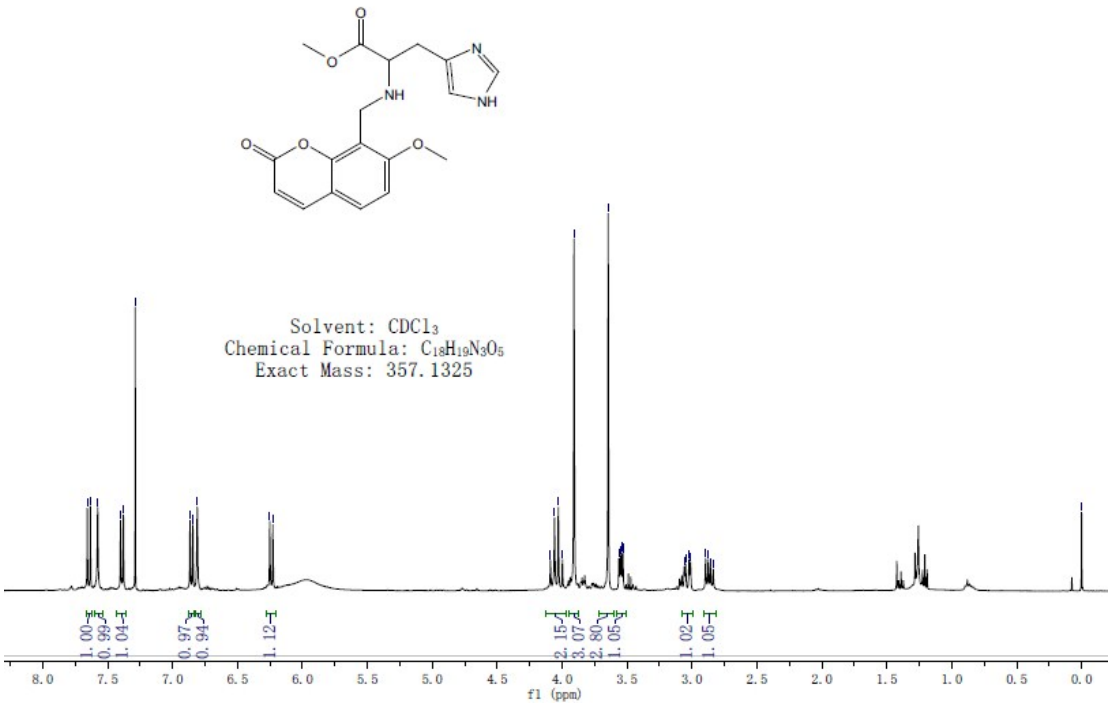

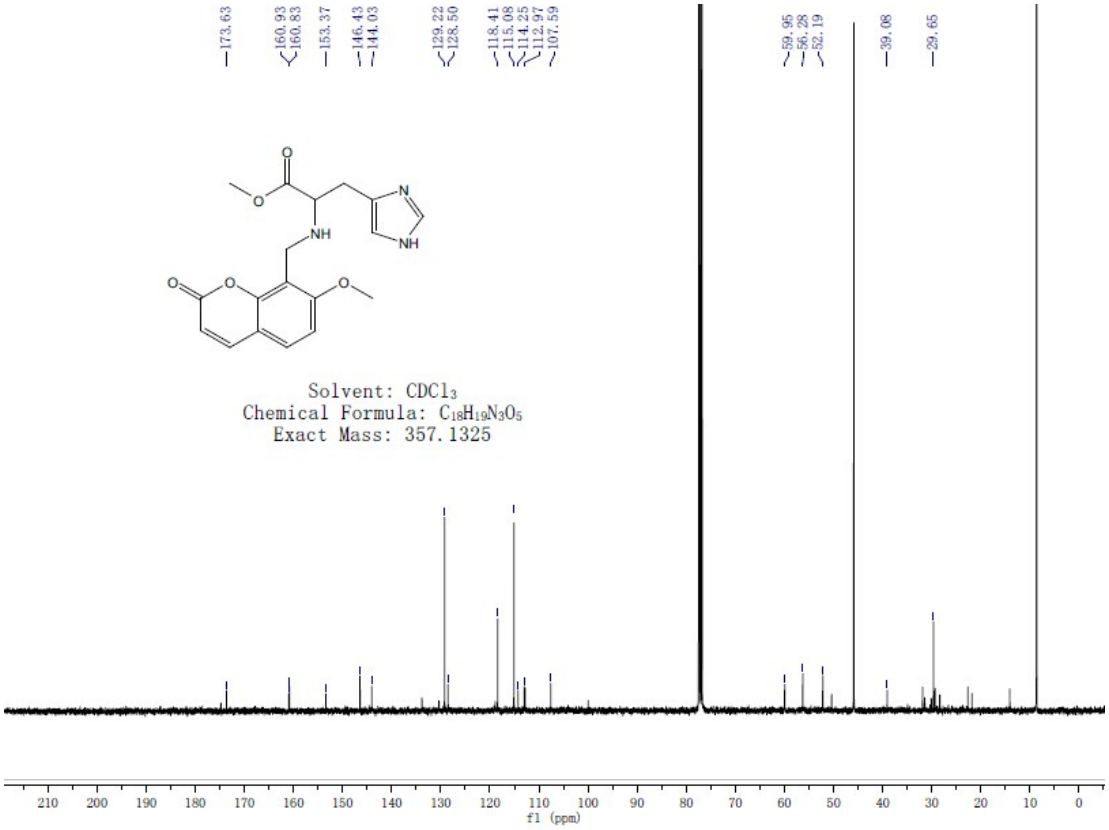

Elemental Composition Report **Page 1**

Single Mass Analysis
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Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
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Elements Used:
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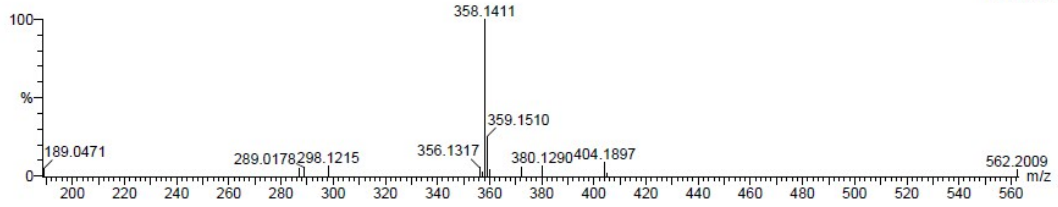

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REFERENCE

1. Rulíšek, L., and Havlas, Z. *J. Am. Chem. Soc.2000,* **122**, 10428-10439