Supporting Information

Unprecedented Intramolecular Association Induced Fluorescence (IAIF) in Tryptophan Conjugated Peptidomimetics

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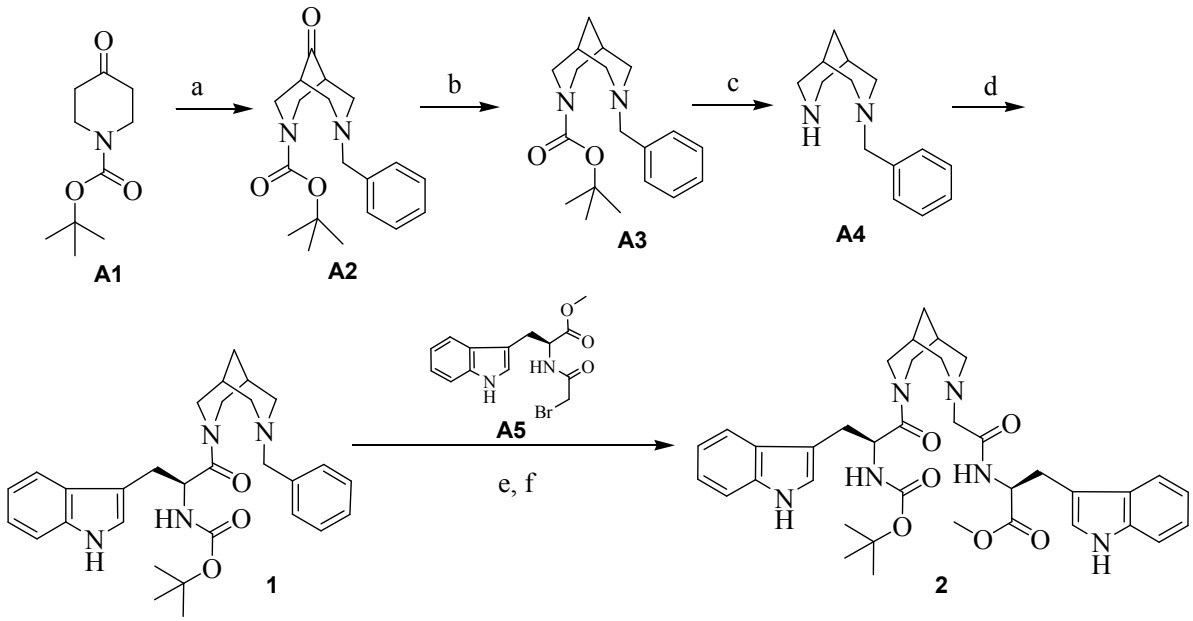
Scheme S1: Synthesis of compounds **1** and **2.**



Reagents:- (a) Benzyl amine, HCHO, AcOH, MeOH, 65 ^{o}C, 10h, 60% (b) NH_2NH_2,Glycol, KOH, 8h,165 ^{o}C, 85% (c) TFA, DCM, rt, 4h (d) Boc-Trp-OH, DCC, NHS, DCM, NEt_3, 24h, rt (e) 10% of Pd/C, MeOH, AcOH, rt, 8h (f) Compound **A5**, ACN, rt, 12h.

Synthesis of compound 1

To a well stirred solution of Boc and benzyl protected bispidine compound **A3** (0.400 g, 1.26 mmol) in dichloromethane (DCM) (10 mL) was added trifluoroacetic acid (1.93 mL, 25.28 mmol), and the reaction mixture was stirred for 4h at room temperature. The reaction mixture was evaporated and used as such for further reaction. The obtained amine was added to the DCM solution containing tert-butyloxy carbonyl (Boc) protected tryptophan (0.321 g, 1.05 mmol), N-hydroxysuccinimide (NHS) (0.145 g, 1.26 mmol), N,N'-Dicyclohexylcarbodiimide (DCC) (0.261 g, 1.26 mmol) and triethylamine (NEt_3) (0.3 mL, 2.11 mmol). The resultant solution was stirred for 24h at room temperature. After completion of reaction, the reaction mixture was evaporated and re-dissolved in ethyl acetate and the filtrate was washed with 0.2N H_2SO_4, saturated aq.$NaHCO_3$ and water. The organic layer was collected and dried over anhyd.

Na_2SO_4 and evaporated under vacuum to obtain the crude product, which was purified by column chromatography (Ethyl acetate/Hexane in 4:6) to give 0.372 g compound **1** as a solid.

In the ^1H NMR spectrum in $CDCl_3$, compound **1** showed signals for major and minor conformers. We have mentioned the signals for minor conformer wherever possible.^{13}C NMR also showed signal for minor conformer, therefore more ^{13}C peaks are observed in the ^{13}C spectrum of compound **1**.

Yield: 70%.

Mp: 72-74^o C; [α] = + 8.13 (*c* 0.010, methanol); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (minor), 1.39 (s, 9H), 1.49-1.65 (m, 2H), 1.66-1.80 (m, 1H), 1.92 (br s, 1H), 2.00-2.20 (m, 2H), 2.23 (minor), 2.47 (d, J=12.4Hz, 1H), 2.63 (d, J=12.8Hz, 1H), 2.78 (minor), 2.80-2.98 (m, 2H), 3.01-3.24 (m, 2H), 3.25-3.41 (m, 1H), 3.47 (d, J=12.4Hz, 1H), 3.70 (d, J=12.8Hz, 1H), 3.78 (minor), 4.30 (minor), 4.50 (d, J=13.2Hz, 1H), 4.98 (br s, 1H), 5.48 (minor), 5.87 (m, 1H), 6.98 (br s, 1H), 7.01-7.37 (m, 8H), 7.51 (minor), 7.62 (m, 1H), 8.27 (minor), 8.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.4, 28.8, 28.9, 29.0, 29.2, 29.5, 29.7, 30.3, 31.5, 34.0, 46.6, 46.8, 49.6, 49.9, 50.7, 51.0, 58.2, 58.4, 58.5, 59.4, 63.4, 79.3, 110.9, 111.0, 111.1, 111.3, 118.7, 119.0, 119.3 119.4, 121.8, 122.7, 123.0, 126.8, 127.0, 127.9, 128.2, 128.3, 128.7, 128.8, 136.0, 136.2, 138.0, 138.4, 155.2, 155.5, 170.3, 171.2; IR (KBr): 3421(br), 2925, 2859, 1710, 1628, 1493, 1455, 1364, 1229, 1169; HRMS calcd. for $C_{30}H_{39}N_4O_3$ m/z 503.3017, found m/z 503.3007.

Synthesis of compound 2

To a well stirred solution of compound **1** (0.219 g, 0.43 mmol) in methanol was added few drops of acetic acid and 10% of Pd/C (0.021 g) and kept under positive pressure of H_2 gas. Stirred the reaction mixture for 8h at room temperature. The reaction mixture was filtered and

evaporated in *vacuo* to obtain the amine. This amine was then added to solution of compound **A5** (0.195 g, 0.52 mmol) and N,N-Diisopropylethylamine (DIPEA) (0.152 ml, 0.87 mmol) in acetonitrile. Stirred the reaction mixture for 24h at room temperature. After completion of reaction, solution was evaporated and re-dissolved in DCM, washed with 0.2N H_2SO_4, saturated aq.$NaHCO_3$ and water. The organic layer was dried over anhyd. Na_2SO_4 and evaporated under vacuum to obtain the crude product which was purified by column chromatography (Ethyl acetate/Hexane in 8:2) to obtain 0.172 g compound **2** as a white solid.

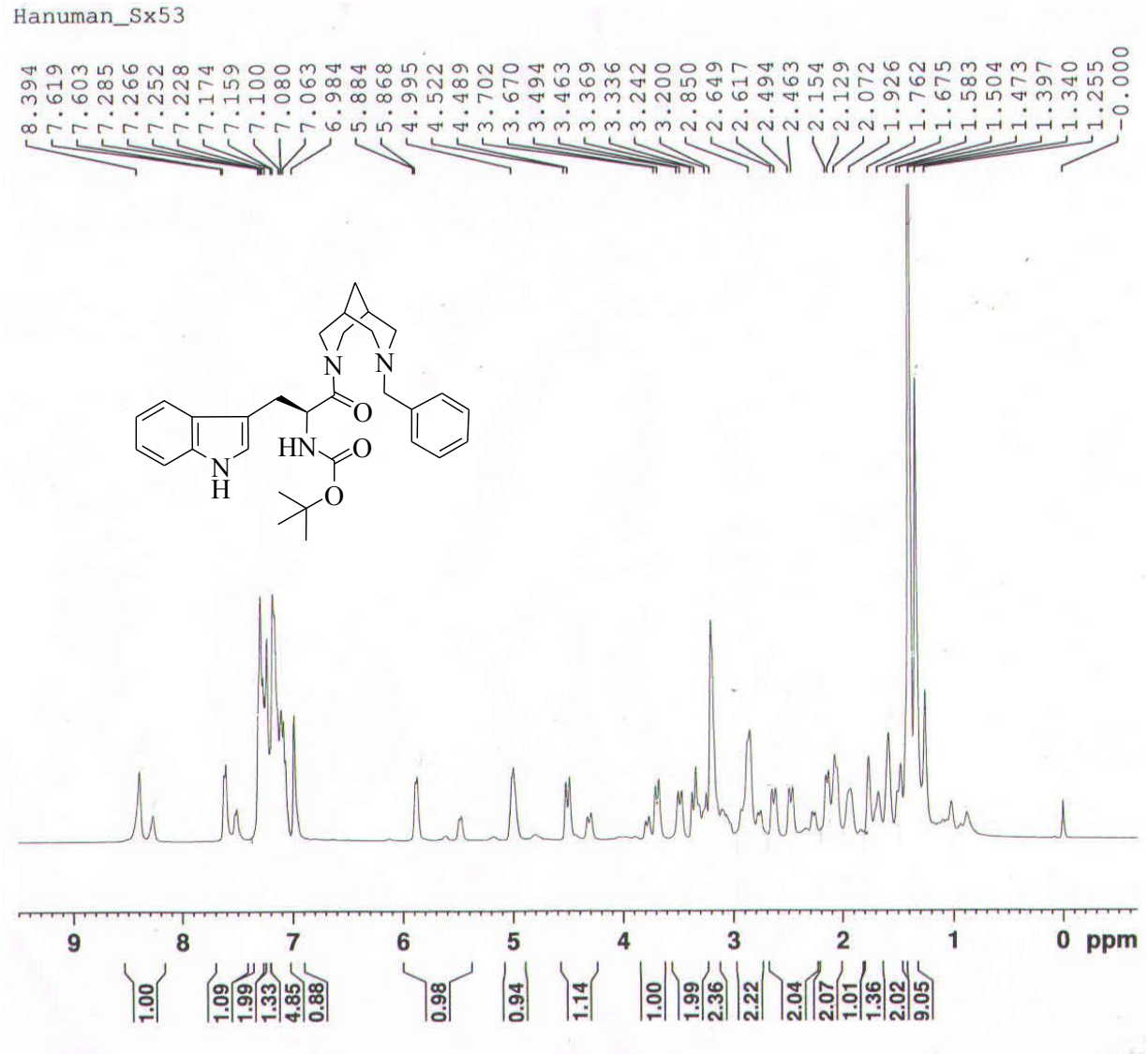
Yield: 59 %

Mp: 118-120^o C; [α] = -10 (*c* 0.01, methanol); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15-1.47 (s + m, 11H), 1.60 (m, 2H), 2.19 (m, 2H), 2.37 (d, J=14Hz, 1H), 2.46 (d, J=13.6Hz, 1H), 2.77 (br d, 2H), 2.98 (d, J=16Hz, 1H), 3.18 (br d, 2H), 3.38-3.70 (m, 3H), 3.79 (s, 3H), 4.02 (d, J=12Hz,1H), 4.32 (d, J=12.8Hz, 1H), 5.20 (m, 2H), 6.59 (m, 1H), 7.00-7.19 (m, 6H), 7.32 (m, 3H), 7.73 (m, 2H), 8.15 (s, 1H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.4, 28.6, 29.6, 29.7, 31.9, 45.7, 50.1, 51.8, 52.5, 57.6, 58.2, 62.7, 79.3, 111.0, 111.5, 119.0, 119.1, 119.2, 119.4, 121.8, 121.9, 122.5, 122.7, 127.8, 136.0, 136.1, 155.6, 170.0, 171.9, 173.4; IR (KBr): 3413(br), 2924, 1704, 1627, 1457, 1365, 1223, 1170; HRMS calcd. for $C_{37}H_{47}N_6O_6$ m/z 671.3552, found m/z 671.3539.

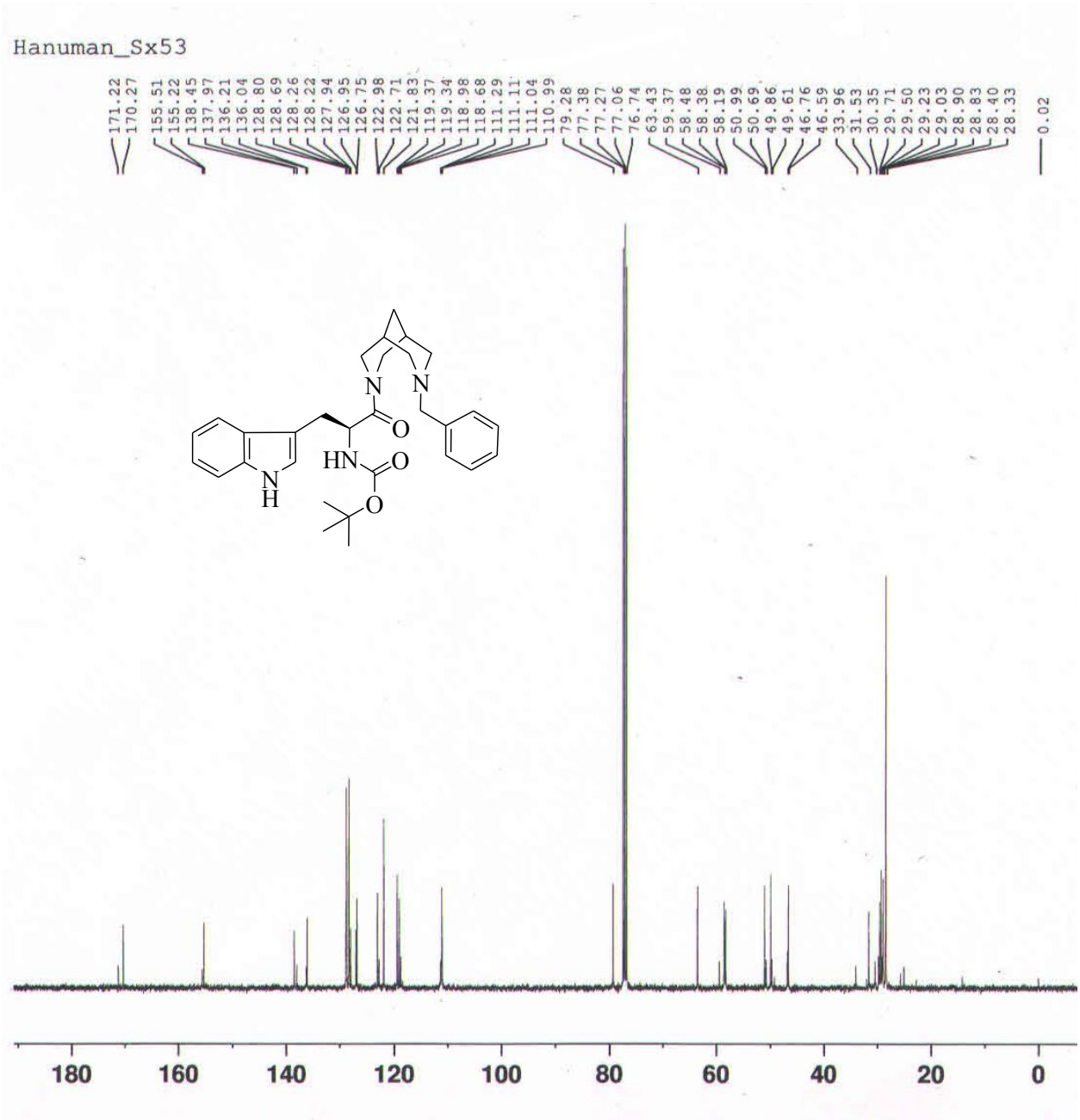
Synthesis of Compound A5

To an ice cold stirred solution of bromoacetic acid (0.200 g, 1.43 mmol) in dry DCM (100 ml) was added sequentially, NHS (0.198 g, 1.76 mmol), DCC (0.356 g, 1.76 mmol) and stirred for 10 min. After that a mixture of L-Tryptophan methyl ester hydrochloride (0.439 g, 1.76 mmol) and NEt_3 (0.2 ml 1.43 mmol) was added and stirred for 24h. After completion of reaction, the reaction mixture was evaporated. Ethyl acetate was added to the residue and the resulting solution was filtered and the filtrate was washed with 0.2N H_2SO_4, saturated aq.$NaHCO_3$ and

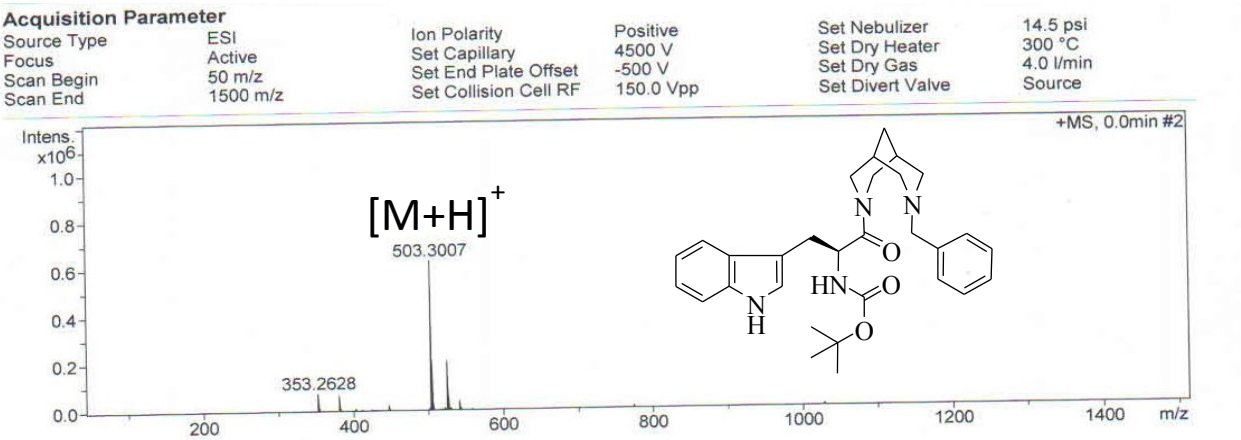
water. The organic layer was collected and dried over anhyd. Na_2SO_4 and evaporated under vacuum to obtain the crude product, which was purified by column chromatography to obtain 0.366 g (75%) compound **A5** as a semi solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (m, 2H), 3.69 (s, 3H), 3.99 (s, 2H), 4.91 (m, 1H), 7.00 (br s, 1H), 7.07 (m, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.35 (br d, 1H), 7.54 (br d, 1H), 8.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 42.4, 52.6, 53.2, 109.6, 111.3, 118.5, 119.8, 122.4, 122.8, 127.4, 136.2, 165.8, 171.7; IR (KBr): 3407(br), 3059, 2926, 2855, 1738, 1659, 1531, 1439, 1361, 1216.



^{1}H NMR ($CDCl_3$, 400 MHz) of compound **1**

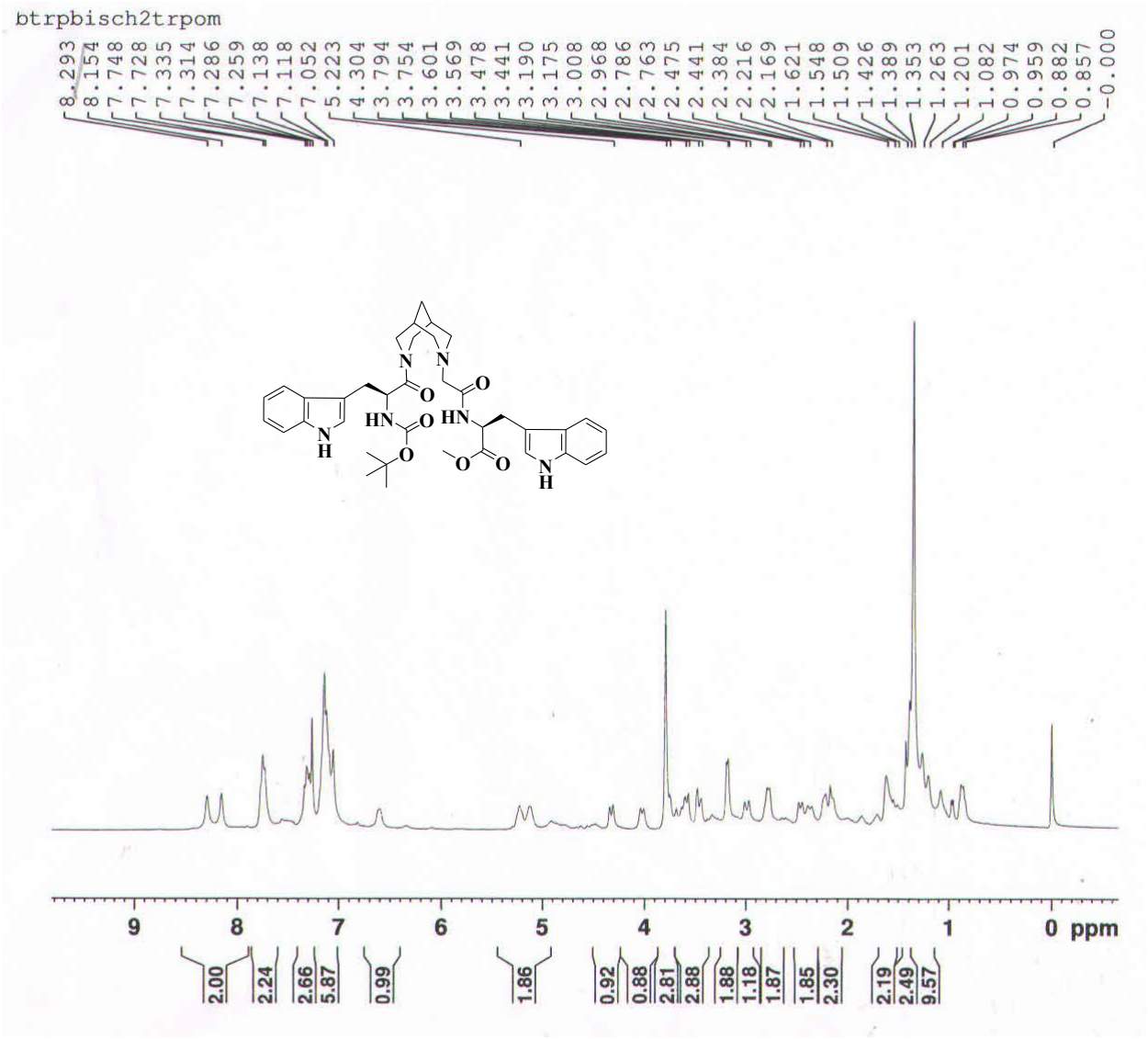


^{13}C NMR (100 MHz, $CDCl_3$) of compound **1**

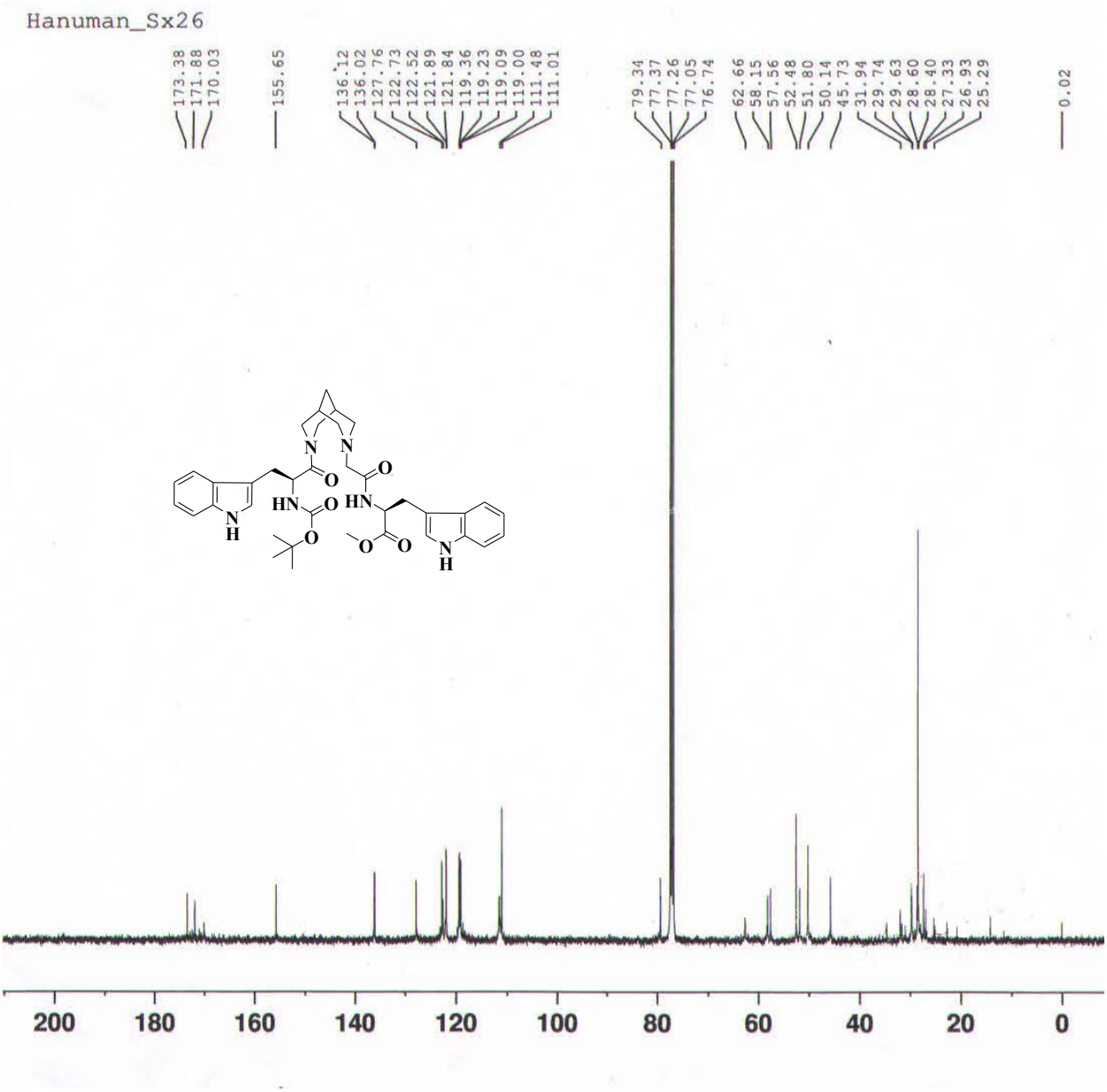


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
503.3007	1	C 30 H 39 N 4 O 3	503.3017	2.0	2.6	13.5	ok	even	8.25	0.0163	0.0014	0.0064	0.0012	0.8427

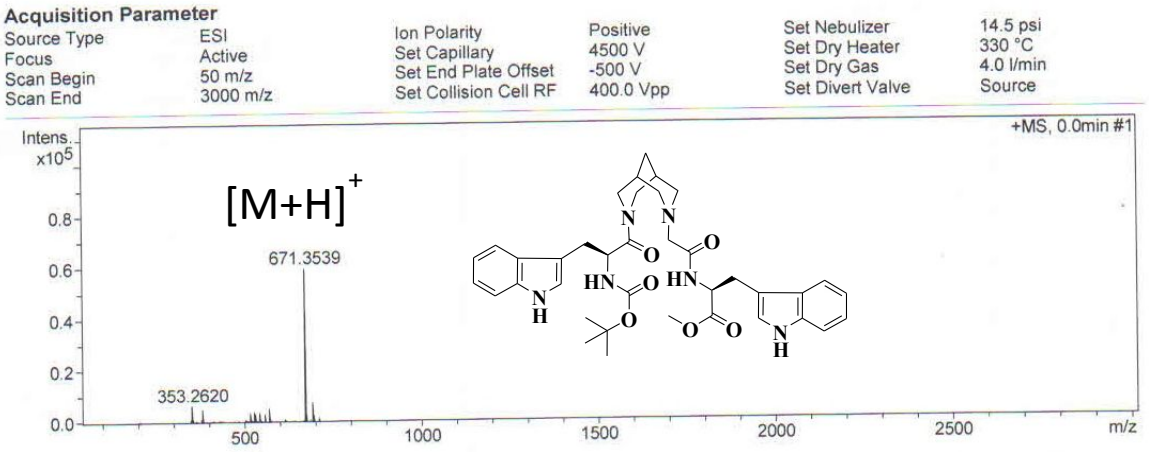
HRMS of compound **1**



^{1} H NMR ($CDCl_3$, 400 MHz) of compound **2**

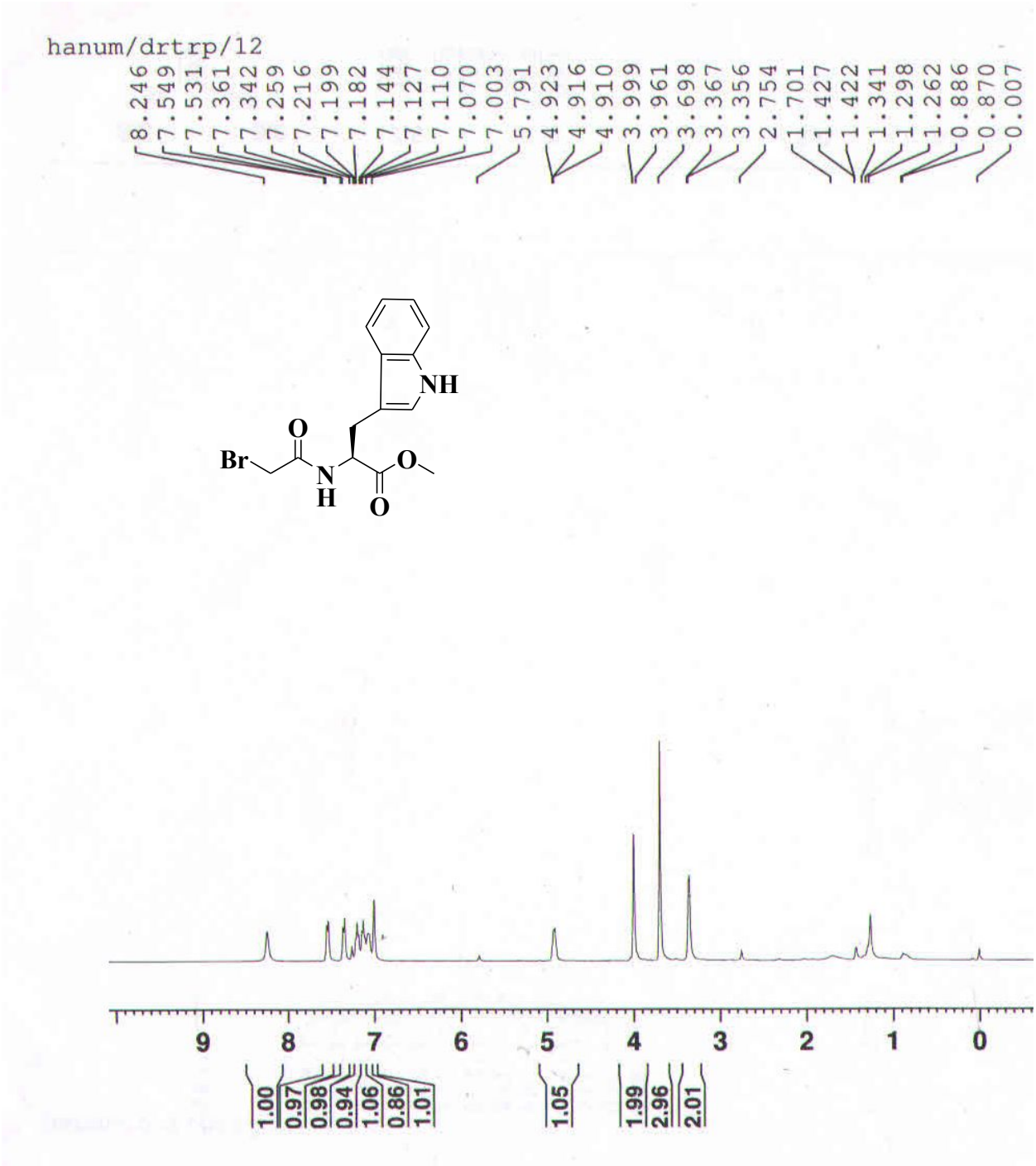


^{13}C NMR (100 MHz, $CDCl_3$) of compound **2**

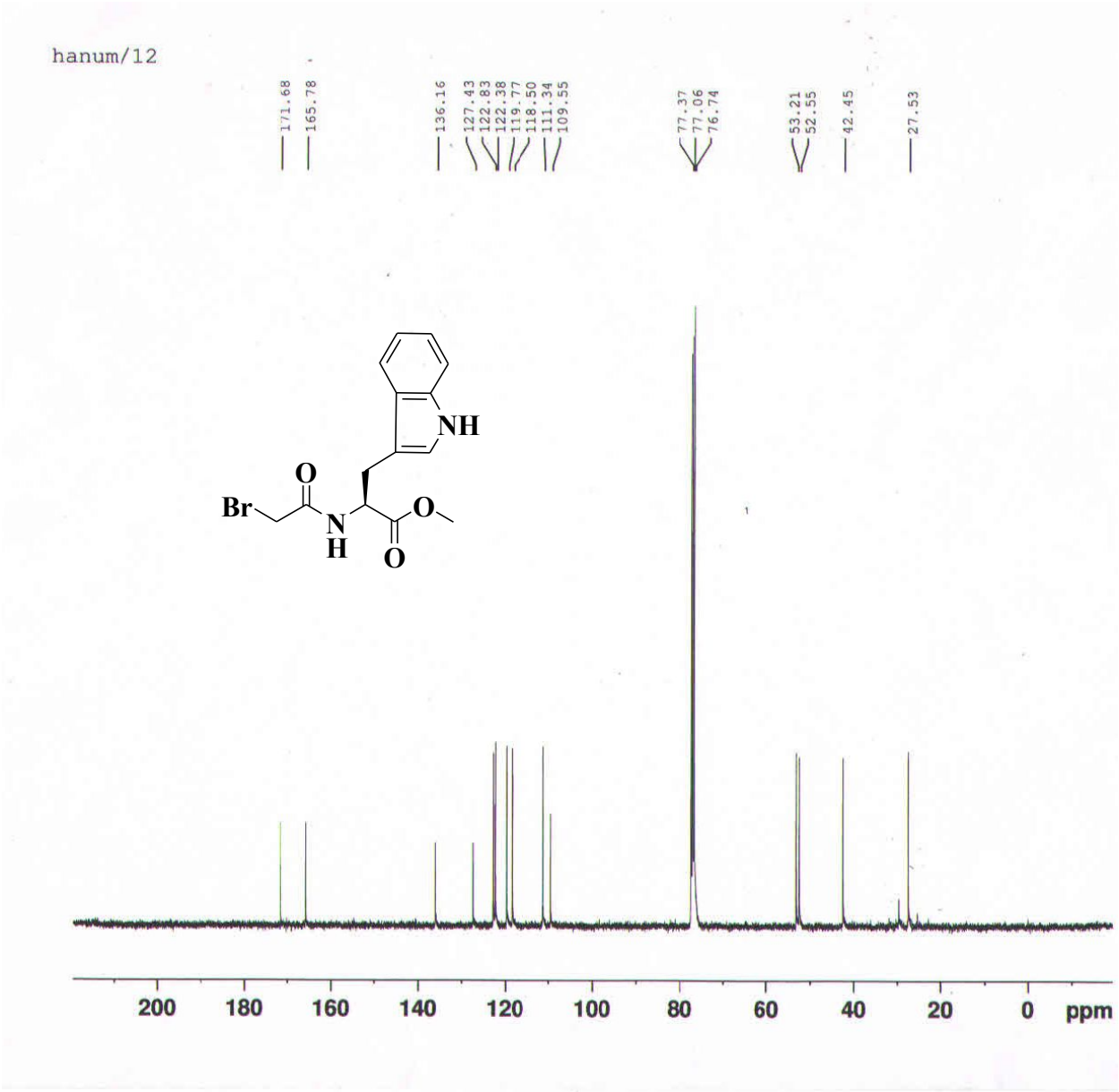


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
671.3539	1	C 37 H 47 N 6 O 6	671.3552	1.9	3.0	17.5	ok	even	46.40	0.0720	0.0023	0.0250	0.0027	0.8427

HRMS of compound **2**



[1] H NMR ($CDCl_3$, 400 MHz) of compound **A5**



^{13}C NMR (100 MHz, $CDCl_3$) of compound **A5**

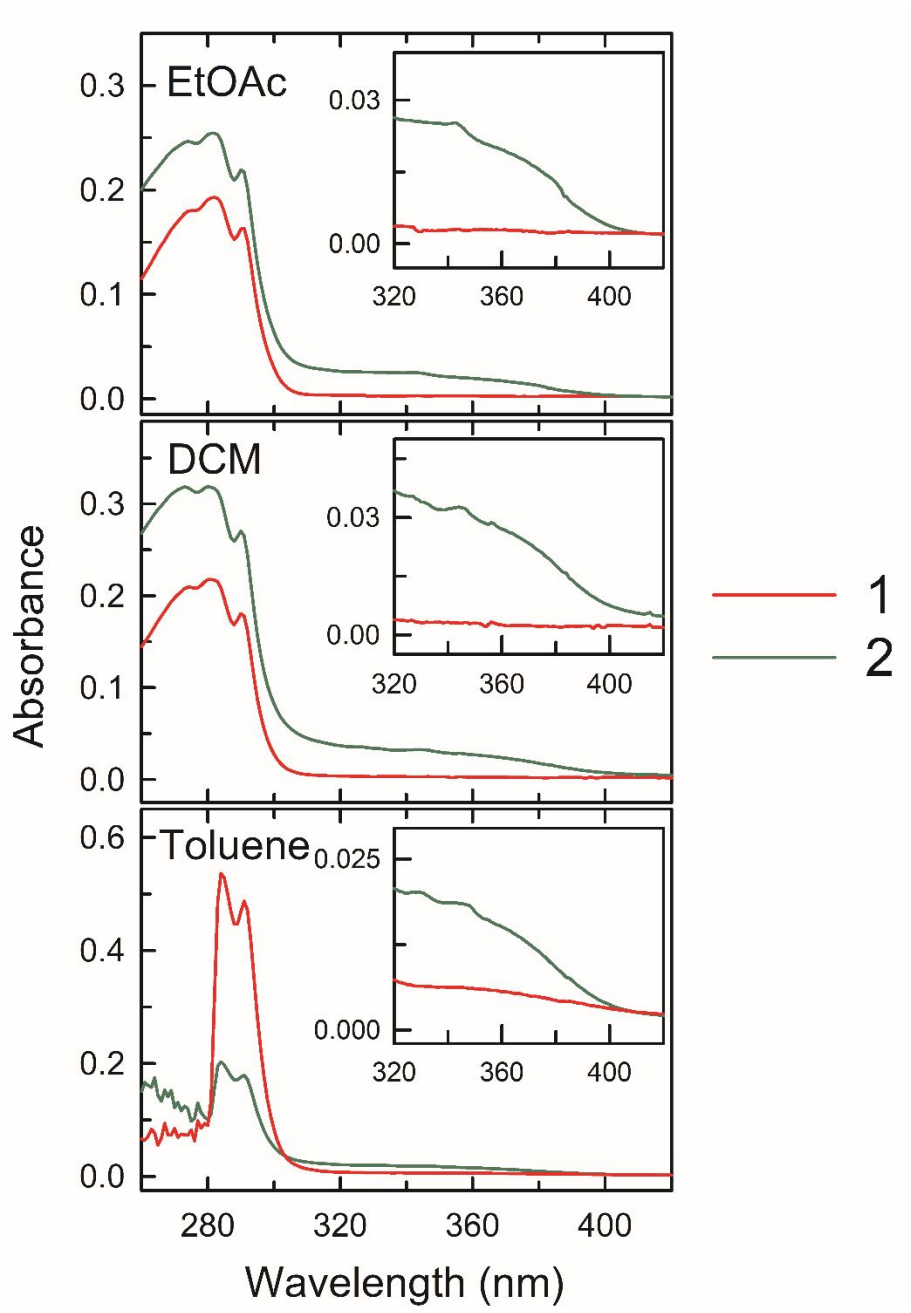


Fig. S1. Absorbance spectra of **1** and **2** (25 μM) dissolved in selected non-polar solvents at 25 °C. Corresponding spectra in the range 320-420 nm highlighting presence/absence of band due to Trp-Trp intramolecular aggregate have been shown in the insets.

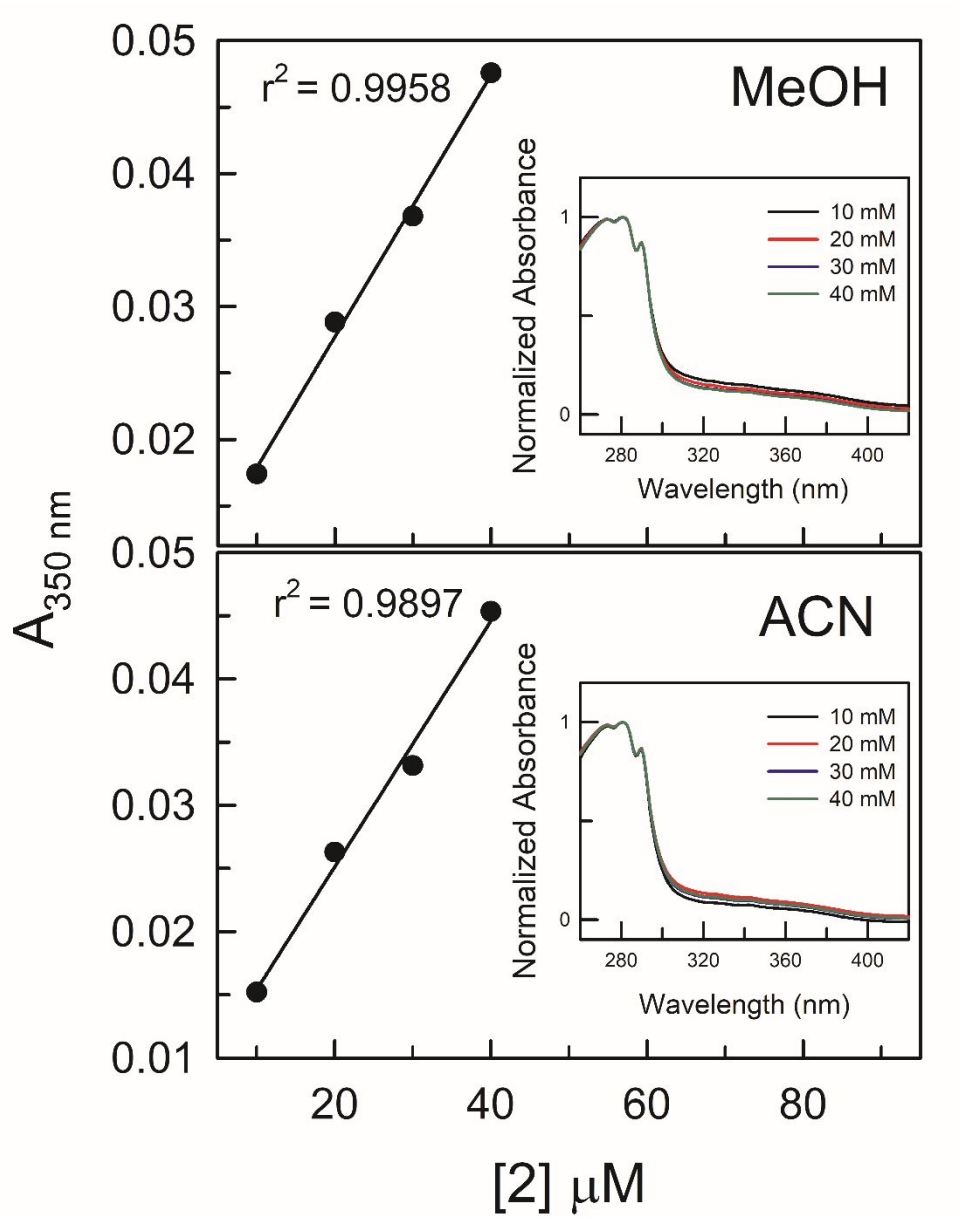


Fig. S2. Absorbance at 350 nm (A_{350nm}, corresponding to the aggregates) versus [**2**] in MeOH (top panel) and ACN (bottom panel). Corresponding normalized absorbance spectra of **2** at different concentrations are provided in insets.

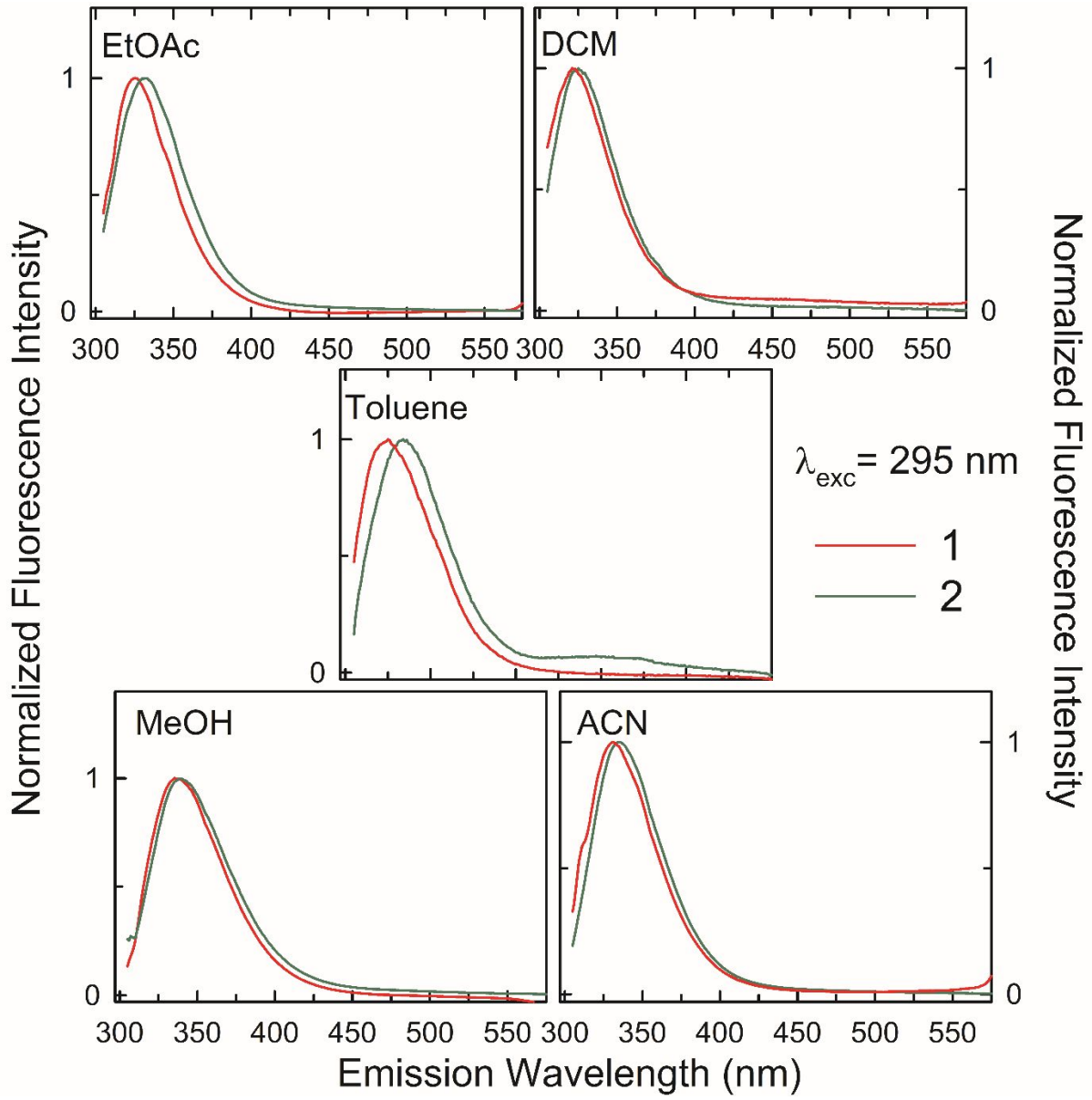


Fig. S3. Normalized fluorescence emission spectra of **1** and **2** (25 μM, λ_{exc} = 295 nm) dissolved in selected solvents at 25 °C.

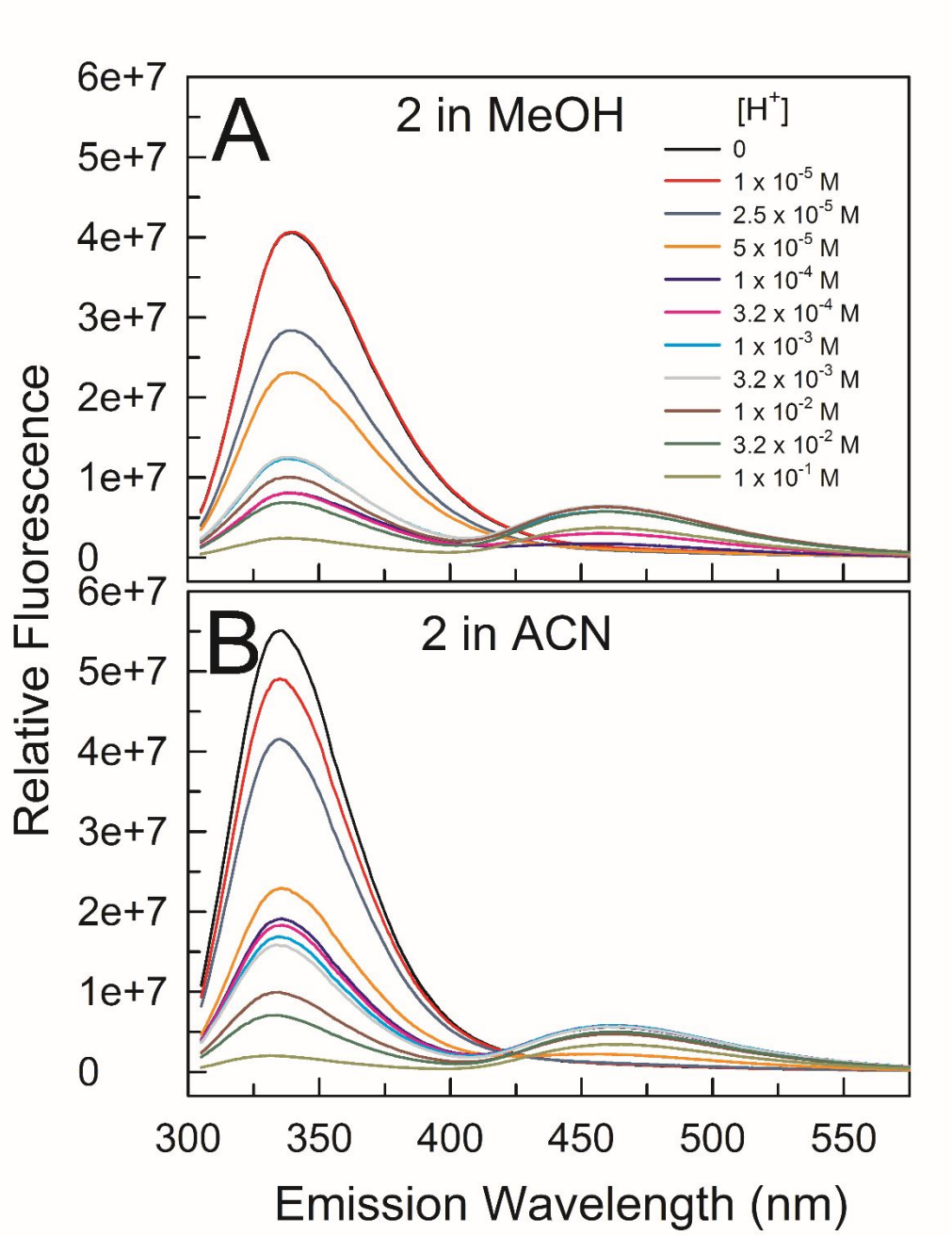


Fig. S4. Relative fluorescence emission spectra of **2** (25 μM, λ_{exc} = 295 nm) in the presence of varying [H^+] at 25 °C in MeOH (panel A) and ACN (panel B), respectively.

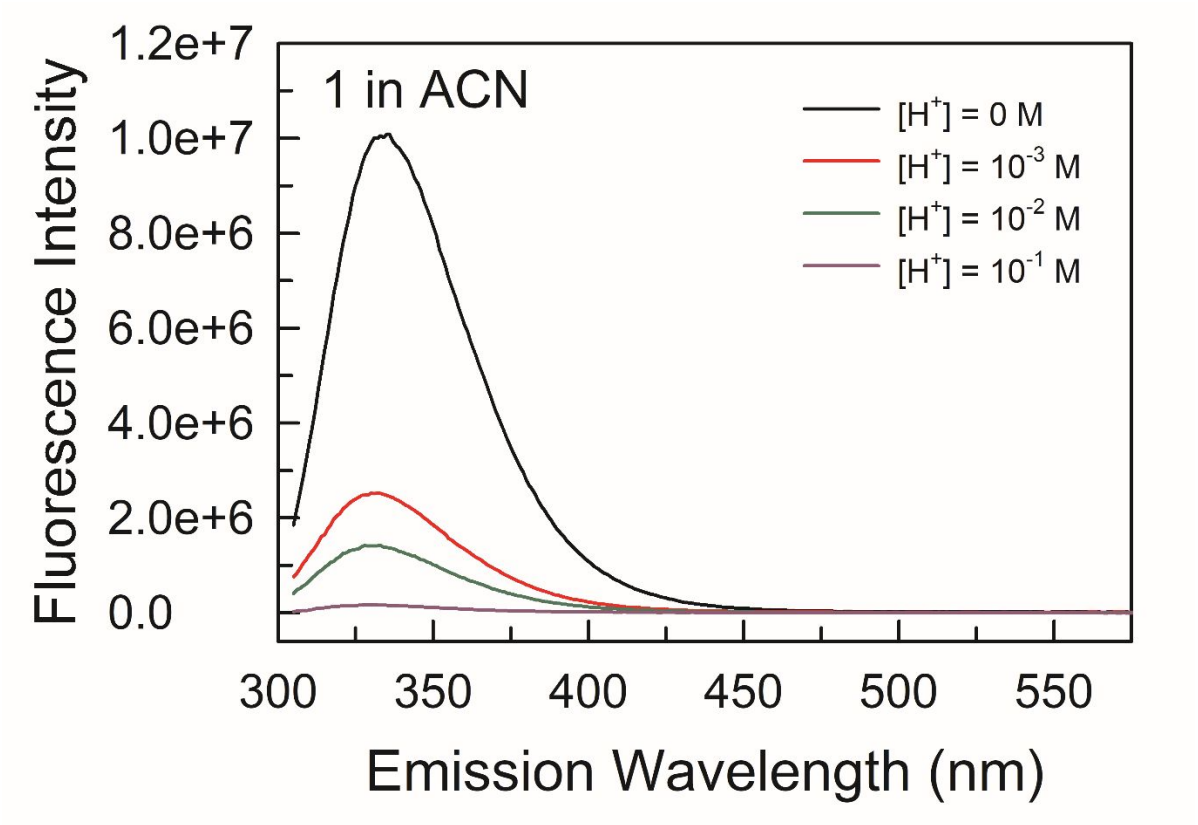


Fig. S5. Relative fluorescence emission spectra of **1** (25 μM, λ_{exc} = 295 nm) in the presence of varying [H^+] at 25 °C in ACN.

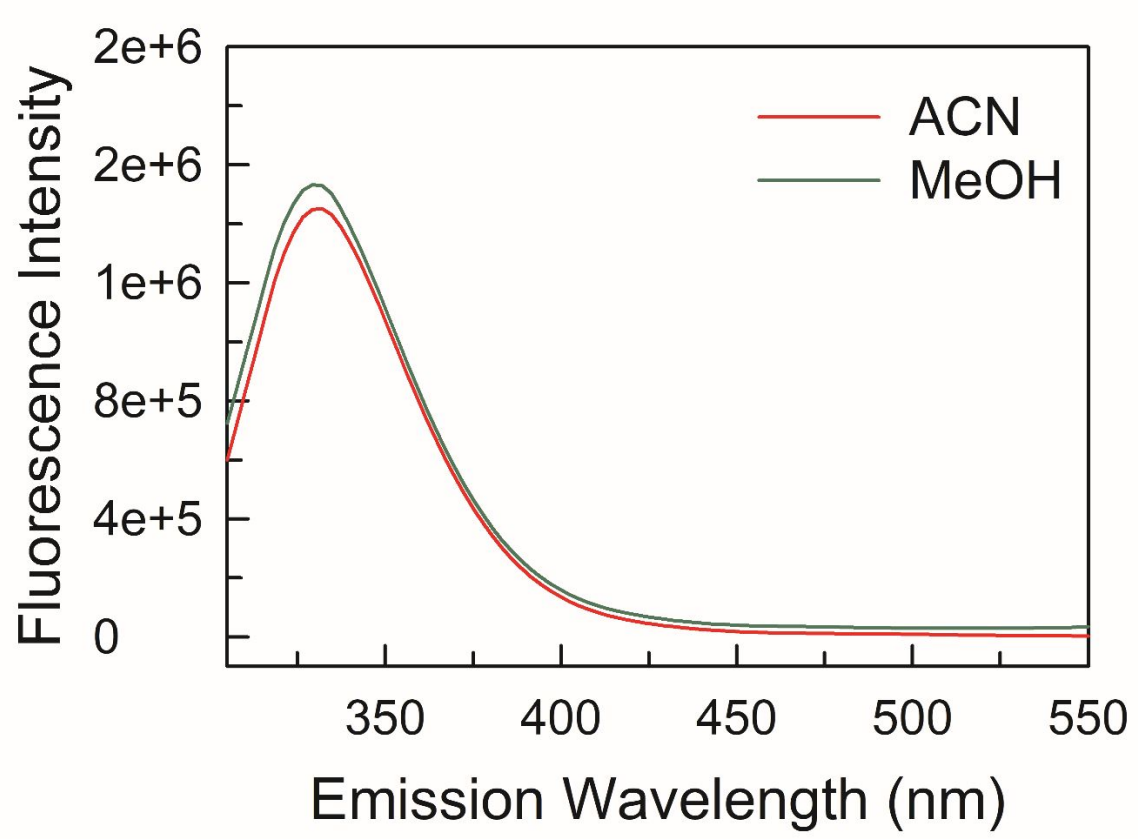


Fig. S6. Relative fluorescence emission spectra of **1** (25 μM, λ_{exc} = 295 nm) in presence of 10^{-2} M [H^+] in MeOH and ACN, at 25 °C.

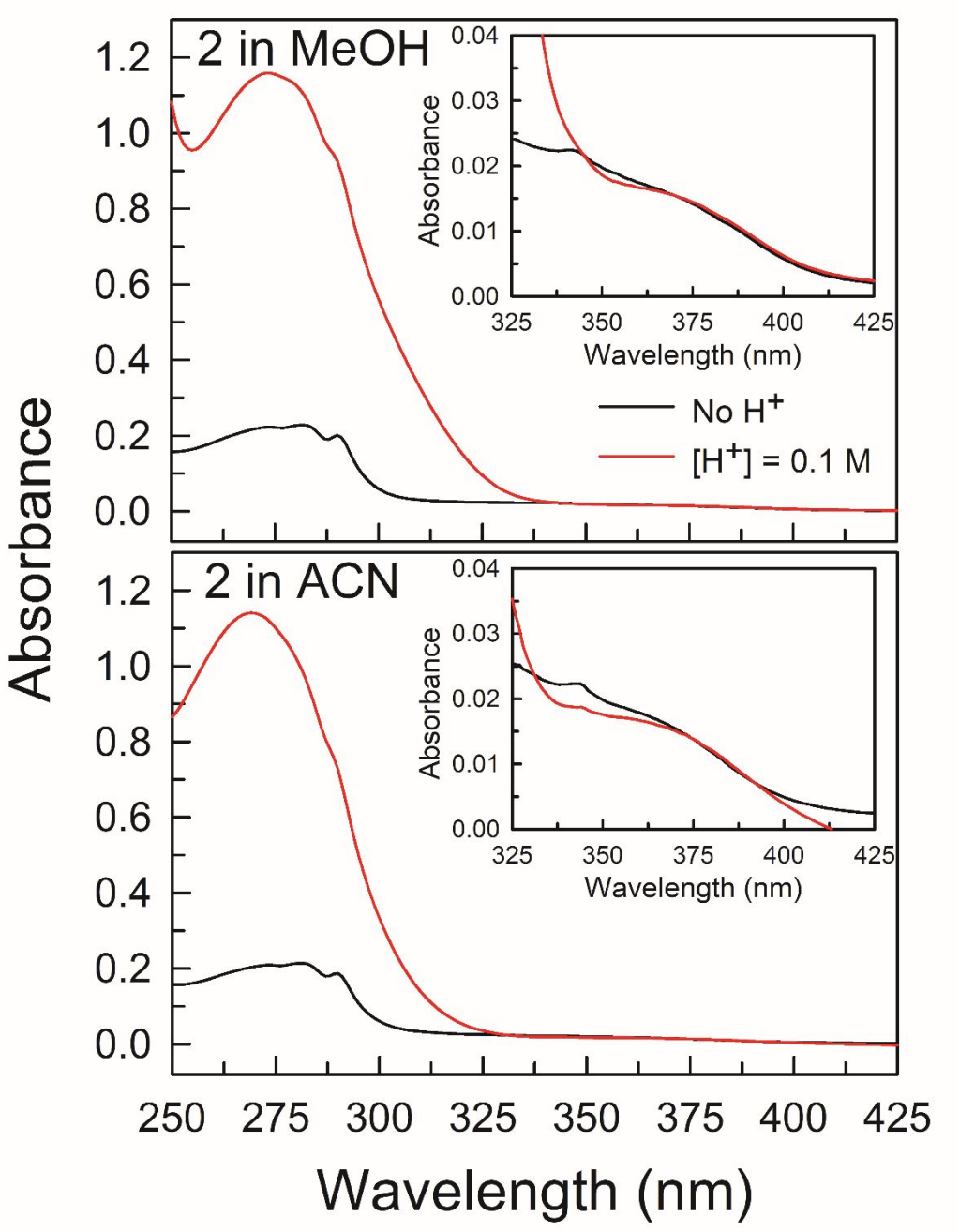


Fig. S7. Absorbance spectra of **2** (25 μM) dissolved in selected polar solvents in the absence and presence 10^{-1} M [H^+] at 25 °C. Corresponding spectra in the range 325-425 nm highlighting presence of band due to Trp-Trp intramolecular aggregate have been shown in the insets.

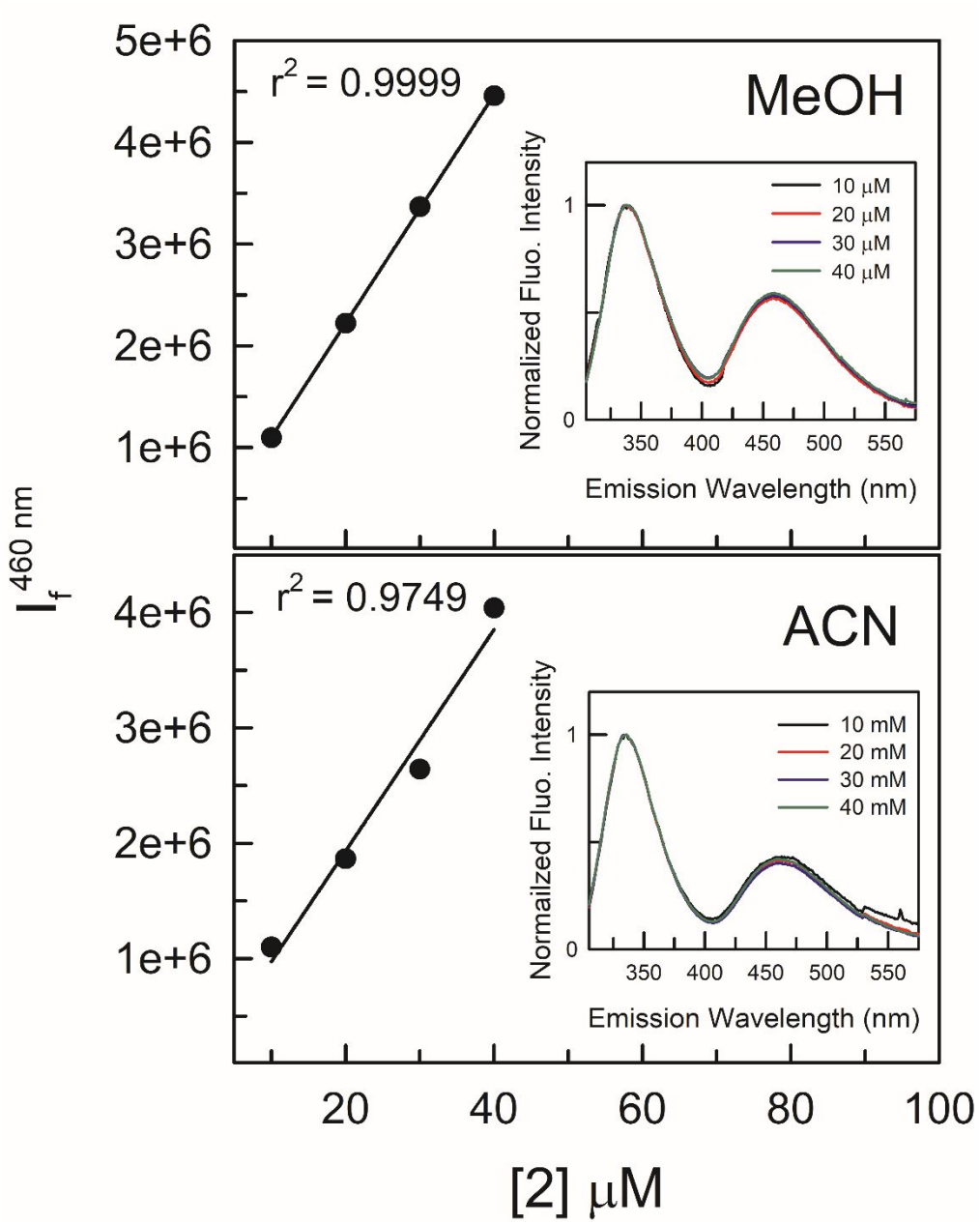


Fig. S8. Fluorescence intensities at 460 nm ($I_f^{460\ nm}$, corresponding to the aggregates, λ_{exc} = 295 nm) versus [**2**] in MeOH (top panel) and ACN (bottom panel) in the presence of $[H^+]$ = 10^{-3} M. Corresponding normalized emission spectra of **2** at different concentrations are provided in insets.

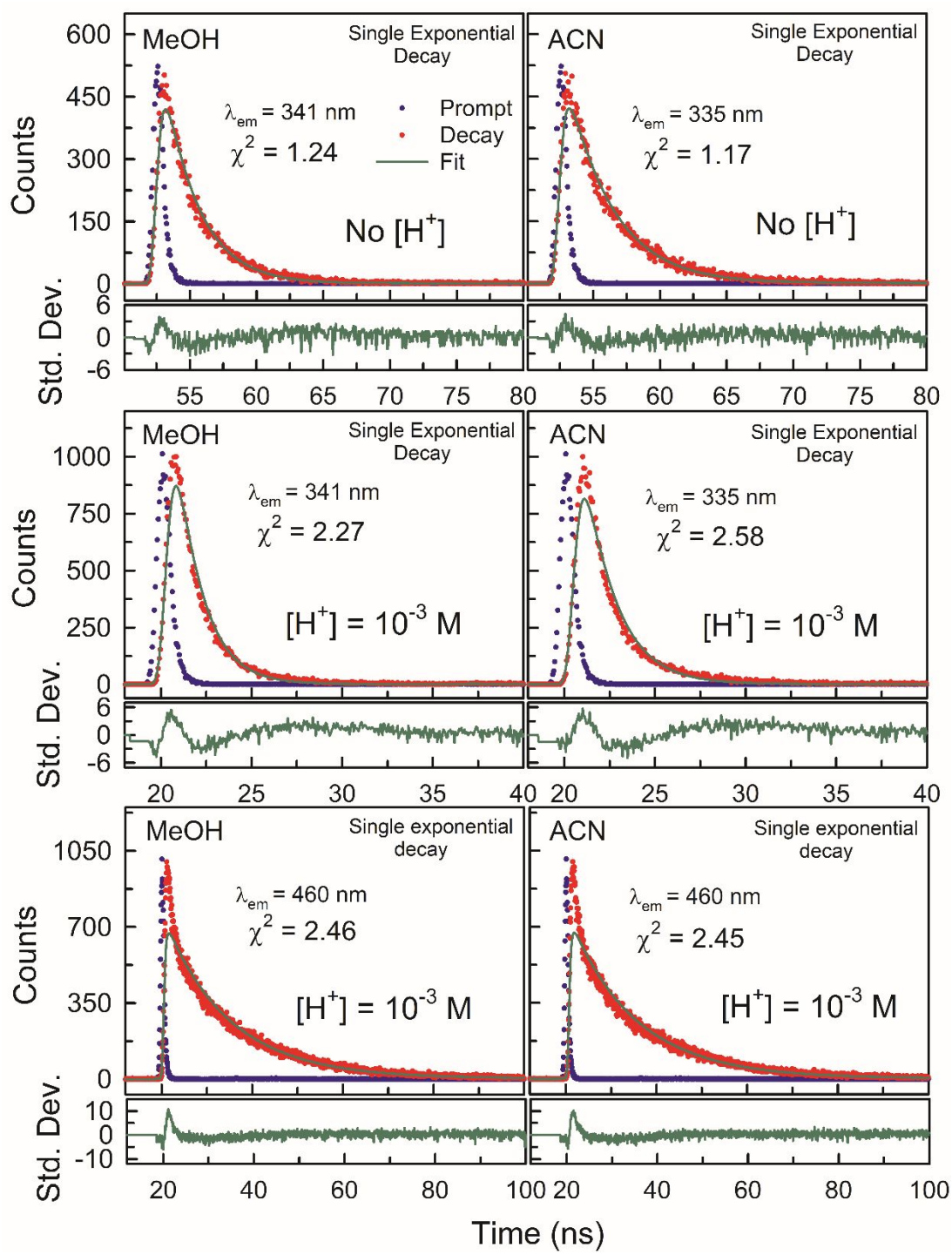


Fig. S9. Fit of excited-state intensity decay data of **2** fitted to single-exponential model in the absence of H^+ (top panels) and presence of 10^{-3} M $[H^+]$ (middle and lower panels), in MeOH and ACN, respectively at 25 °C. Emission wavelengths (λ_{em}) are mentioned in the respective panels. Excitation was carried out using a 295 nm LED. Residuals are provided below each panel.

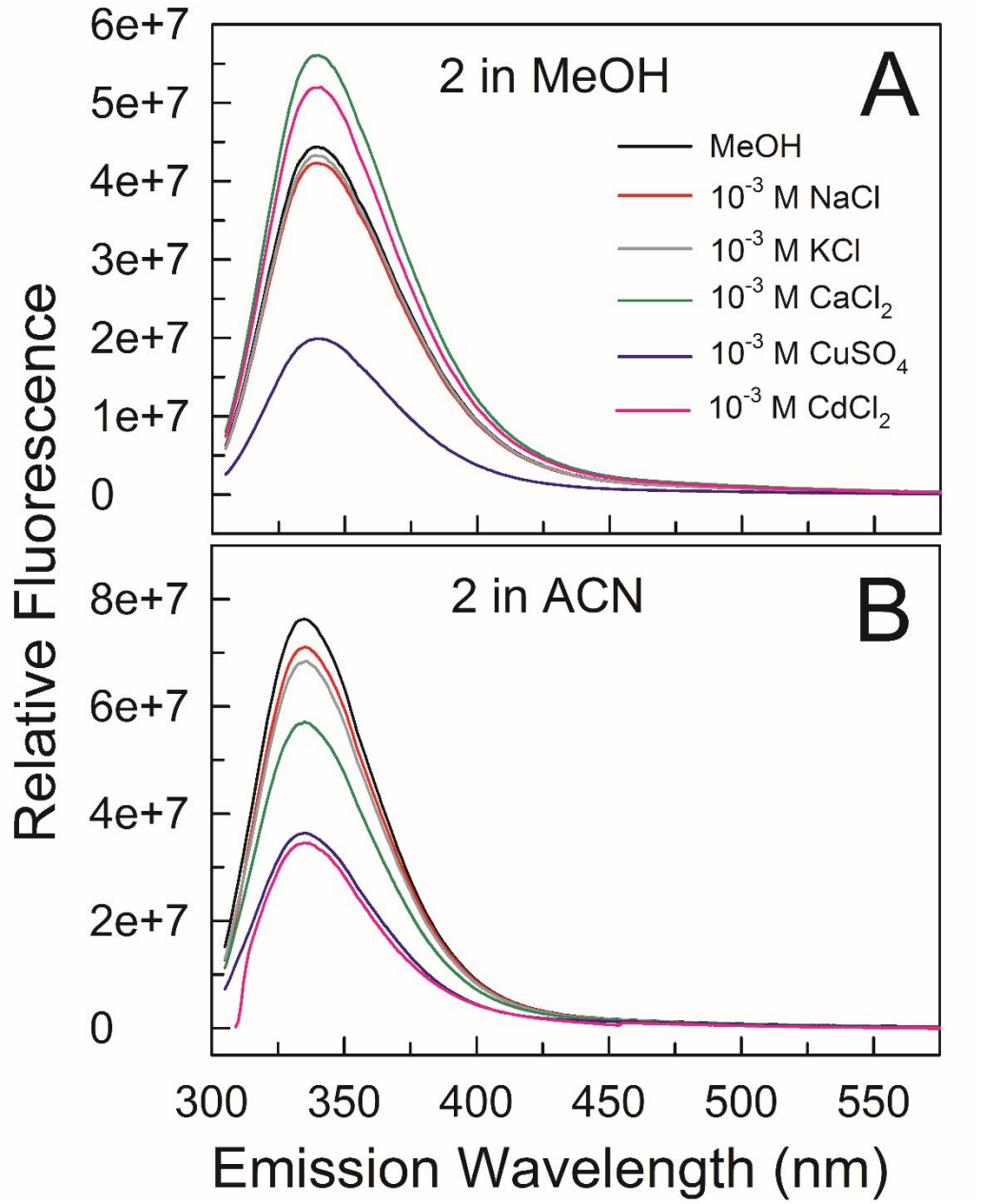


Fig. S10. Relative fluorescence emission spectra of **2** (25 μM, λ_{exc} = 295 nm) in the presence of various salts (10^{-3} M) at 25 °C in MeOH (panel A) and ACN (panel B), respectively.