Supporting Information

Discovery of a sensitive, selective, and tight binding fluorogenic substrate of bovine plasma amine oxidase

Ke-Qing Ling and Lawrence M. Sayre

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106

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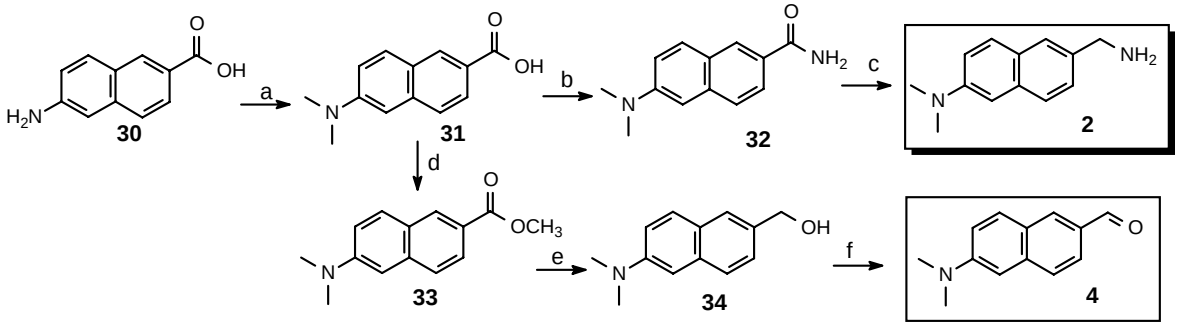
Synthesis of compounds 2, 4-7, 13-16, and 19-22

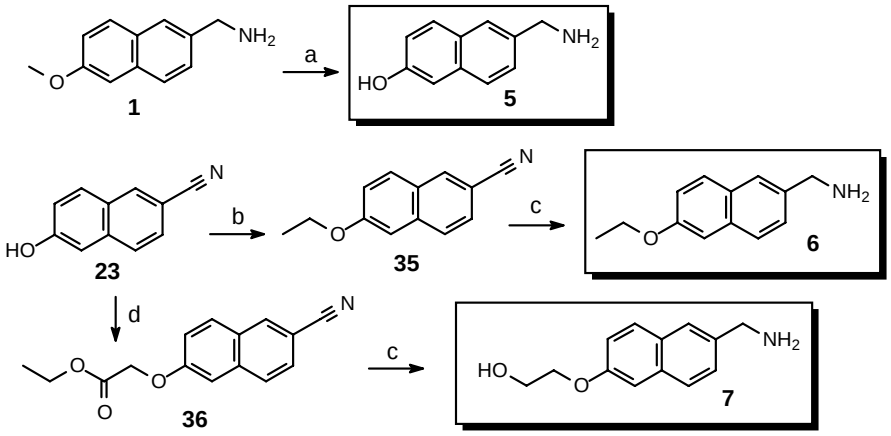
Syntheses of **2** and the corresponding aldehyde **4** started with the commercially available acid **30** (Scheme S1), which was first converted to **31** by reductive amination with CH_2O using $NaCNBH_3$, followed by amidation of **31** to amide **32**. The latter was then reduced with LAH to give **2**. On the other hand, treatment of **31** with $SOCl_2$ in methanol afforded ester **33**. Attempt to reduce **33** directly to **4** with stoichiometric DIBAL-H failed. The reaction did not stop at the aldehyde stage. Thus, one more equivalent of DIBAL-H was added, and alcohol **34** was obtained in high yield, which was then oxidized with Dess-Martin reagent, yielding **4** (Scheme S1)

Scheme S1



a: $CH_2O/NaCNBH_3/MeOH$; b: (1) DCC/N-hydroxysuccinimide/DMF, (2) NH_3; c: LAH/Et_2O
d: $SOCl_2/MeOH$; e: DIBAL-H/CH_2Cl_2; f: Dess-Martin reagent/CH_2Cl_2

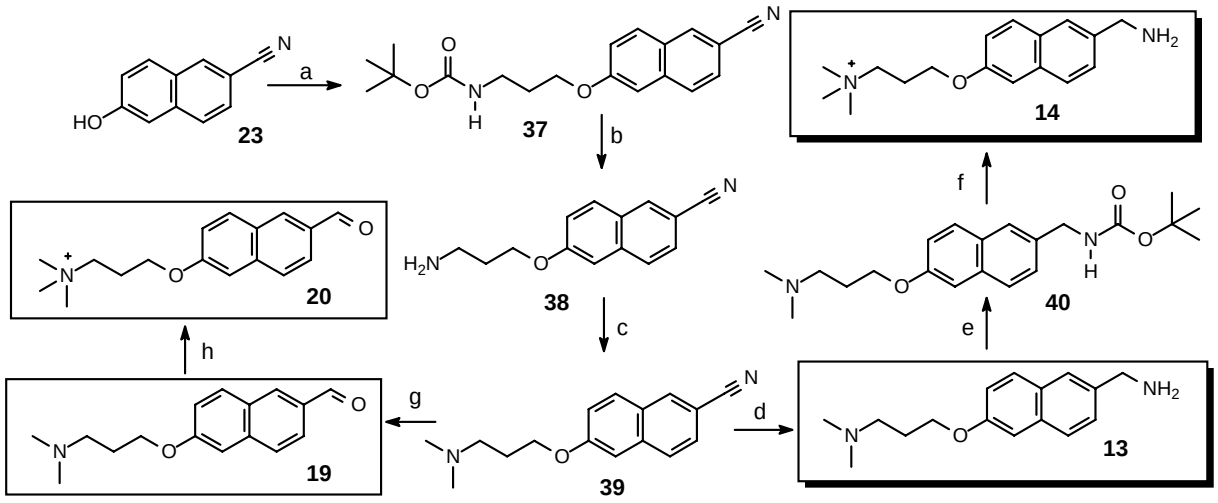
Scheme S2



a: 48% HBr; b: $EtBr/K_2CO_3/KI/DMF$; c: LAH/Et_2O; d: $BrCH_2CO_2Et/K_2CO_3/KI/DMF$

Compound **5** in its hydrobromide form was easily obtained by dimethylation of **1** with 48% aqueous HBr (Scheme S2). Compound **6** was synthesized by coupling 6-cyano-2-naphthol (**23**) with EtBr, followed by LAH reduction of the cyanonaphthyl ether **35** (Scheme S3). Similarly, compound **7** was synthesized by coupling **23** with ethyl 2-bromoacetate, followed by LAH reduction of the intermediate **36** (Scheme S2).

Scheme S3



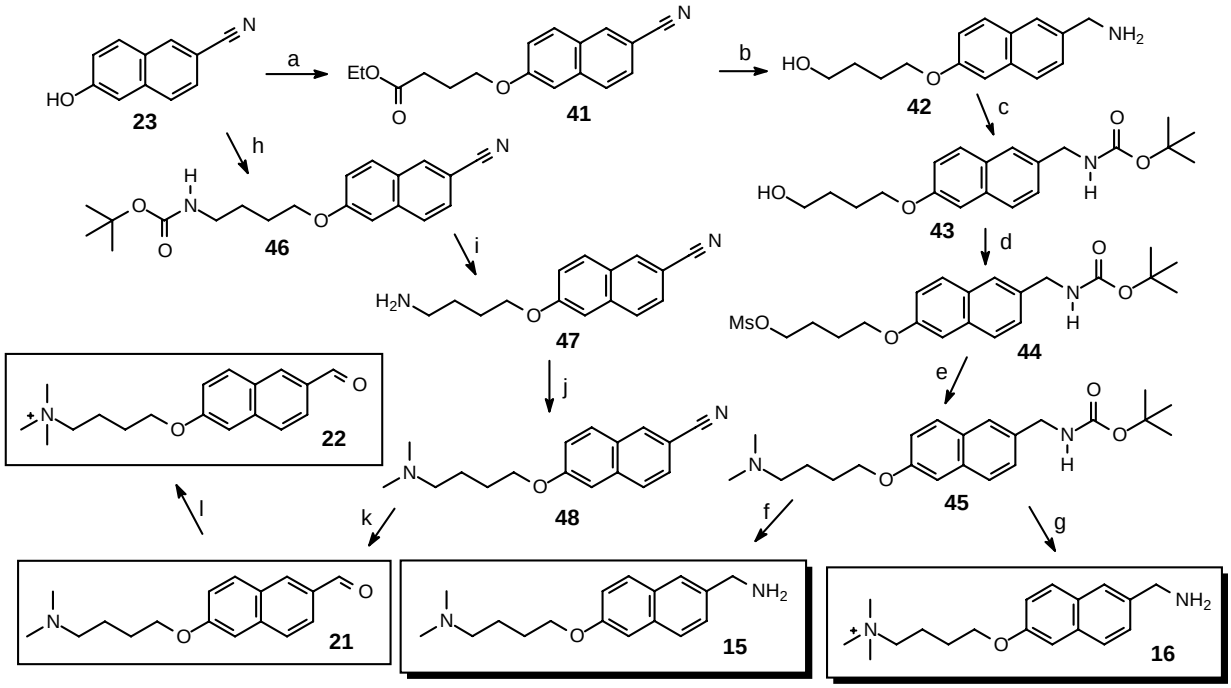
a: $BrCH_2CH_2CH_2NHBoc/K_2CO_3/KI/DMF$; b: TFA/CH_2Cl_2; c: $CH_2O/NaCNBH_3/MeOH$; d: LAH/Et_2O;
e: $Boc_2O/TEA/CH_2Cl_2$; f: (1) CH_3I/Et_2O, (2) $Ag_2CO_3/MeOH$, (3) HCl; g: DIBAL-H/CH_2Cl_2; h: CH_3I.

Syntheses of the C_3 tether diamine substrates **13** and **14**, along with the corresponding aldehydes **19** and **20** were accomplished following the same strategy as in the C_2 tether cases (Scheme S3). Thus, reaction of **23** with Boc protected 3-aminopropyl bromide, followed by deprotection of ether **37** afforded **38**, which was converted to **39** by reductive methylation with CH_2O. Reduction of **39** with LAH gave **13**. Boc protection of **13**, followed by quaternization of **40** with MeI, anion exchange with Ag_2CO_3, and deprotection with aqueous HCl gave **14**. Reduction of **39** with DIBAL-H afforded aldehyde **19**. The latter was quaternized with MeI to give aldehyde **20**.

A different strategy was used to synthesize the C_4 tether diamine substrates **15** and **16** (Scheme S4). Thus, coupling of **23** with ethyl 4-bromobutyrate gave ester **41**, which was reduced with LAH to **42**. The latter was Boc protected to give **43**, and the latter mesylated to give **44**, which was allowed to react with $HNMe_2$ to afford tertiary amine **45**. Deprotection of **45** gave **15**,

whereas quaternization of **45** with MeI, followed by anion exchange and deprotection yielded **16** (Scheme S4). The corresponding aldehydes **21** and **22** were prepared following the same strategy as in the cases of C_3 and C_4 aldehydes, though the total yields in both cases were extremely low (Scheme S4).

Scheme S4



a: $BrCH_2CH_2CH_2CO_2Et/K_2CO_3/KI/DMF$; b: LAH/Et_2O; c: $Boc_2O/Et_3N/CH_2Cl_2$; d: $MsCl/DIEA/CH_2Cl_2$; e: $Me_2NH/MeOH$; f: HCl;
g: (1) MeI/Et_2O, (2) $Ag_2CO_3/MeOH$, (3) HCl; h: $BrCH_2CH_2CH_2CH_2NHBoc/K_2CO_3/KI/DMF$; i: TFA/CH_2Cl_2;
j: $CH_2O/NaCNBH_3/MeOH$;k: $DIBAL\text{-}H/CH_2Cl_2$; l: MeI/Et_2O

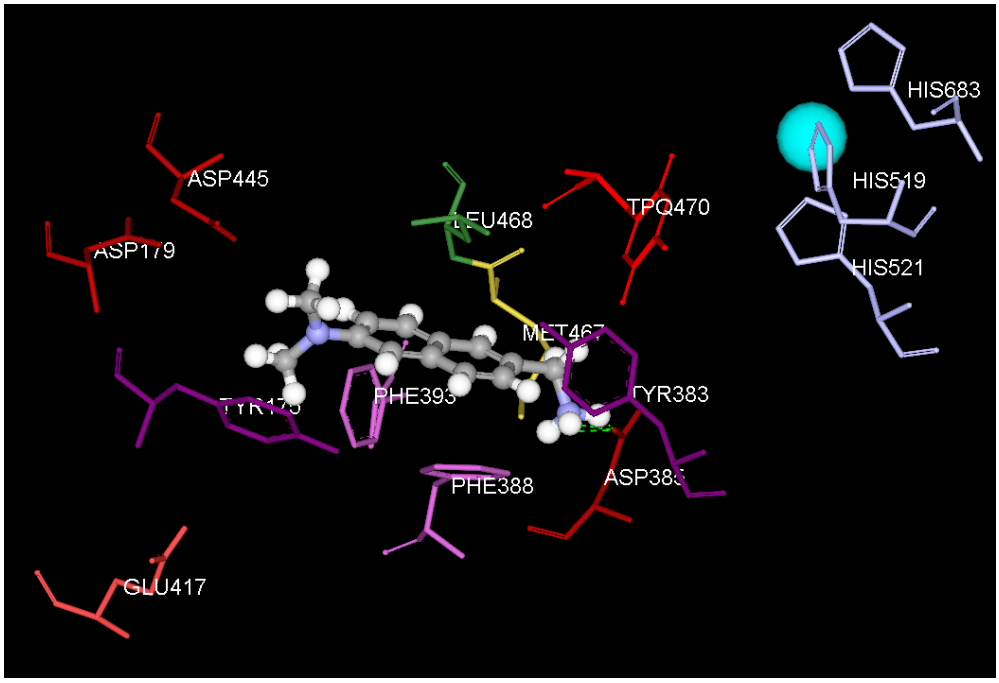


Figure S1. The best scored productive docking mode of compound **2** with native BPAO.

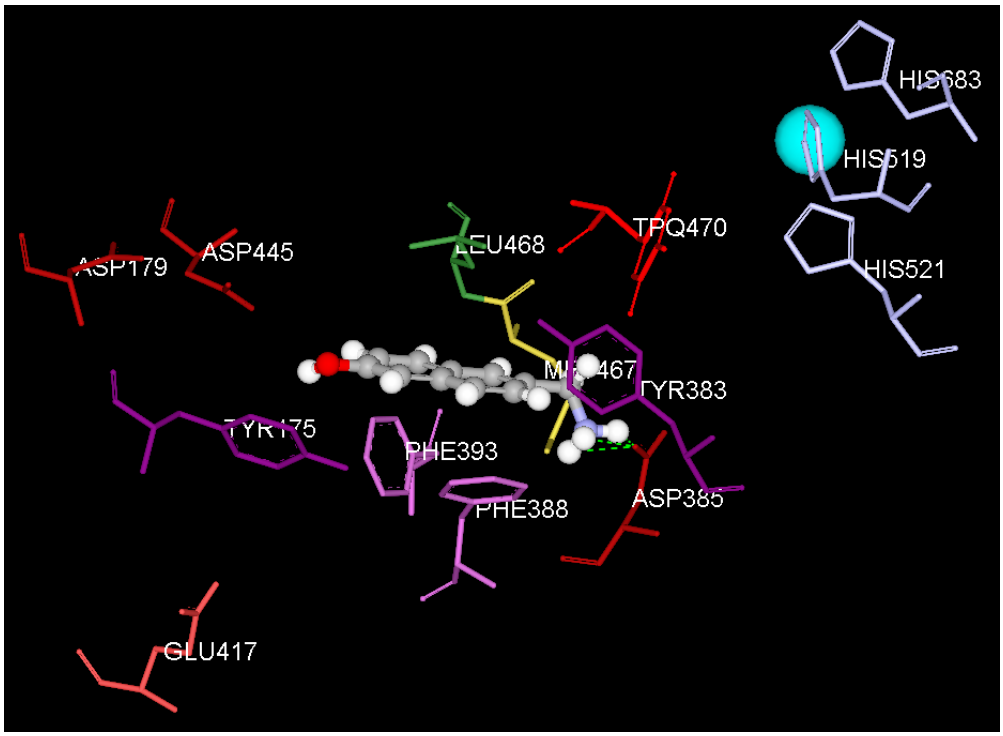


Figure S2. The best scored productive docking mode of compound **5** with native BPAO.

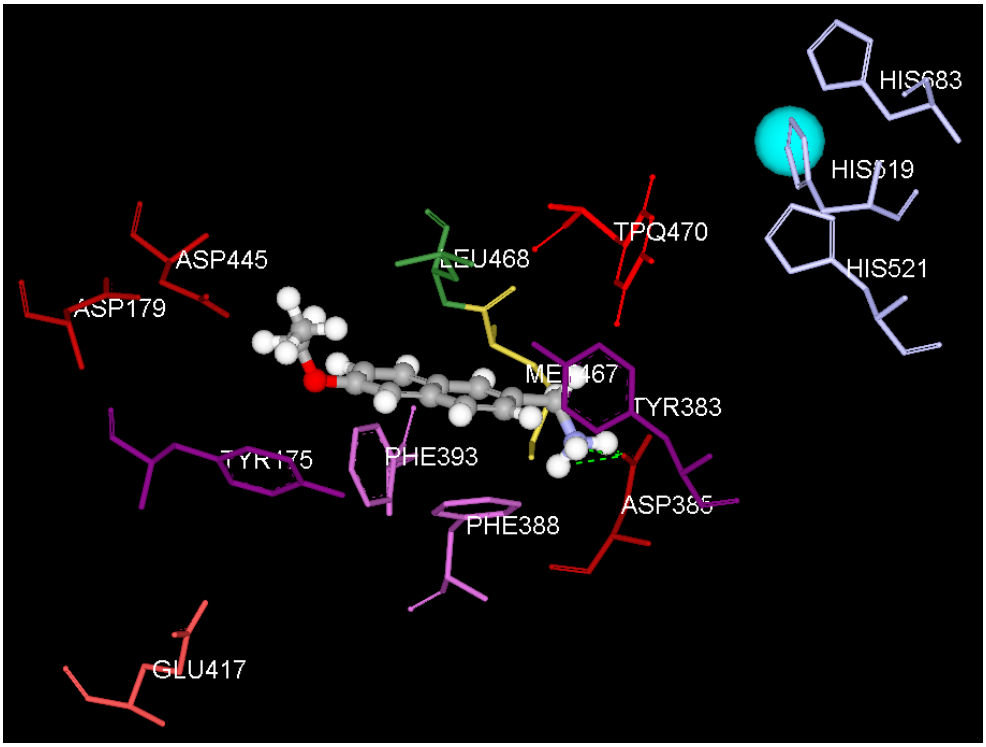


Figure S3. The best scored productive docking mode of compound **6** with native BPAO.

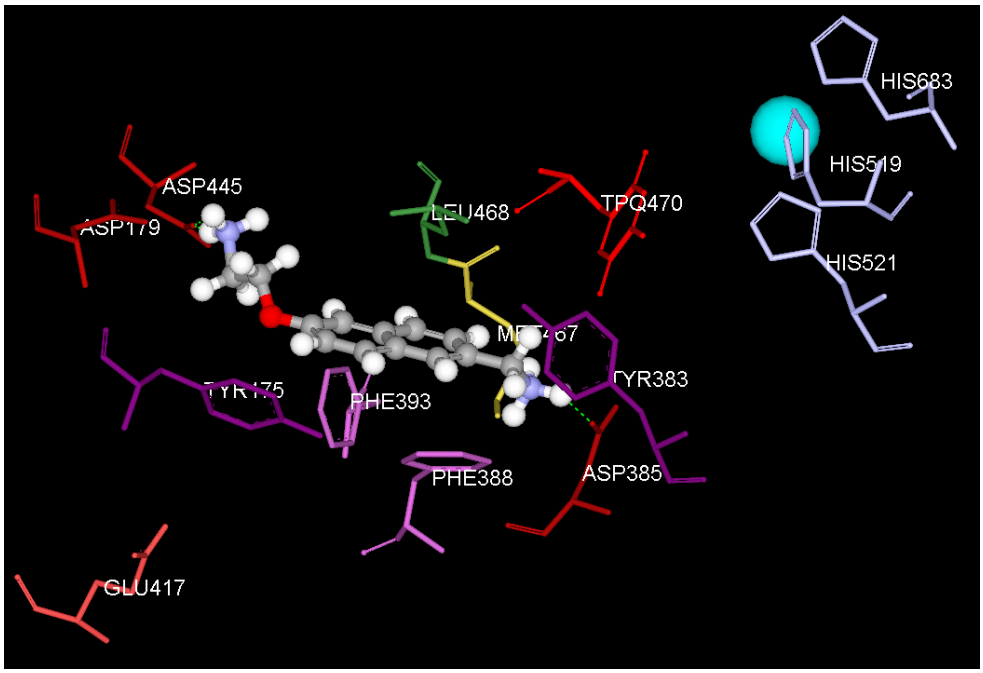


Figure S4. The best scored productive docking mode of compound **9** with native BPAO. Note that the two substrate amino groups are interacting with Asp445 and Asp385 through hydrogen bonding.

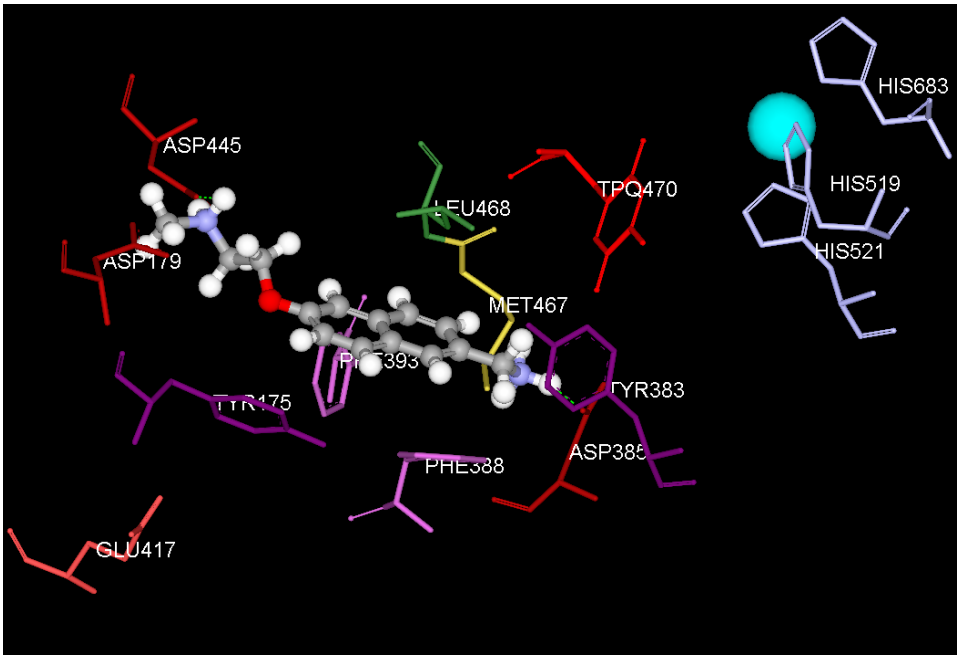


Figure S5. The best scored productive docking mode of compound **10** with native BPAO. Note that the two substrate amino groups are interacting with Asp445 and Asp385 through hydrogen bonding.

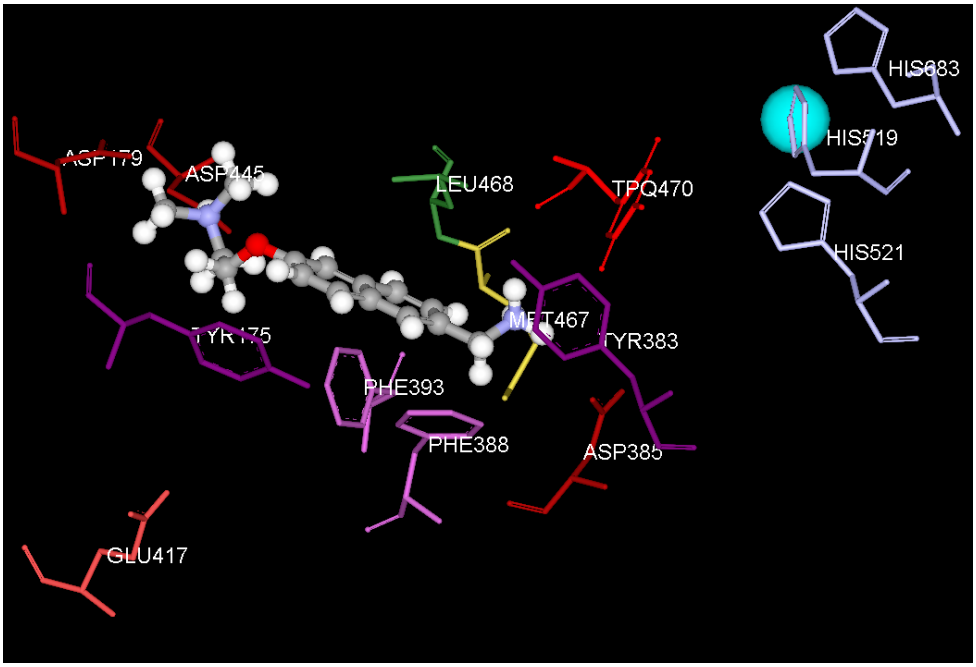


Figure S6. The best scored productive docking mode of compound **11** with native BPAO. Note that the substrate dimethylamino group is interacting with Asp445 through hydrogen bonding while the substrate amino group is located in between the TPQ O_5 and the Asp385.

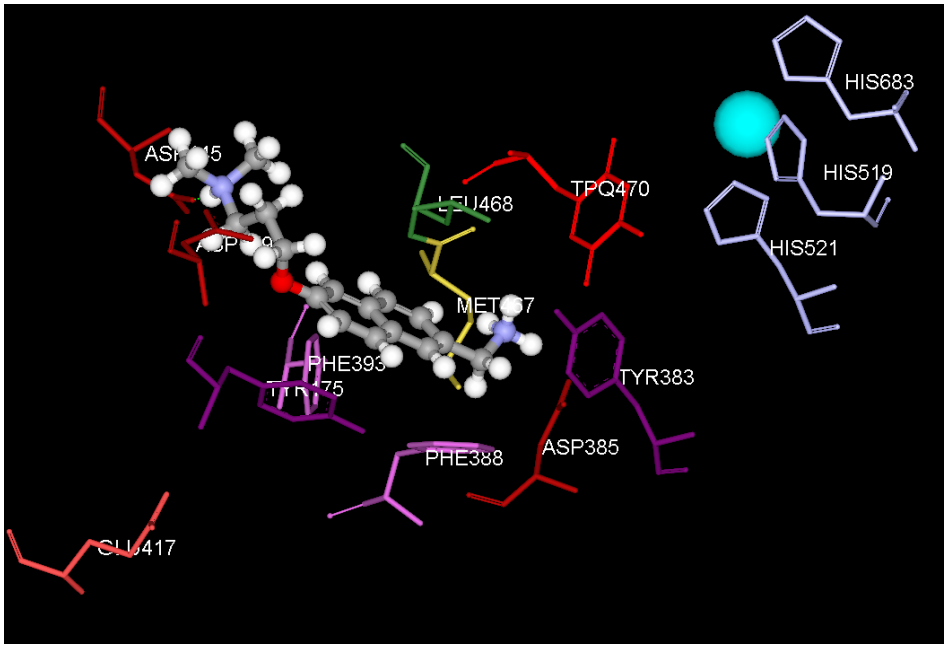


Figure S7. The best scored productive docking mode of compound **13** with native BPAO. Note that the substrate dimethylamino group is interacting with Asp445 through hydrogen bonding while the substrate amino group is located in between the TPQ O_5 and the Asp385.

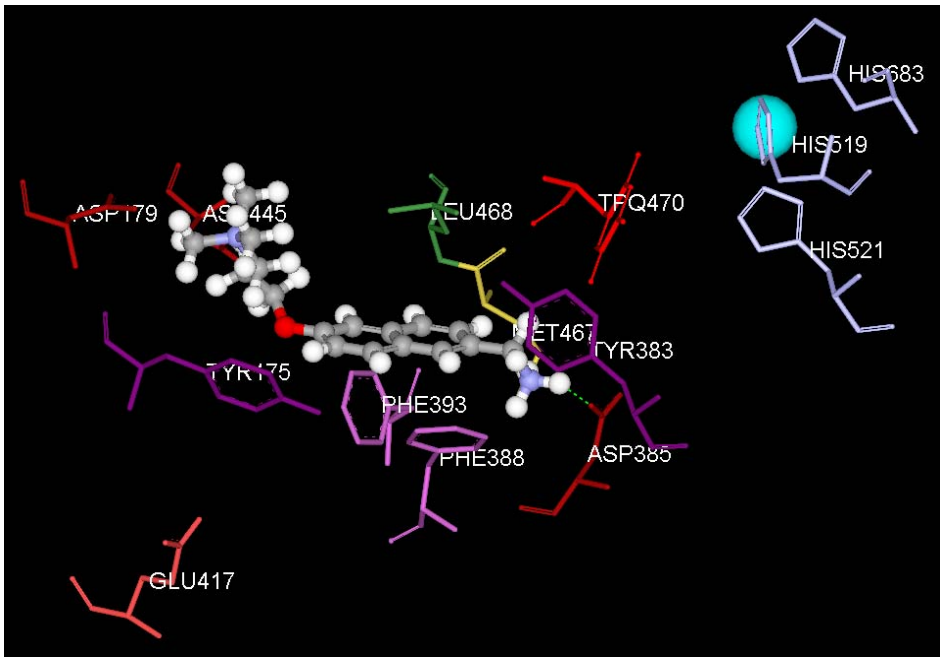


Figure S8. The best scored productive docking mode of compound **14** with native BPAO. Note that the substrate trimethylamino group is interacting with Asp179 through electrostatic attraction while the substrate amino group is interacting with Asp385 through hydrogen bonding.

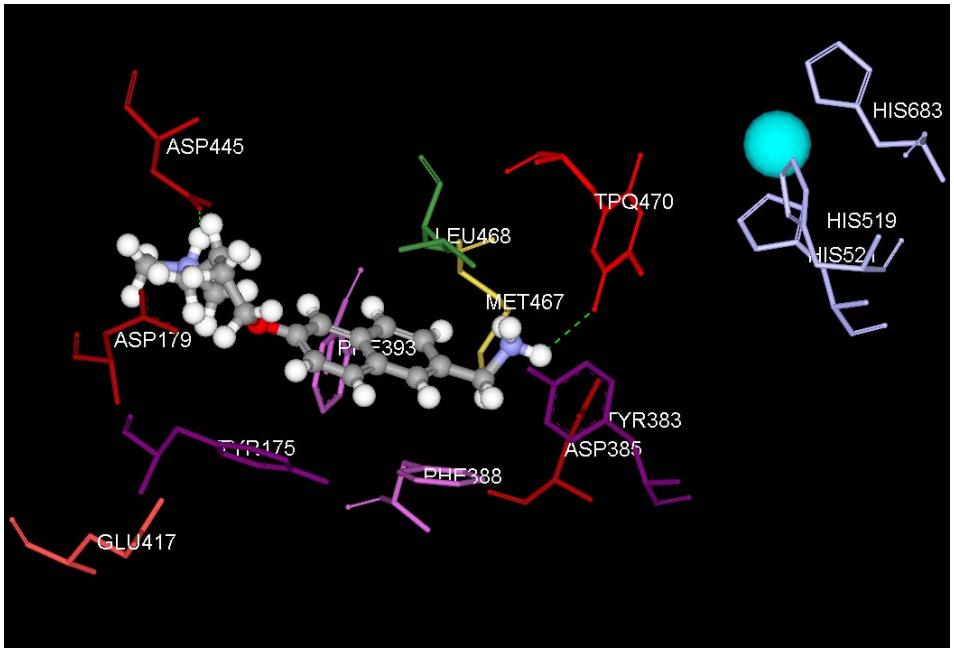


Figure S9. The best scored productive docking mode of compound **15** with native BPAO. Note that the substrate dimethylamino group is interacting with Asp445 through hydrogen bonding while the substrate amino group is interacting with TPQ O_5 through hydrogen bonding.

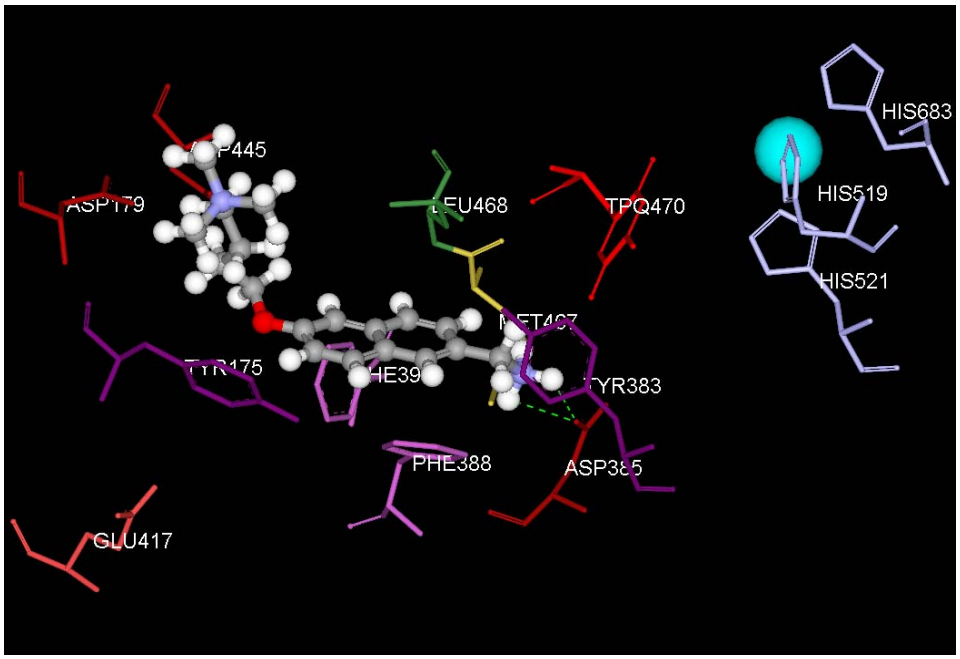


Figure S10. The best scored productive docking mode of compound **16** with native BPAO. Note that the substrate trimethylamino group is interacting with Asp179 through electrostatic attraction while the substrate amino group is interacting with Asp385 through hydrogen bonding.

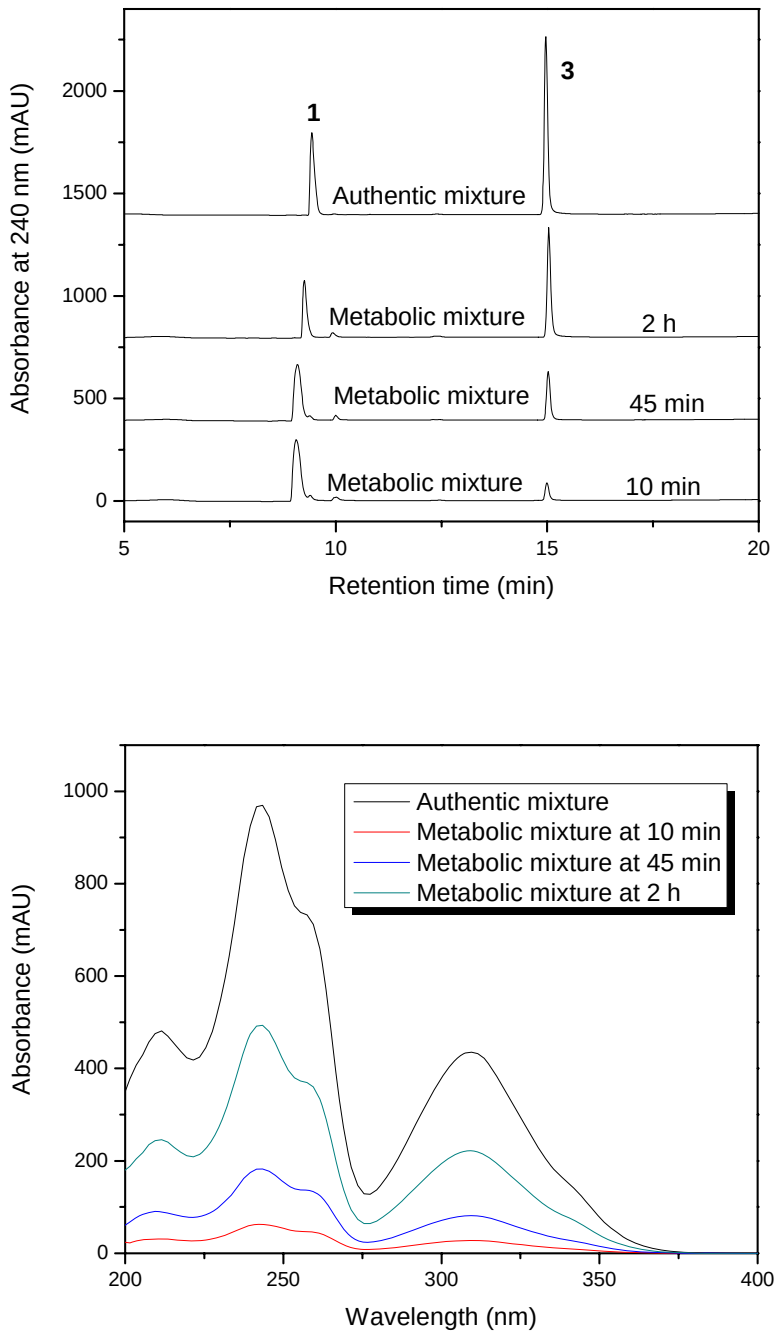
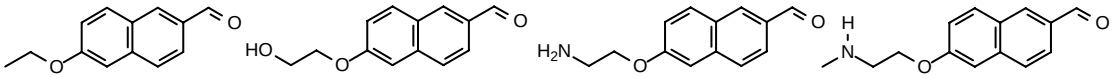


Figure S11. Top panel: HPLC diagram of a mixture of authentic **1** and **3** (both 200 μM), and time dependent HPLC diagrams of a metabolic mixture of **1** (200 μM) with BPAO (0.1 μM) in 0.1 M of pH 7.2 phosphate buffer at 25 °C. Bottom panel: the corresponding DAD spectra of peaks at 15 min (**3**).

Electronic effect of distal side chain on the optical properties of turnover products

Optical properties of all available authentic aldehydes were examined (Table S1). Despite that the extinction coefficients (ε) of **3** and **17-22** are similar; there are 3 nm blue shifts in maximum absorption wavelength (λ_{max}) of C_2 tether aldehydes **17** and **18** as compared to **3** (Table S1 and Figure S12). Furthermore, 7 nm blue shifts in maximum emission wavelength (λ_{em}) and slight decreases in the relative fluorescence intensities (I_{max}) were also observed in the fluorescence spectra of **17** and **18** as compared to that of **3**, whereas in the C_3 and C_4 tether cases (**19-22**), the blue shifts are smaller (3 and 2 nm) and the I_{max} are essentially the same as that of **3** (Table S1). These phenomena can be understood in terms of partial cancellation of the "push" character of the alkoxy groups in **17-22** by the adjacent electron-withdrawing amino groups, which is most severe in the C_2 tether cases, such that the "push-pull" effects are weakened compared to that in **3**, causing the blue shifts in UV spectra and decreases in Stokes' shifts and emission intensities in fluorescence spectra. Based on this rational and the electronic effects of different RO groups, it is reasonable to assume that the optical properties of **49** are similar to those of **3**, and the optical properties of **50-52** are similar to those of **17**. Thus, although compounds **49-52** were not synthesized, the k_{cat} value of substrate **6** was estimated using the I_{max} value of **3**, whereas the k_{cat} values of **7**, **9** and **10** were estimated based on the I_{max} values of **17** (Table S1).



49 **50** **51** **52**

Table S1. Optical properties of turnover products[a]

turnover product	UV-vis		fluorescence		
	λ_{max} (nm)	$\varepsilon \times 10^{-4}$ (M^{-1} cm^{-1})	λ_{ex} (nm)	λ_{em} (nm)	relative intensity ratio[b]
3	313	1.33	350	460	[1.00]
4	377	1.23	420	530	0.46
8[c]	316	1.08			
17	310	1.38	350	453	0.93
18	310	1.37	350	453	0.87
19	313	1.37	350	457	1.08
20	313	1.36	350	457	1.03
21	313	1.33	350	458	1.07
22	313	1.32	350	458	1.02

[a]All parameters were measured in 0.1 M of pH 7.2 phosphate buffer at 30 °C. [b]Fluorescence intensity relative to **3**. [c]Compound **8** was only weakly fluorescent.

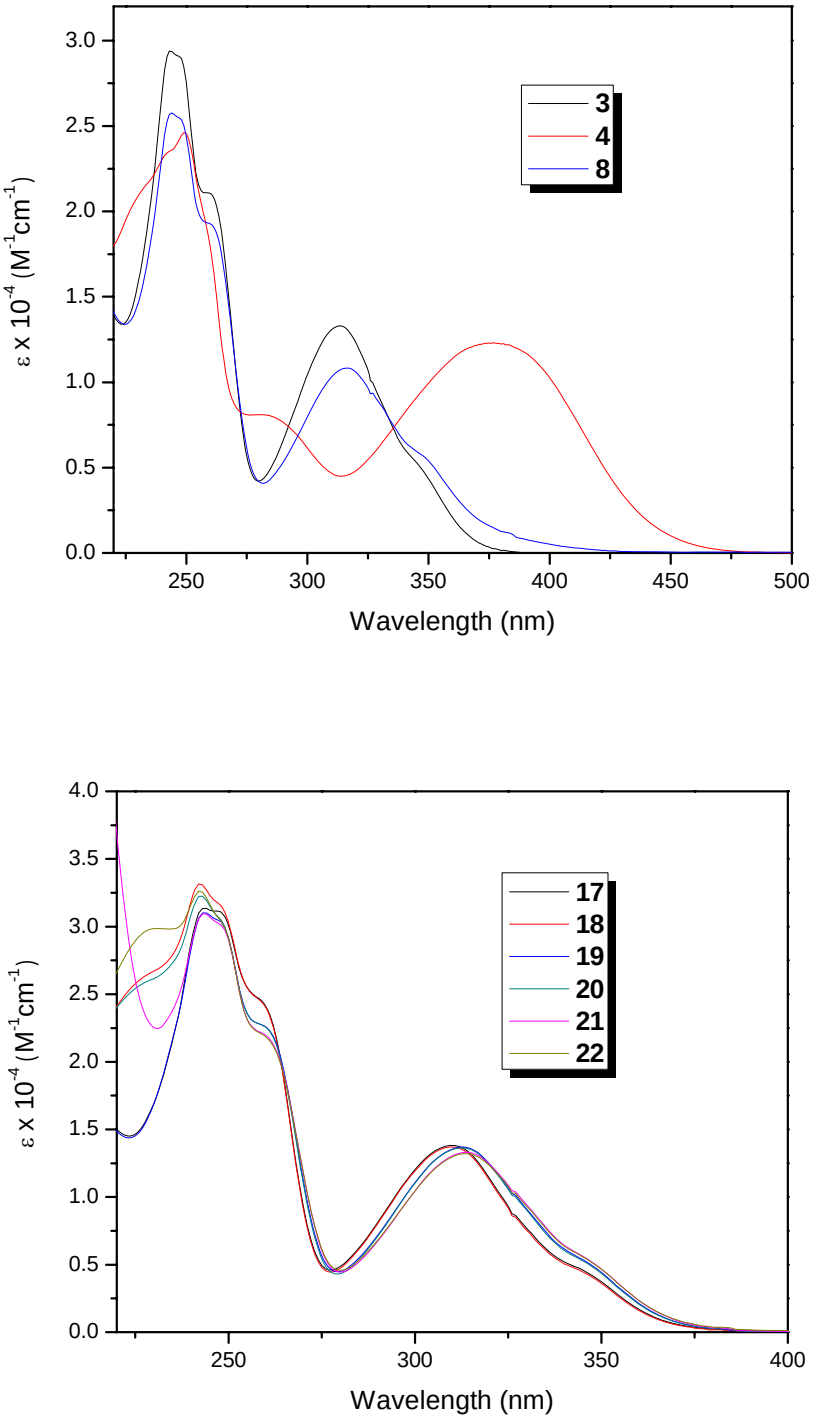


Figure S12. Molar absorption spectra of authentic aldehyde turnover products in 0.1 M of pH 7.2 phosphate buffer at 30 °C.

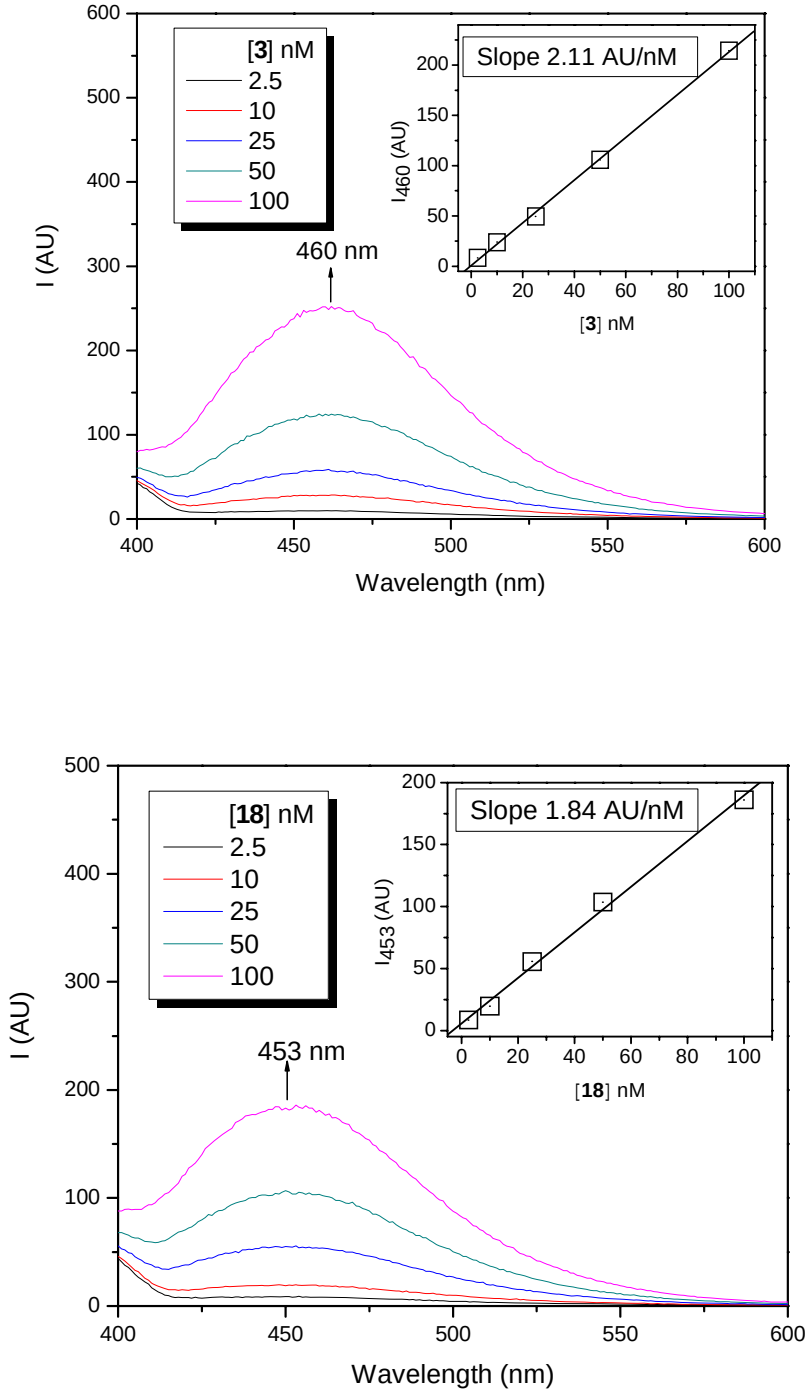


Figure S13. Fluorescence spectra of aldehydes **3** (top) and **18** (bottom) in 0.1 M of pH 7.2 phosphate buffer at 30 °C and the corresponding calibration plot (insets). The excitation wavelengths (λ_{ex}) were both 350 nm.

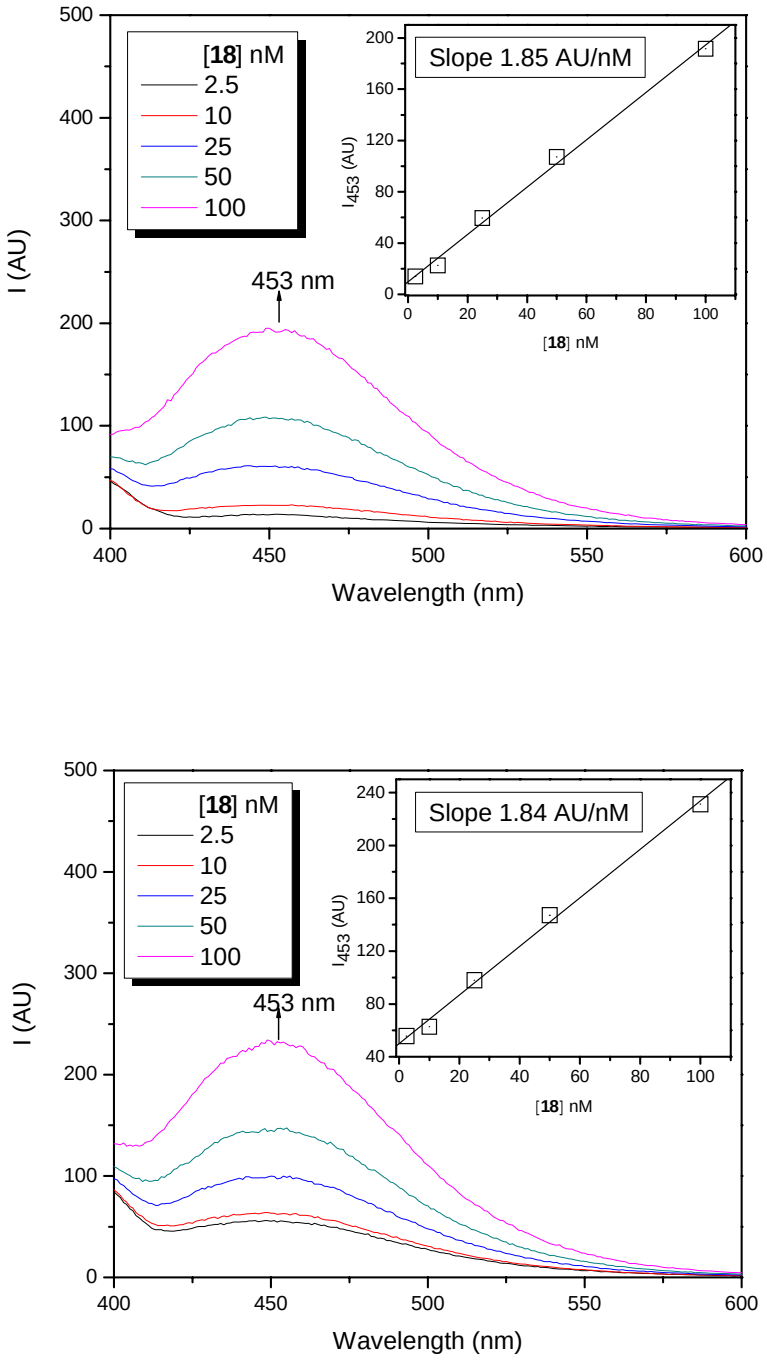


Figure S14. Fluorescence spectra of aldehyde **18** in 0.1 M of pH 7.2 phosphate buffer in the presence of 10 nM of BPAO (top) or 10 μM of **12** (bottom) at 30 °C and the corresponding calibration plot (insets). The excitation wavelength (λ_{ex}) was 350 nm.

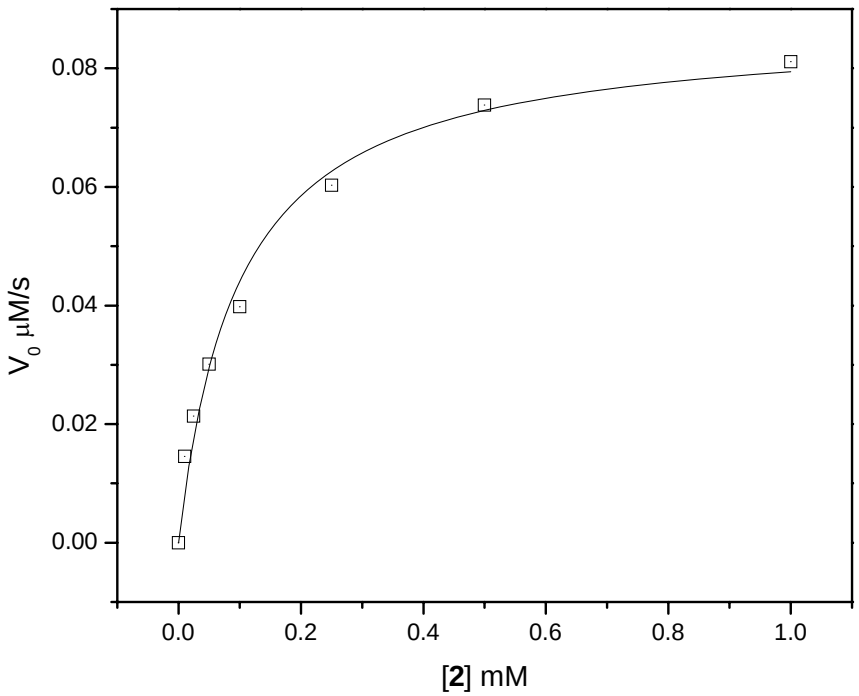


Figure S15. Plot of initial oxidation velocity (V_0) versus substrate concentration for **2** in 33 mM of pH 7.2 phosphate buffer in the presence of BPAO (0.2 μM) at 30 °C. The monitoring wavelength (λ) was 400 nm.

Table S2. Detailed conditions for substrate activity evaluation of arylmethylamines with BPAO in pH 7.2 phosphate buffer at 30 °C[a]

substrate	method	λ or $\lambda_{ex}/\lambda_{em}$	buffer concentration	concentration of BPAO
BA	UV	250 nm	0.1 M	0.1 μM
1	UV	340 nm	33 mM[b]	0.1 μM
1	Fluorescence	350/460 nm	33 mM[b]	5 nM
2	UV	400 nm	33 mM[c]	0.2 μM
5	UV	340 nm	0.1 M	0.1 μM
6	Fluorescence	350/460 nm	33 mM[d]	5 nM
7	Fluorescence	350/450 nm	0.1 M	5 nM
9	Fluorescence	350/453 nm	0.1 M	5 nM
10	Fluorescence	350/453 nm	0.1 M	5 nM
11	Fluorescence	350/453 nm	0.1 M	5 nM
12	Fluorescence	350/453 nm	0.1 M	2 nM
13	Fluorescence	350/457 nm	0.1 M	5 nM
14	Fluorescence	350/457 nm	0.1 M	5 nM
15	Fluorescence	350/458 nm	0.1 M	5 nM
16	Fluorescence	350/458 nm	0.1 M	5 nM

[a]The listed working wavelengths (λ) for UV-vis measurements and the excitation wavelengths (λ_{ex}) for fluorescence measurements were chosen such that interference from substrates can be minimized. This is especially crucial for substrates with large K_m, where high substrate concentrations have to be employed. [b]The substrate started to precipitate at 3 mM. [c]The substrate started to precipitate at 2 mM. [d]The substrate started to precipitate at 1 mM.

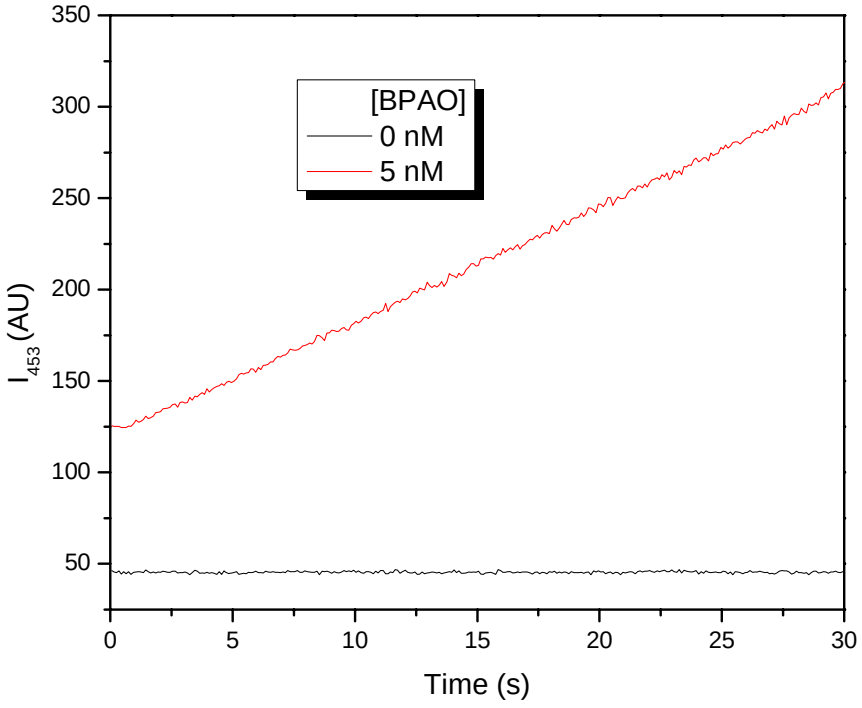


Figure S16. Time-dependent ΔI_{453} of **12** (10 μM) in 0.1 M of pH 7.2 phosphate buffer in the absence (black) and presence (red) of BPAO (5.0 nM) at 30 °C. The excitation wavelength (λ_{ex}) was 350 nm.

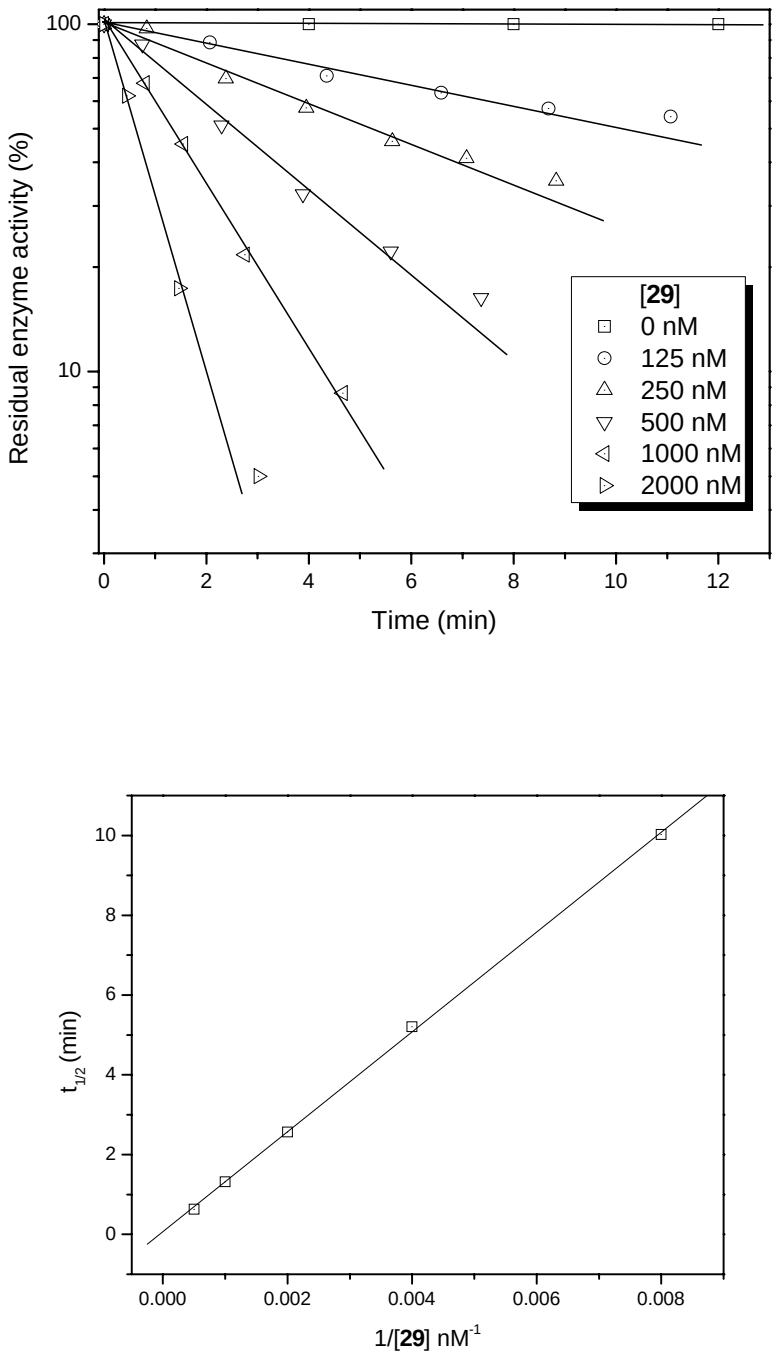


Figure S17. Top panel: time dependent activity loss of BPAO (50 nM) incubated with various concentrations of 1-amino-2,3-butadiene (**29**) in 0.1 M of pH 7.2 phosphate buffer at 30 °C as monitored by the new fluorescence assay. Bottom panel: the corresponding Kitz and Wilson plot.

Experimental

General. NMR spectra were obtained on a 400 MHz instrument (^{1}H NMR at 399.75 MHz, ^{13}C NMR at 99.94 MHz), with chemical shifts being referenced to the solvent peak. High resolution mass spectra (HRMS) were obtained in the FAB mode. UV-visible spectra were obtained using a spectrophotometer equipped with a temperature-controlled multiple-cell compartment. Fluorescence measurements were conducted on a fluorescence spectrophotometer equipped with a temperature-controlled single-cell compartment, and the excitation/emission slits were set at 10/20 nm. All solutions were prepared using double distilled water. 6-Methoxy-2-naphthaldehyde (**3**), 6-methoxy-2-naphthonitrile, 6-cyano-2-naphthol (**23**) and *p*-xylylenediamine (PXDA) were commercially available reagents. 6-Hydroxynaphthalene-2-carboxaldehyde (**8**) was synthesized according to a literature approach.[1] 1-Amino-2,3-butadiene (**29**) was prepared as previously described.[2]

(6-(Aminomethyl)naphthalen-2-yl)-dimethylamine dihydrochloride (2·2HCl). To a solution of 6-amino-2-naphthoic acid **(30**) (3.74 g, 20 mmol, Aldrich Chemical Co.), glacial HOAc (10 mL), and 37% aqueous CH_2O (4 mL, 54 mmol) in 100 mL of MeOH was added in small portions solid $NaCNBH_3$ (3.78 g, 60 mmol) under ice-bath cooling and vigorous electromagnetic stirring. The mixture was then stirred at room temperature for 2 h and MeOH was evaporated. The residual mixture was diluted with 200 mL of brine, adjusted to pH 6 with solid $NaHCO_3$, and extracted with EtOAc (3×200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give a residue that was crystallized from EtOAc-hexanes to afford 6-(dimethylamino)-2-naphthoic acid (**31**) as a light brown solid (3.74 g, 17.4 mmol, 87%).

A mixture of **31** (1.83 g, 8.5 mmol), *N*,*N*'-dicyclohexylcarbodimide (1.80 g, 8.7 mmol), and N-hydroxysuccinimide (1.04 g, 9.0 mmol) in 20 mL of dimethylformamide (DMF) was stirred at room temperature for 2 h, at which point dry NH_3 was bubbled through the solution for 5 min. The mixture was further stirred for 1 h and then was diluted with 200 mL of Et_2O. The solid was filtered out and washed with Et_2O. The combined filtrates were washed with brine (3×50 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from EtOAc-hexanes to afford 6-(dimethylamino)-2-naphthoic amide (**32**) as a light brown solid (1.67 g, 7.8 mmol, 94%).

A mixture of **32** (1.5 g, 7.0 mmol) and lithium aluminum hydride (LAH, 1.1 g, 29 mmol) in 100 mL of absolute Et_2O was stirred at room temperature overnight. The excess LAH was decomposed by EtOAc as in the synthesis of **1**·HCl described in the text, and the mixture was further treated with ice and sodium tartrate. The organic layer was separated, the aqueous layer was saturated with solid NaCl and extracted with Et_2O (3×50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated, and the residue was taken up in 10 mL of 12 *N* aqueous HCl. Evaporation of solvent and crystallization of the residue from EtOH-*i*PrOH afforded pure **2**·2HCl (1.04 g, 4.4 mmol, 63%): white plates, mp 240-243 ^{o}C (decomp); ^{1}H NMR (CD_3OD/H_2O) δ 3.38 (s, 6H), 4.38 (s, 2H), 7.73 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.78 (dd, 1H, *J* = 2.4, 8.8 Hz), 8.10 (s, 1H), 8.11 (d, 1H, *J* = 8.8 Hz), 8.19 (d, 1H, *J* = 6.0 Hz), 8.21 (s, 1H, exchangeable); ^{13}C NMR (CD_3OD/H_2O) δ 44.1, 47.1, 119.2, 120.0, 128.9, 129.2, 130.4, 132.4, 133.6, 133.9, 141.8; HRMS (FAB) *m/z* calcd $C_{13}H_{17}N_2$ (MH^+) 201.1392, found 201.1379.

6-(Dimethylamino)naphthalene-2-carboxaldehyde (4). A solution of **31** (1.5 g, 6.97 mmol) in 50 mL of MeOH was titrated with $SOCl_2$ under cooling (ice bath) and stirring until TLC showed complete disappearance of starting acid. The mixture was evaporated to dryness and the residue was crystallized from hexanes-EtOAc to afford pure methyl 6-(dimethylamino)-2-naphthoate (**33**, 1.31 g, 5.71 mmol, 82%).

To a solution of **33** (1.0 g, 4.36 mmol) in 50 mL of dry CH_2Cl_2 was added under argon within 30 min 1.5 M diisobutylaluminum hydride (DIBAL-H) solution in toluene (6 mL, 9 mmol) under vigorous stirring and cooling at –78 ^{o}C. The mixture was slowly warmed up to room temperature and was further stirred for 1 h. To this was added 50 mL of 0.5 N aqueous HCl, and the resulting mixture was stirred at room temperature for 30 min. After addition of 2 g of sodium tartrate, the mixture was adjusted to pH 7 with solid $NaHCO_3$, saturated with solid NaCl and transferred to a 250 mL separatory funnel. After shaking thoroughly, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give crude 6-(dimethylamino)naphthalene-2-methanol (**34**) as a colorless oil.

The latter oil was taken up into 20 mL of dry CH_2Cl_2, and 1.11 g (2.62 mmol) of 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess-Martin reagent) was added in small portions with cooling to 0 ^{o}C and vigorous stirring. The mixture was further stirred at room

temperature for 10 min, transferred on to the top of a silica gel column, and eluted with hexanes and EtOAc. Fractions containing the yellow band were collected, concentrated and crystallized to afford pure **4** (217 mg, 1.09 mmol, 25%): yellow plates, mp 118-120 °C; ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 6H), 6.87 (d, 1H, *J* = 2.8 Hz), 7.16 (dd, 1H, *J* = 2.8, 9.2 Hz), 7.65 (d, 1H, *J* = 8.8 Hz), 7.81 (d, 1H, *J* = 9.2 Hz), 7.82 (dd, 1H, *J* = 1.8, 8.8 Hz), 8.13 (d, 1H, *J* = 1.2 Hz), 10.00 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 40.5, 105.6, 116.4, 123.6, 125.2, 127.0, 130.7, 130.9, 135.0, 138.8, 150.8, 192.0; HRMS *m/z* calcd $C_{13}H_{14}NO$ (MH^+) 200.1075, found 200.1076.

6-(Aminomethyl)naphthalen-2-ol hydrobromide (5·HBr). A solution of **1**·HCl (1.0 g, 4.5 mmol) in 50 mL of 48% aqueous HBr was heated at 110 °C under argon for 3 h, and then was evaporated to dryness. The residue was crystallized from EtOH-*i*PrOH to afford pure **5**·HBr as a pink solid (0.87 g, 3.4 mmol, 76%): mp 237-239 °C (decomp); ^{1}H NMR (CD_3OD) δ 4.23 (s, 2H), 7.14 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.16 (d, 1H, *J* = 2.4 Hz), 7.47 (dd, 1H, *J* = 1.6, 8.8 Hz), 7.72 (d, 1H, *J* = 8.4 Hz), 7.77 (d, 1H, *J* = 8.8 Hz), 7.86 (s, 1H); ^{13}C NMR (CD_3OD) δ 44.5, 109.8, 120.2, 127.4, 128.3, 128.5, 129.4, 129.5, 130.7, 136.4, 157.4; HRMS (FAB) *m/z* calcd $C_{11}H_{12}NO$ (MH^+) 174.0919, found 174.0928.

6-Ethoxy-2-naphthalenemethaneamine hydrochloride (6·HCl). A mixture of **23** (1.69 g, 10 mmol), ethyl bromide (1.09 g, 10 mmol), anhydrous K_2CO_3 (1.38 g, 10 mmol) and KI (1.66 g, 10 mmol) in 50 mL of dry DMF was stirred under argon at room temperature for 3 d. The mixture was partitioned between 200 mL of CH_2Cl_2 and 200 mL of 5% aqueous K_2CO_3. The organic layer was separated, washed with 5% aqueous K_2CO_3 (3×50 mL), dried (Na_2SO_4), and evaporated to dryness to afford crude 6-ethoxynaphthalene-2-carbonitrile (**35**) as a light brown solid.

The above crude **35** was dissolved in 100 mL of absolute Et_2O and treated with LAH (1.0 g, 26 mmol) as in the synthesis of **1**·HCl described in the text. The excess LAH was decomposed with EtOAc and further decomposed with ice and sodium tartrate. The organic layer was separated and the aqueous layer was extracted with Et_2O (2×50 mL). The combined organic layers were extracted with 200 mL of 0.5 *N* aqueous HCl. The aqueous layer was separated, washed with Et_2O (2×50 mL), adjusted to pH 11 with NaOH, saturated with solid NaCl, and extracted with Et_2O (3×100 mL). The latter organic layers were collected, dried (Na_2SO_4), and evaporated to dryness to give a residue, which was dissolved in 10 mL of 12 *N* aqueous HCl and

then evaporated to dryness. The final residue was crystallized from EtOH-*i*PrOH to give pure **6**·HCl (1.26 g, 5.3 mmol, an overall yield of 53%): white plates, mp 277-279 °C (decomp); ^{1}H NMR (CD_3OD) δ 1.43 (t, 3H, *J* = 7.0 Hz), 4.12 (q, 2H, *J* = 7.0 Hz), 4.23 (s, 2H), 7.16 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.22 (d, 1H, *J* = 2.4 Hz), 7.51 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.78 (d, 1H, *J* = 9.2 Hz), 7.82 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 0.4 Hz); ^{13}C NMR (CD_3OD) δ 15.1, 44.5, 64.6, 107.4, 120.8, 127.5, 128.9, 129.2, 129.4, 130.0, 130.5, 136.2, 159.1; HRMS (FAB) *m/z* calcd $C_{13}H_{16}NO$ (MH^+) 202.1232, found 202.1250.

2-(6-(Aminomethyl)naphthalen-2-yloxy)ethanol hydrochloride (7·HCl). A mixture of **23** (1.69 g, 10 mmol), ethyl bromoacetate (1.67 g, 10 mmol), anhydrous K_2CO_3 (1.38 g, 10 mmol), and KI (1.66 g, 10 mmol) in 50 mL of dry DMF was stirred under argon at 50 °C for 24 h. The mixture was partitioned between 200 mL of CH_2Cl_2 and 200 mL of 5% aqueous K_2CO_3. The organic layer was separated, washed with 5% aqueous K_2CO_3 (3×50 mL), dried (Na_2SO_4), and evaporated to dryness to afford crude ethyl 6-cyanonaphthalen-2-yloxyacetate (**36**) as a light brown solid.

The above crude **36** was dissolved in 100 mL of absolute Et_2O and treated with LAH (2.0 g, 52 mmol) as in the synthesis of **1**·HCl described in the text. The excess LAH was decomposed with EtOAc and further decomposed with ice and sodium tartrate. The organic layer was separated, and the aqueous layer was saturated with solid NaCl and extracted with Et_2O (3×50 mL). The combined organic layers were extracted with 100 mL of 0.5 *N* aqueous HCl. The aqueous layer was separated, washed with Et_2O (2×50 mL), brought to pH 11 with NaOH, saturated with solid NaCl, and extracted with Et_2O (3×100 mL). The latter organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 mL of 12 *N* aqueous HCl, and then evaporated to dryness to give crude **7**·HCl as a brown viscous oil. Purification by crystallization was unsuccessful.

The above oil was taken up into 100 mL of CH_2Cl_2, to which was added di-*tert*-butyl dicarbonate (2.40 g, 11 mmol) and triethylamine (Et_3N, 10 mL). The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was separated by silica gel column chromatography with hexanes and EtOAc as eluent to afford pure *N*-Boc protected **7** ((6-(2-hydroxyethoxy)naphthalen-2-ylmethyl)carbamic acid *tert*-butyl ester) as a white solid.

The above ester was mixed with 50 mL of 12 *N* aqueous HCl and heated at 60 °C for 30 min. The resulting solution was evaporated to dryness, and the residue was crystallized from *i*PrOH to give pure **7**·HCl as a white solid (1.20 g, 4.7 mmol, an overall yield of 47%): mp 246-248 °C (decomp); ^{1}H NMR (CD_3OD) δ 3.94 (t, 2H, *J* = 4.6 Hz), 4.17 (t, 2H, *J* = 4.6 Hz), 4.24 (s, 2H), 7.23 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.28 (d, 1H, *J* = 2.4 Hz), 7.51 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.81 (d, 1H, *J* = 8.8 Hz), 7.84 (d, 1H, *J* = 8.8 Hz), 7.88 (s, 1H); ^{13}C NMR (CD_3OD) δ 44.5, 61.7, 70.7, 107.6, 120.9, 127.5, 129.0, 129.4, 130.2, 130.6, 136.2, 159.2; HRMS (FAB) *m/z* calcd $C_{13}H_{16}NO_2$ (MH^+) 218.1181, found 218.1189.

6-(3-(Dimethylamino)propoxy)naphthalene-2-carbonitrile (39). A mixture of 3-bromopropylamine hydrobromide (8.76 g, 40 mmol), di-*tert*-butyl dicarbonate (8.72 g, 40 mmol) and diisopropylethylamine (DIEA, 20 mL) in 200 mL of CH_2Cl_2 was stirred at room temperature overnight. The solvent was evaporated at room temperature, and the residue was partitioned between 200 mL of Et_2O and 200 mL of brine. The organic layer was separated, washed with brine (3×50 mL), dried (Na_2SO_4), and evaporated to dryness to afford crude (3-bromopropyl)carbamic acid *tert*-butyl ester as a light brown oil, which solidified on standing (8.87 g, 37.3 mmol, 93%).

A mixture of the latter ester (4.76 g, 20 mmol), **23** (3.38 g, 20 mmol), anhydrous K_2CO_3 (2.76 g, 20 mmol), and KI (3.32 g, 20 mmol) in 100 mL of dry DMF was stirred under argon at 50 °C for 24 h. The mixture was partitioned between 1 L of CH_2Cl_2 and 1 L of 5% aqueous K_2CO_3. The organic layer was separated, washed with 5% aqueous K_2CO_3 (3×100 mL), dried (Na_2SO_4), and evaporated to dryness to give crude 3-(6-cyano-2-naphthoxy)propylcarbamic acid *tert*-butyl ester **(37**) as a light brown oil.

To the latter oil was carefully added 30 mL of dry trifluoroacetic acid (TFA) with cooling at 0 °C. The solution was stirred at room temperature for 20 min and then evaporated to dryness. Crystallization of the residue from hexanes-EtOAc afforded pure 6-(3-aminopropoxy)naphthalene-2-carbonitrile·CF_3CO_2H **(38**) as a light brown solid.

The latter solid was dissolved in 100 mL of MeOH, followed by addition of glacial HOAc (10 mL) and 37% aqueous CH_2O (2.3 mL, 30 mmol). To this was added in small portions solid $NaCNBH_3$ (3.15 g, 50 mmol) under ice-bath cooling and vigorous stirring. The mixture was then stirred at room temperature for 2 h and MeOH was evaporated. The residual solution was diluted

with 200 mL of brine, neutralized with solid $NaHCO_3$ to pH 7, basified with NaOH to pH 11, and extracted with Et_2O (3×200 mL). The combined organic layers were extracted with 200 mL of 0.5 *N* aqueous HCl. The aqueous layer was separated, washed with Et_2O (2×50 mL), neutralized with solid $NaHCO_3$ to pH 7, brought to pH 11 with NaOH, saturated with solid NaCl, and extracted with Et_2O (3×100 mL). The latter organic layers were collected, dried (Na_2SO_4), and evaporated to dryness to give pure **39** as a light brown solid (3.7 g, 14.5 mmol, 73%): ^{1}H NMR ($CDCl_3$) δ 2.03 (quintet, 2H, *J* = 6.8 Hz), 2.28 (s, 6H), 2.50 (t, 2H, *J* = 7.2 Hz), 4.15 (t, 2H, *J* = 6.4 Hz), 7.14 (d, 1H, *J* = 2.0 Hz), 7.23 (dd, 1H, *J* = 2.6, 9.2 Hz), 7.53 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.73 (d, 1H, *J* = 8.4 Hz), 7.75 (d, 1H, *J* = 8.8 Hz), 8.10 (d, 1H, *J* = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 27.4, 45.6, 56.4, 66.6, 106.7, 106.8, 119.8, 121.0, 127.1, 127.8, 127.9, 130.0, 133.9, 136.6, 159.5.

(3-(6-(Aminomethyl)naphthalen-2-yloxy)propyl)dimethylamine dihydrochloride (13·2HCl). A solution of **39** (2.5 g, 9.83 mmol) in 100 mL of absolute Et_2O was treated with LAH (1.0 g, 26 mmol). The excess LAH was decomposed with EtOAc and further decomposed with ice and sodium tartrate. The organic layer was separated, and the aqueous layer was saturated with solid NaCl and extracted with Et_2O (3×50 mL). The combined organic layers were extracted with 100 mL of 0.5 *N* aqueous HCl. The aqueous layer was separated, washed with Et_2O (2×50 mL), brought to pH 11 with NaOH, saturated with solid NaCl, and extracted with Et_2O (3×100 mL). The latter organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 mL of 12 *N* aqueous HCl, and then evaporated to dryness. The final residue was crystallized from EtOH-MeOH to give pure **13**·2HCl (2.65 g, 8.0 mmol, 81%): white microscopic plates, mp 254-256 ^{o}C (decomp); ^{1}H NMR (CD_3OD) δ 2.32 (m, 2H), 2.97 (s, 6H), 3.42 (m, 2H), 4.25 (s, 2H), 4.25 (t, 2H, *J* = 5.8 Hz), 7.23 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.33 (d, 1H, *J* = 2.4 Hz), 7.54 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.84 (d, 1H, *J* = 9.2 Hz), 7.87 (d, 1H, *J* = 8.8 Hz), 7.91 (s, 1H); ^{13}C NMR (CD_3OD) δ 25.8, 43.7, 44.5, 56.8, 66.1, 107.8, 120.6, 127.8, 129.1, 129.6, 129.8, 130.4, 130.7, 136.2, 158.7; HRMS (FAB) *m/z* calcd $C_{16}H_{23}N_2O$ (MH^+) 259.1810, found 259.1812.

(3-(6-(Aminomethyl)naphthalen-2-yloxy)propyl)trimethylammonium chloride hydrochloride (14Cl$^-$·HCl). A mixture of **13**·2HCl (1.00 g, 3.02 mmol), Et_3N (5 mL), and di-*tert*-butyl dicarbonate (0.67 g, 3.08 mmol) in 50 mL dry CH_2Cl_2 was stirred at room temperature

overnight. Solvent was evaporated at room temperature and the residue was partitioned between 100 mL of Et_2O and 100 mL of alkaline brine (pH 11). The organic layer was separated, washed with alkaline brine (3×50 mL), dried (Na_2SO_4), and evaporated to dryness to give 6-(3-(dimethylamino)propoxy)naphthalene-2-ylmethylcarbomic acid *tert*-butyl ester (**40**) as a colorless oil.

The latter oil was dissolved in 10 mL of absolute Et_2O and the solution was filtered. To the clear filtrate was added iodomethane (0.71 g, 5 mmol). The solution was mixed thoroughly, sealed, and was allowed to stand at room temperature overnight. The precipitates were collected, washed with Et_2O, and dried to give (3-(6-(*tert*-butoxycarbonylaminomethyl)naphthalen-2-yloxy)propyl)trimethylammonium iodide as a light yellow solid.

The latter was dissolved in 20 mL of MeOH, followed by addition of finely ground solid Ag_2CO_3 (1.4 g, 5.1 mmol), and the mixture was stirred at room temperature for 1 h. The solid material was filtered off and washed with MeOH. To the combined filtrates was added 50 mL of 12 *N* aqueous HCl. The mixture was heated at 60 °C for 30 min and then evaporated to dryness. The residue was crystallized from *i*PrOH to afford pure **14Cl**$^-$·HCl as a pale brown solid (1.04 g, 2.79 mmol, 92%): mp 272-274 ^oC (decomp); ^1H NMR (CD_3OD) δ 2.38 (m, 2H), 3.24 (s, 9H), 3.67 (m, 2H), 4.26 (s, 2H), 4.26 (t, 2H, *J* = 6.8 Hz), 7.24 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.34 (d, 1H, *J* = 2.0 Hz), 7.55 (dd, 1H, *J* = 1.6, 8.4 Hz), 7.84 (d, 1H, *J* = 9.2 Hz), 7.88 (d, 1H, *J* = 8.4 Hz), 7.91 (s, 1H); ^{13}C NMR (CD_3OD) δ 24.4, 44.5, 53.8, 65.5, 65.9, 107.8, 120.6, 127.8, 129.1, 129.5, 129.7, 130.4, 130.8, 136.2, 158.7; HRMS (FAB) *m/z* calcd $C_{17}H_{25}N_2O$ (M^+) 273.1967, found 273.1968.

6-(3-(Dimethylamino)propoxy)naphthalene-2-carboxaldehyde (19). To a solution of **39** (1.0 g, 3.9 mmol) in 50 mL of dry CH_2Cl_2 was added under argon with stirring 2.67 mL (4 mmol) of 1.5 M DIBAL-H in toluene at room temperature. The mixture was stirred for 1 h and then was diluted with 100 mL of 0.5 *N* aqueous HCl. The mixture was stirred at room temperature for 30 min and then neutralized with solid $NaHCO_3$ to pH 7. To this was added 2 g of sodium tartrate with stirring, and the resulting mixture was brought to pH 11 with NaOH and then saturated with solid NaCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by silica gel column chromatography, eluting with hexanes-EtOAc

containing 5% methanolic NH_3, to afford pure **19** as a light brown viscous oil (709 mg, 2.76 mmol, 71%): ^{1}H NMR ($CDCl_3$) δ 2.01 (quintet, 2H, *J* = 7.2 Hz), 2.25 (s, 6H), 2.47 (t, 2H, *J* = 7.2 Hz), 4.13 (t, 2H, *J* = 7.2 Hz), 7.15 (s, 1H), 7.19 (dd, 1H, *J* = 2.4, 9.2 Hz), 7.73 (d, 1H, *J* = 8.4 Hz), 7.83 (d, 1H, *J* = 8.8 Hz), 7.86 (dd, 1H, *J* = 1.6, 8.4 Hz), 8.18 (s, 1H), 10.04 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 27.4, 45.5, 56.3, 66.3, 106.9, 120.2, 123.5, 127.7, 127.8, 131.1, 132.3, 134.3, 138.3, 159.7, 192.0; HRMS (FAB) *m/z* calcd $C_{16}H_{20}NO_2$ (MH^+) 258.1494, found 258.1499.

(3-(6-Formylnaphthalen-2-yloxy)propyl)trimethylammonium iodide (20I⁻). A solution of **19** (300 mg, 1.17 mmol) in 5 mL of Et_2O was filtered, and the filtrate was treated with excess MeI as in the synthesis of **18I⁻** described in the text. The precipitate was collected, washed with Et_2O, and crystallized from MeOH to afford pure **20I⁻** (440 mg, 1.10 mmol, 94%): light yellow prisms, mp 209-211 °C; ^{1}H NMR (CD_3OD) δ 2.40 (m, 2H), 3.26 (s, 9H), 3.70 (m, 2H), 4.29 (t, 2H, *J* = 4.6 Hz), 7.28 (d, 1H, *J* = 8.8 Hz), 7.37 (s, 1H), 7.87 (br, 2H), 7.97 (d, 1H, *J* = 9.2 Hz), 8.35 (s, 1H), 10.04 (s, 1H, CHO); ^{13}C NMR (CD_3OD) δ 24.3, 53.9, 65.4, 66.0, 108.3, 121.0, 124.1, 129.0, 129.6, 132.4, 133.9, 135.8, 139.7, 160.5, 194.0; HRMS (FAB) *m/z* calcd $C_{17}H_{22}NO_2$ (M^+) 272.1651, found 272.1648.

(4-(6-(Aminomethyl)naphthalen-2-yloxy)butyl)dimethylamine dihydrochloride (15·2HCl). A mixture of **23** (3.38 g, 20 mmol), ethyl 4-bromobutyrate (3.90 g, 20 mmol), anhydrous K_2CO_3 (2.76 g, 20 mmol), and KI (3.32 g, 20 mmol) in 100 mL of dry DMF was stirred under argon at 50 °C for 24 h. The mixture was partitioned between 1 L of CH_2Cl_2 and 1 L of 5% aqueous K_2CO_3. The organic layer was separated, washed with 5% aqueous K_2CO_3 (3×100 mL), dried (Na_2SO_4), and evaporated to dryness to afford crude ethyl 4-(6-cyanonaphthoxy)butryate (**41**) as a light brown solid.

The latter ester was dissolved in 300 mL of absolute Et_2O and treated with LAH (3.42 g, 90 mmol). The excess LAH was decomposed with EtOAc and further decomposed with ice and sodium tartrate. The organic layer was separated, and the aqueous layer was saturated with solid NaCl and extracted with Et_2O (3×100 mL). The combined organic layers were extracted with 200 mL of 0.5 *N* aqueous HCl. The aqueous layer was separated, washed with Et_2O (2×100 mL), adjusted to pH 11 with NaOH, saturated with solid NaCl, and extracted with Et_2O (3×100 mL). The latter organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 mL of 12 *N* aqueous HCl, and then evaporated to dryness to leave a residue

that was crystallized from EtOH-EtOAc to give pure 4-(6-(aminomethyl)naphthalen-2-yloxy)butanol (**42**) as a light brown solid (3.0 g, 10.6 mmol, an overall yield of 53%).

To a suspension of **42** (2.9 g, 10.3 mmol) in 100 mL of CH_2Cl_2 were added di-*tert*-butyl dicarbonate (2.40 g, 11 mmol) and Et_3N (10 mL). The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was extracted with Et_2O (200 mL). The solid material was filtered off and washed with Et_2O. The combined filtrates were evaporated to dryness to afford crude 6-(4-hydroxybutoxy)naphthylen-2-ylmethylcarbamic acid *tert*-butyl ester (**43**) as a light brown viscous oil which solidified on standing.

The latter solid was dissolved in 100 mL of CH_2Cl_2, followed by addition of DIEA (10 mL). The mixture was cooled in an ice bath under electromagnetic stirring while a solution of methanesulfonyl chloride (1.26 g, 11 mmol) in 10 mL of CH_2Cl_2 was added dropwise within a period of 10 min. The mixture was stirred at 0 °C for 1 h and then was slowly warmed to room temperature. After further stirring at room temperature for 1 h, the solution was washed with brine (3×100 mL), dried (Na_2SO_4), and evaporated to dryness to give crude 4-(6-(*tert*-butoxycarbonylaminomethyl)naphthalene-2-yloxy)butyl methanesulfonate (**44**) as a light brown solid.

The latter solid was dissolved in 50 mL of 2.0 M dimethylamine solution in MeOH, and the reaction mixture was sealed in a high pressure bottle and stirred at 50 °C overnight. Evaporation of solvent, followed by column chromatographic separation of the residue on silica gel, eluting with hexanes-EtOAc containing 5% methanolic NH_3, afforded pure 6-(4-(dimethylamino)butoxy)naphthylen-2-ylmethylcarbamic acid *tert*-butyl ester (**45**) as a colorless oil which solidified on standing (2.61 g, 7.01 mmol, an overall yield of 68%).

To a solution of **45** (1.5 g, 4.03 mmol) in MeOH (10 mL) was added 20 mL of 12 *N* aqueous HCl. The mixture was heated at 60 °C for 30 min and then evaporated to dryness. The residue was crystallized from EtOH to afford pure **15**·2HCl as a white powder (1.4 g, 100%): mp 247-249 ^{o}C (decomp); ^{1}H NMR (CD_3OD) δ 1.92-2.05 (4H), 2.92 (s, 6H), 3.26 (m, 2H), 4.18 (t, 2H, J = 5.8 Hz), 4.25 (s, 2H), 7.21 (dd, 1H, J = 2.4, 8.8 Hz), 7.31 (d, 1H, J = 2.0 Hz), 7.53 (dd, 1H, J = 1.6, 8.4 Hz), 7.82 (d, 1H, J = 9.2 Hz), 7.86 (d, 1H, J = 8.8 Hz), 7.89 (s, 1H); ^{13}C NMR (CD_3OD) δ 22.8, 27.2, 43.5, 44.5, 58.8, 68.2, 107.7, 120.8, 127.7, 129.0, 129.4, 129.5, 130.2, 130.7, 136.2, 159.0; HRMS (FAB) *m/z* calcd $C_{17}H_{25}N_2O$ (MH^+) 273.1967, found 273.1965.

(4-(6-(Aminomethyl)naphthalen-2-yloxy)butyl)trimethylammonium chloride hydrochloride (16Cl$^-$·HCl). Intermediate **45** (1.0 g, 2.68 mmol) was dissolved in 10 mL of absolute Et_2O and the solution was filtered. To the clear filtrate was added iodomethane (1.0 g, 7 mmol). The solution was mixed thoroughly, sealed, and was allowed to stand at room temperature overnight. The precipitate was collected, washed with Et_2O, and dried to give (4-(6-(*tert*-butoxycarbonylaminomethyl)naphthalen-2-yloxy)butyl)trimethylammonium iodide as a light yellow solid.

The latter was dissolved in 20 mL of MeOH, followed by addition of solid Ag_2CO_3 (2 g, 7.3 mmol), and the mixture was stirred at room temperature for 1 h. The solid material was filtered off and washed with MeOH. To the combined filtrates was added 50 mL of 12 *N* aqueous HCl. The mixture was heated at 60 °C for 30 min and then evaporated to dryness. The residue was crystallized from *i*PrOH to afford pure **16Cl**$^-$·HCl (0.89 g, 2.48 mmol, 93%): white solid, mp 267-269 ^oC (decomp); ^1H NMR (CD_3OD) δ 1.94 (m, 2H), 2.05 (m, 2H), 3.18 (s, 9H), 3.49 (m, 2H), 4.20 (t, 2H, *J* = 5.8 Hz), 4.25 (s, 2H), 7.22 (dd, 1H, *J* = 2.0, 8.8 Hz), 7.31 (d, 1H, *J* = 1.6 Hz), 7.53 (dd, 1H, *J* = 1.6, 8.8 Hz), 7.82 (d, 1H, *J* = 9.2 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 7.90 (s, 1H); ^{13}C NMR (CD_3OD) δ 21.2, 27.1, 44.5, 53.7, 67.5, 68.2, 107.7, 120.8, 127.7, 129.0, 129.48, 129.52, 130.2, 130.7, 136.2, 159.0; HRMS (FAB) *m/z* calcd $C_{18}H_{27}N_2O$ (M^+) 287.2123, found 287.2125.

6-(4-Dimethylaminobutoxy)naphthalene-2-carboxaldehyde (21). A mixture of **23** (676 mg, 4 mmol), (4-bromobutyl)carbamic acid *tert*-butyl ester (1.0 g, 3.97 mmol, Fluka), anhydrous K_2CO_3 (552 mg, 4 mmol), and KI (664 mg, 4 mmol) in 20 mL of dry DMF was stirred under argon at 50 ^oC for 24 h. The mixture was partitioned between 200 mL of CH_2Cl_2 and 200 mL of 5% aqueous K_2CO_3. The organic layer was separated, washed with 5% aqueous K_2CO_3 (3×100 mL), dried (Na_2SO_4), and evaporated to dryness to give crude 4-(6-cyano-2-naphthoxy)butylcarbamic acid *tert*-butyl ester (**46**) as a light brown solid.

The latter solid was dissolved in 5 mL of dry TFA with cooling at 0 ^oC. The solution was stirred at room temperature for 20 min and then evaporated to dryness to give crude 6-(4-aminobutoxy)naphthalene-2-carbonitrile·CF_3CO_2H (**47**) as a light brown solid.

The latter solid was dissolved in 50 mL of MeOH, followed by addition of glacial HOAc (5 mL) and 37% aqueous CH_2O (0.46 mL, 6 mmol). To this was added in small portions solid

$NaCNBH_3$ (0.63 g, 10 mmol) at 0 °C with vigorous stirring. The mixture was then stirred at room temperature for 2 h and MeOH was evaporated. The residual solution was diluted with 100 mL of brine, neutralized with solid $NaHCO_3$ to pH 7, basified with NaOH to pH 11, and extracted with Et_2O (3×50 mL). The combined organic layers were extracted with 100 mL of 0.5 *N* aqueous HCl. The aqueous layer was separated, washed with Et_2O (2×50 mL), neutralized with solid $NaHCO_3$ to pH 7, brought to pH 11 with NaOH, saturated with solid NaCl, and extracted with Et_2O (3×50 mL). The latter organic layers were collected, dried (Na_2SO_4), and evaporated to dryness to give a residue that was purified by silica gel column chromatography, eluting with hexanes-EtOAc containing 5% methanolic NH_3, to afford pure (4-(dimethylamino)butoxy)naphthalene-2-carbonitrile (**48**) as a light brown oil (80 mg, 0.30 mmol, an overall yield of 7.5%).

To a solution of **48** (75 mg, 0.28 mmol) in 5 mL of dry CH_2Cl_2 was added under argon and electromagnetic stirring 0.2 mL (0.3 mmol) of 1.5 M DIBAL-H in toluene at room temperature. The mixture was stirred at room temperature for 1 h, at which point 5 mL of 0.5 N aqueous HCl was added. The resulting mixture was stirred at room temperature for 30 min and then neutralized with solid $NaHCO_3$ to pH 7. To this was added 0.5 g of sodium tartrate under stirring, and the mixture was brought to pH 11 with NaOH and saturated with solid NaCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by silica gel column chromatography, eluting with hexanes-EtOAc containing 5% methanolic NH_3, to afford pure **21** as a light brown viscous oil (55 mg, 0.20 mmol, 71%): ^{1}H NMR ($CDCl_3$) δ 1.70 (quintet, 2H, *J* = 7.0 Hz), 1.90 (quintet, 2H, *J* = 7.0 Hz), 2.26 (s, 6H), 2.37 (t, 2H, *J* = 7.0 Hz), 4.13 (t, 2H, *J* = 7.0 Hz), 7.17 (d, 1H, *J* = 2.0 Hz), 7.22 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.78 (d, 1H, *J* = 8.8 Hz), 7.88 (d, 1H, *J* = 9.2 Hz), 7.90 (dd, 1H, *J* = 1.6, 8.4 Hz), 8.25 (s, 1H), 10.09 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 24.4, 27.1, 45.6, 59.5, 68.0, 106.9, 120.4, 123.7, 127.8, 128.0, 131.2, 132.4, 134.5, 138.5, 159.9, 192.2; HRMS (FAB) *m/z* calcd $C_{17}H_{22}NO_2$ (MH^+) 272.1651, found 272.1666

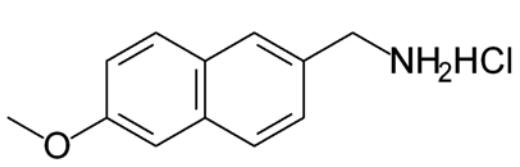
(4-(6-Formylnaphthalen-2-yloxy)butyl)trimethylammonium iodide (22I$^-$). A solution of **21** (25 mg, 0.092 mmol) in 1 mL of Et_2O was filtered, and the filtrate was treated with excess MeI as in the synthesis of **18I$^-$** described in the text. The precipitate was collected, washed with

Et_2O, and crystallized in EtOH to afford pure **22I**$^-$ (34 mg, 0.082 mmol, 89%): light yellow prisms, mp 138-140 ^oC; ^1H NMR (CD_3OD) δ 1.96 (m, 2H), 2.06 (m, 2H), 3.18 (s, 9H), 3.50 (m, 2H), 4.25 (t, 2H, *J* = 5.8 Hz), 7.28 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.37 (d, 1H, *J* = 2.4 Hz), 7.88 (d, 1H, *J* = 1.2 Hz), 7.98 (d, 1H, *J* = 9.2 Hz), 8.37 (d, 1H, *J* = 0.8 Hz), 10.04 (s, 1H, CHO); ^{13}C NMR (CD_3OD) δ 20.3, 27.0, 53.6, 67.5, 68.4, 108.1, 121.1, 124.1, 128.9, 129.5, 132.4, 133.9, 135.8, 139.9, 160.9, 194.0; HRMS (FAB) *m/z* calcd $C_{18}H_{24}NO_2$ (M^+) 286.1807, found 286.1807.

Optical properties of turnover products. A solution of an authentic aldehyde (25 μM) in 0.1 M of pH 7.2 phosphate buffer was prepared, and the UV-vis spectrum was recorded at 30 °C. The baseline was precorrected by autozeroing using the same cuvette containing only the buffer solution. The UV-vis spectrum was then converted to the molar absorption spectrum using Origin 7.5 (Figure S12), and maximum absorbance wavelengths (λ_{max}) and extinction coefficients (ε) data were collected (Table S1).

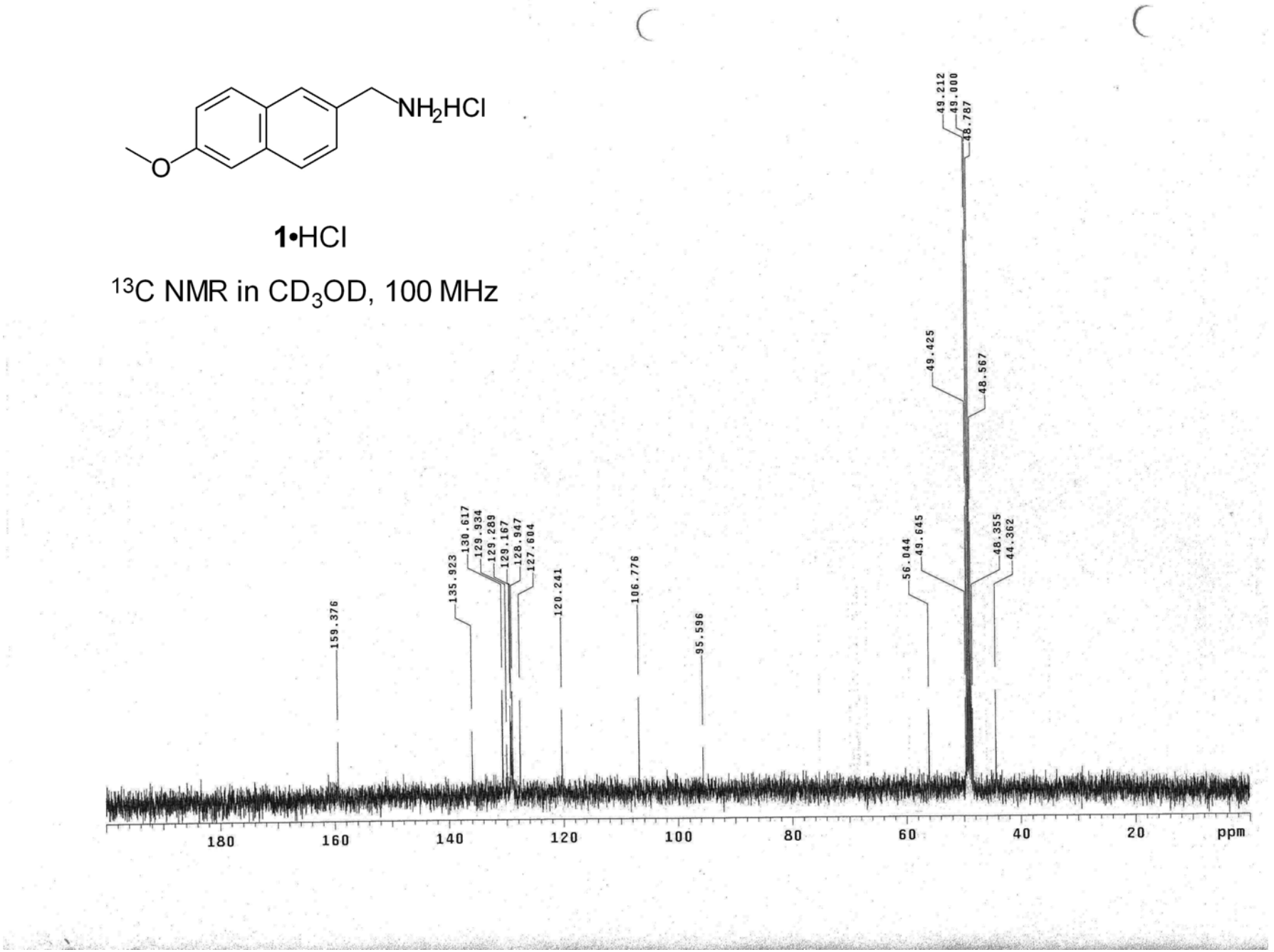
For fluorescence spectrophotometry, the excitation wavelengths (λ_{ex}) were first optimized manually using a 100 nM solution of each authentic aldehyde (Table S1). Then the relative fluorescence intensities were determined by the calibration curve method. In a typical experiment, a series of solutions of **18I**$^-$ (2.5-100 nM) in 0.1 M of pH 7.2 phosphate buffer were prepared, which were then subjected to fluorescence scanning at 30 °C (Figure S13). The relative intensities at 453 nm were collected and plotted against [**18**]. The linear fit of the plot gave a slope that represents the relative fluorescence intensity of **18** in terms of AU nM^{-1} (Figure S13). The relative fluorescence intensity of **18** versus **3** was then calculated (Table S1). The same experiment was repeated in the presence of BPAO (10 nM) or **12** (10 μM), and the slopes were obtained similarly (Figure S14).

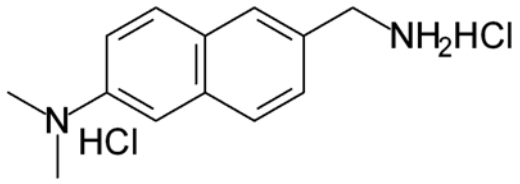
1. Kolasa, T.; Gunn, D. E.; Bhatia, P.; Woods, K. W.; Gane, T.; Stewart, A. O.; Bouska, J. B.; Harris, R. R.; Hulkower, K. I.; Malo, P. E.; Bell, R. L.; Carter, G. W.; Brooks, C. D. W. *J. Med. Chem.* **2000**, *43,* 690-705.
2. Qiao, C.; Jeon, H. B.; Sayre, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 8038-8045.



1•HCl

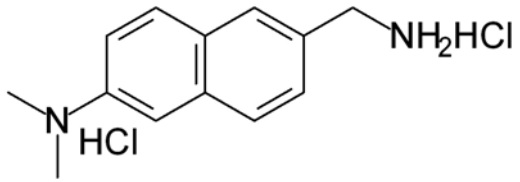
^{1}H NMR in CD_3OD, 400 MHz


NH2HCl
O
1•HCl
13C NMR in CD3OD, 100 MHz
49.212
49.000
48.787
49.425
48.567
135.923
130.617
129.934
129.289
129.167
128.947
127.604
120.241
106.776
95.596
159.376
56.044
49.645
48.355
44.362
180
160
140
120
100
80
60
40
20
ppm



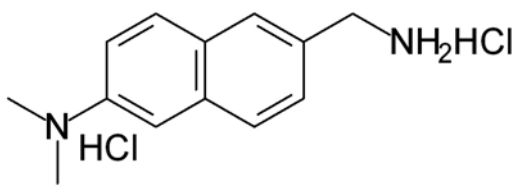
2•2HCl

^{1}H NMR in CD_3OD, 400 MHz



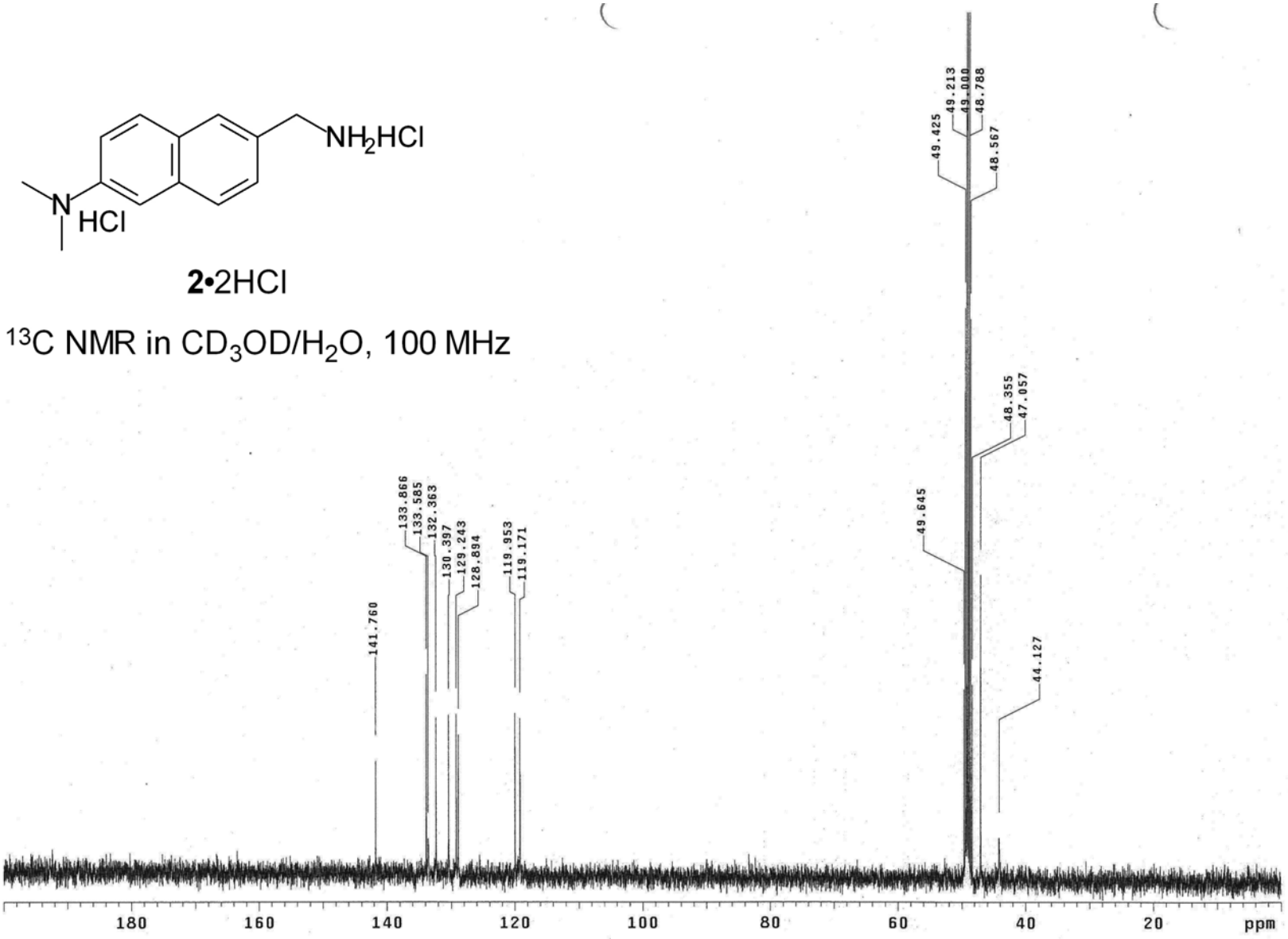
2•2HCl

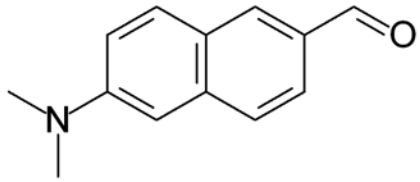
^{1}H NMR in CD_3OD/H_2O, 400 MHz



2•2HCl

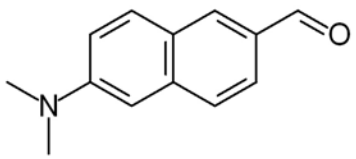
^{13}C NMR in CD_3OD, 100 MHz


NH2HCl
N
HCl
2•2HCl
13C NMR in CD3OD/H2O, 100 MHz
49.425
49.213
49.000
48.788
48.567
48.355
47.057
49.645
44.127
141.760
133.866
133.585
132.363
130.397
129.243
128.894
119.953
119.171
180
160
140
120
100
80
60
40
20
ppm



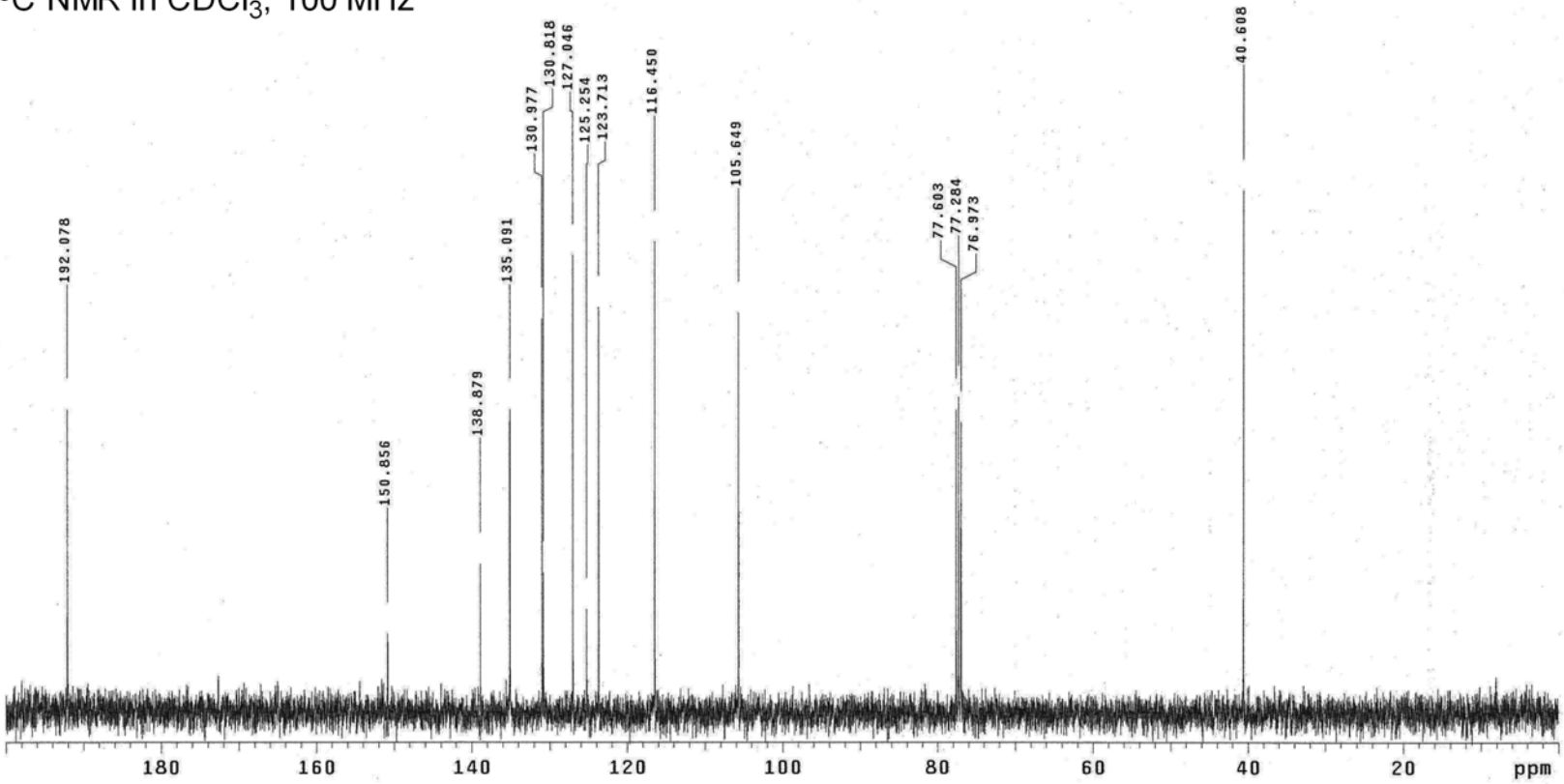
4

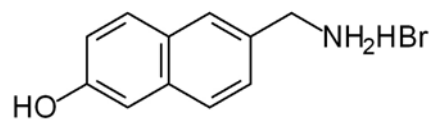
^{1}H NMR in $CDCl_3$, 400 MHz



4

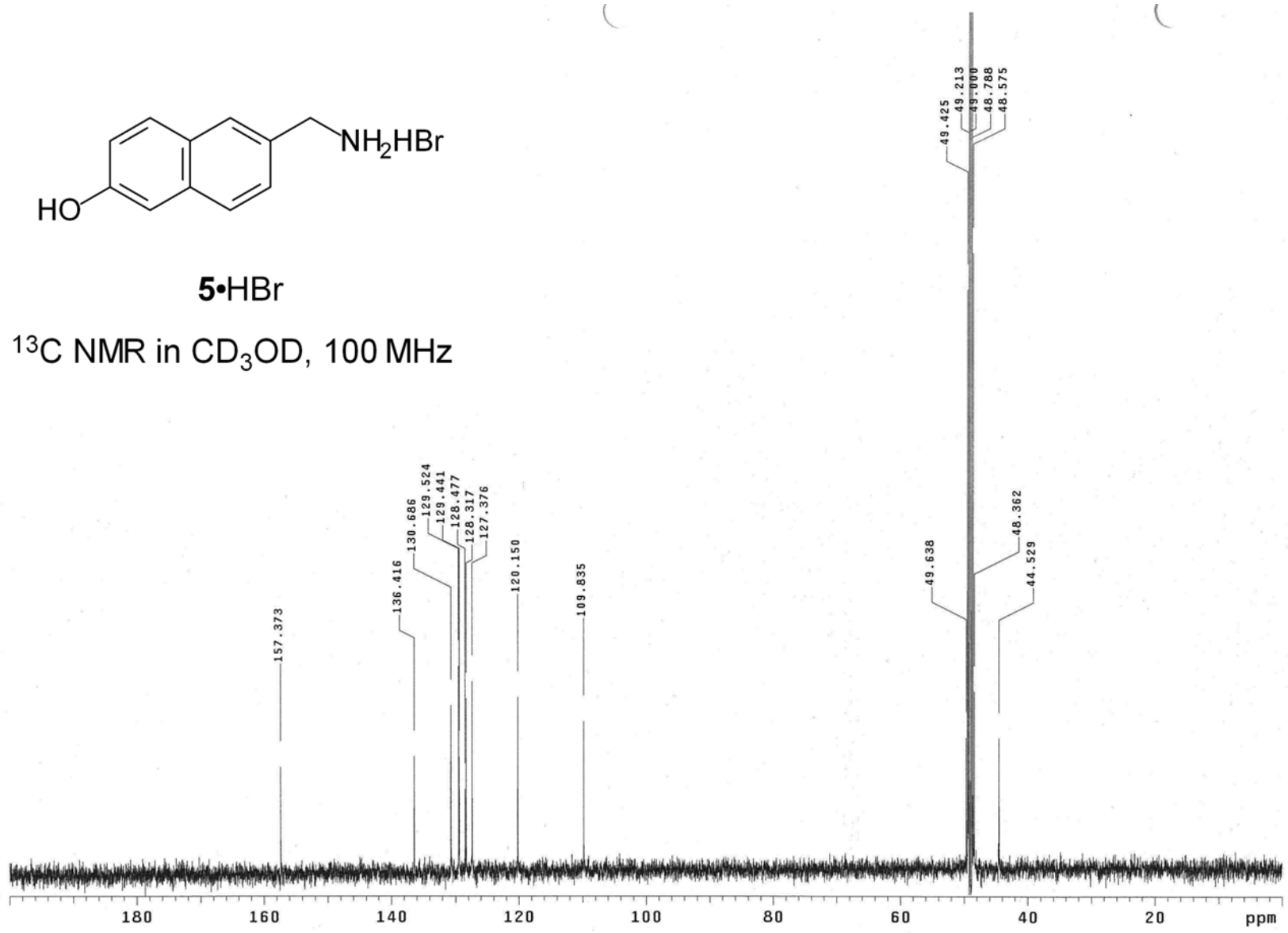
^{13}C NMR in $CDCl_3$, 100 MHz

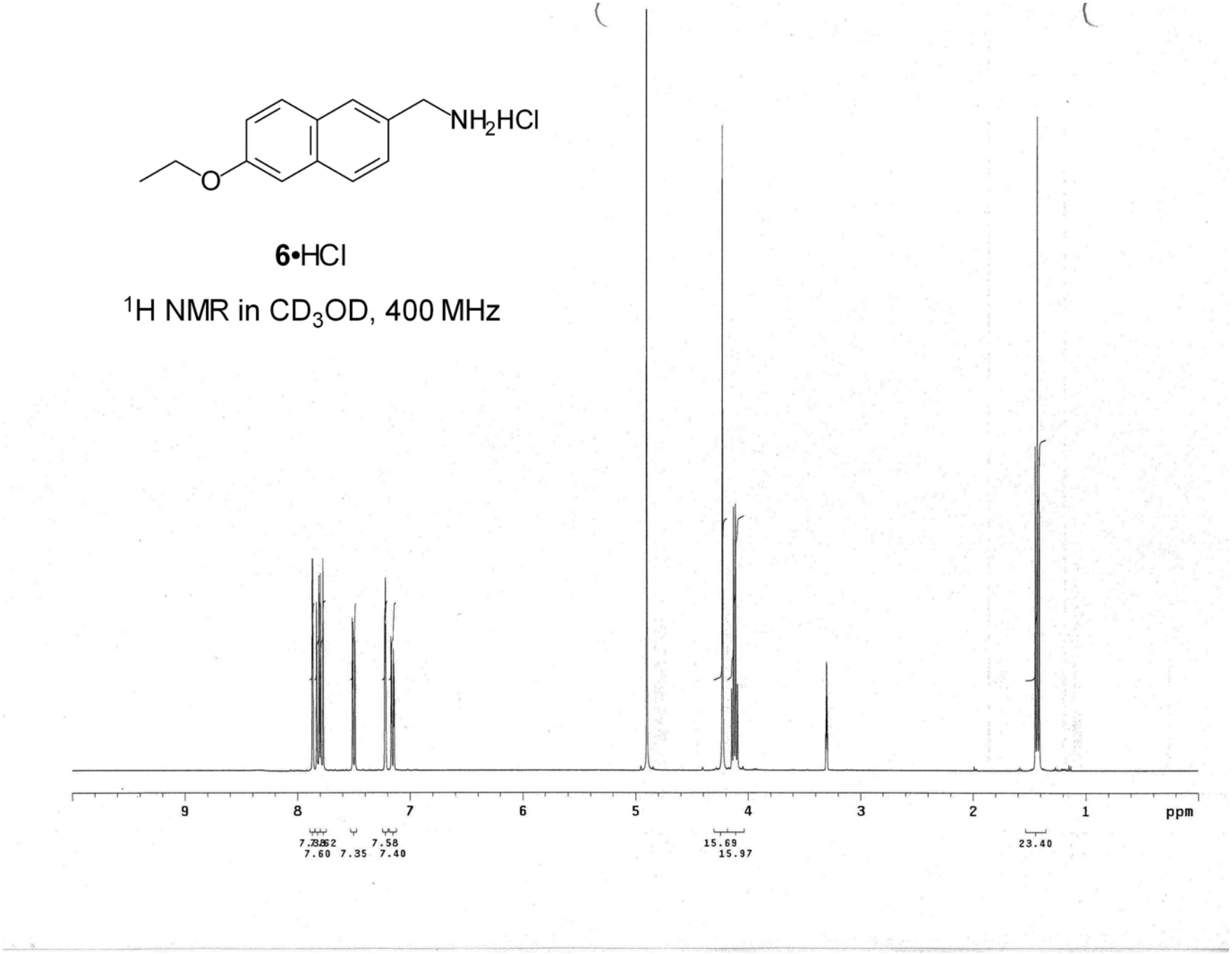


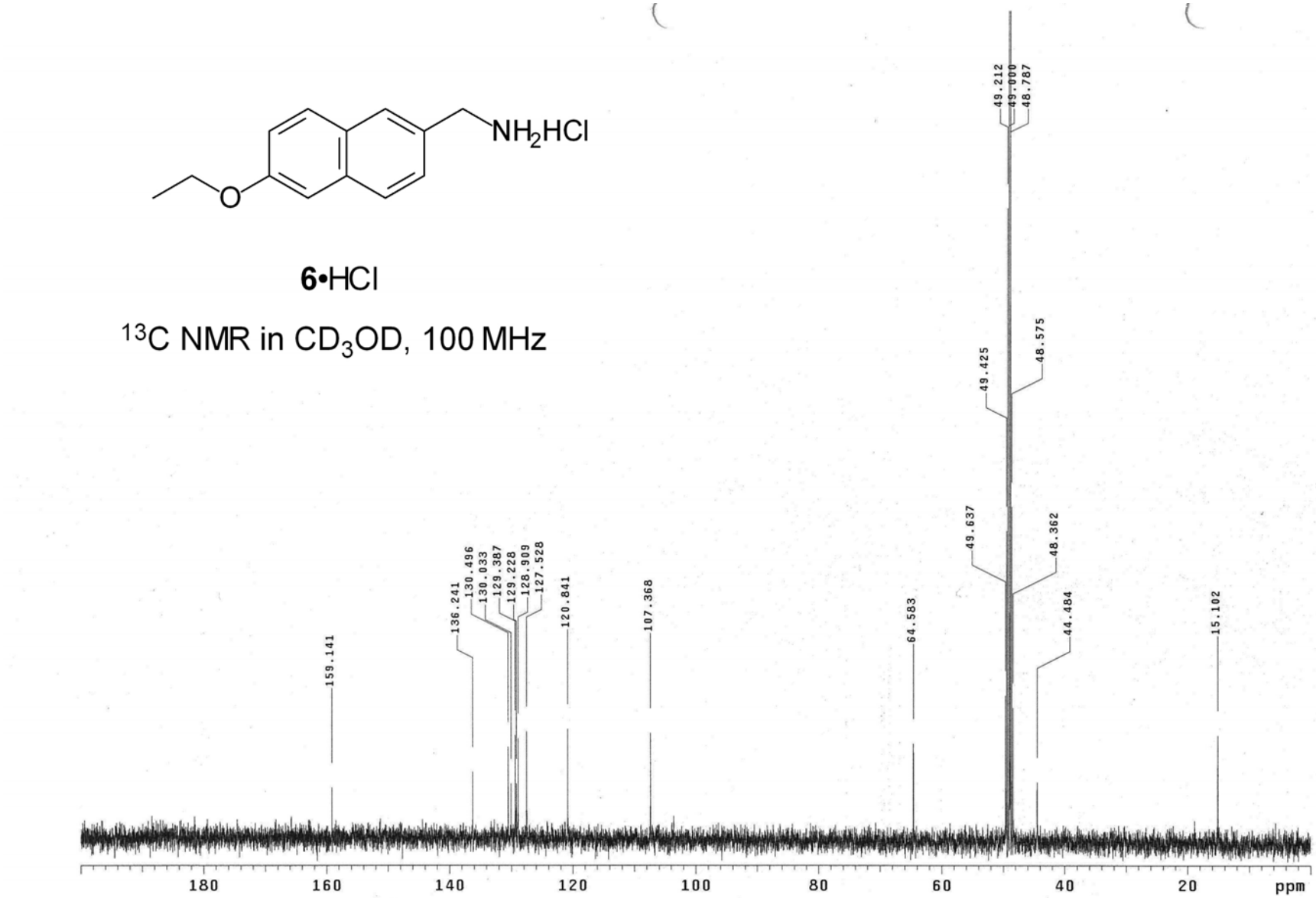


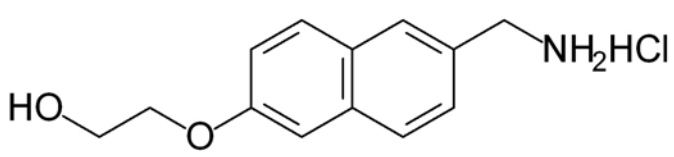
5•HBr

^{1}H NMR in CD_3OD, 400 MHz


NH2HBr
HO
5•HBr
13C NMR in CD3OD, 100 MHz
157.373
136.416
130.686
129.524
129.441
128.477
128.317
127.376
120.150
109.835
49.638
49.425
49.213
49.000
48.788
48.575
48.362
44.529
180
160
140
120
100
80
60
40
20
ppm

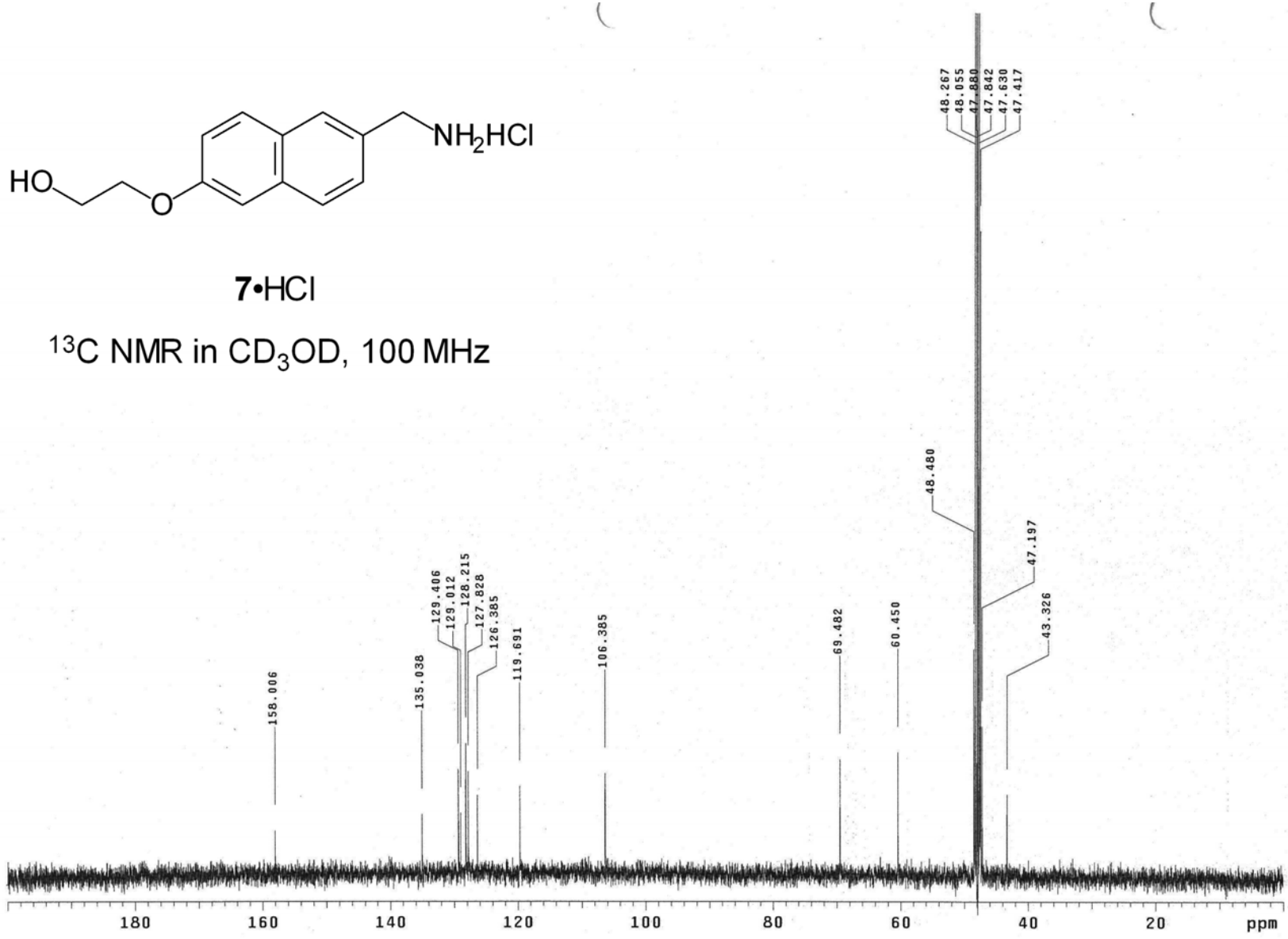

NH2HCl
O
6•HCl
1H NMR in CD3OD, 400 MHz
9
8
7
6
5
4
3
2
1
ppm
7.60
7.35
7.40
15.69
15.97
23.40

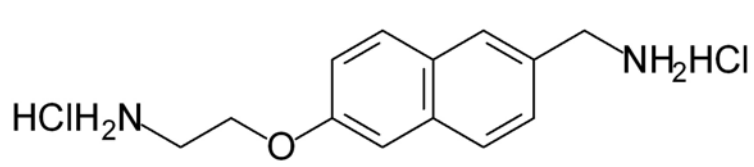

NH2HCl
O
6•HCl
13C NMR in CD3OD, 100 MHz
49.212
49.000
48.787
49.425
48.575
49.637
48.362
44.484
64.583
15.102
107.368
120.841
136.241
130.496
130.033
129.387
129.228
128.909
127.528
159.141
180
160
140
120
100
80
60
40
20
ppm



7•HCl

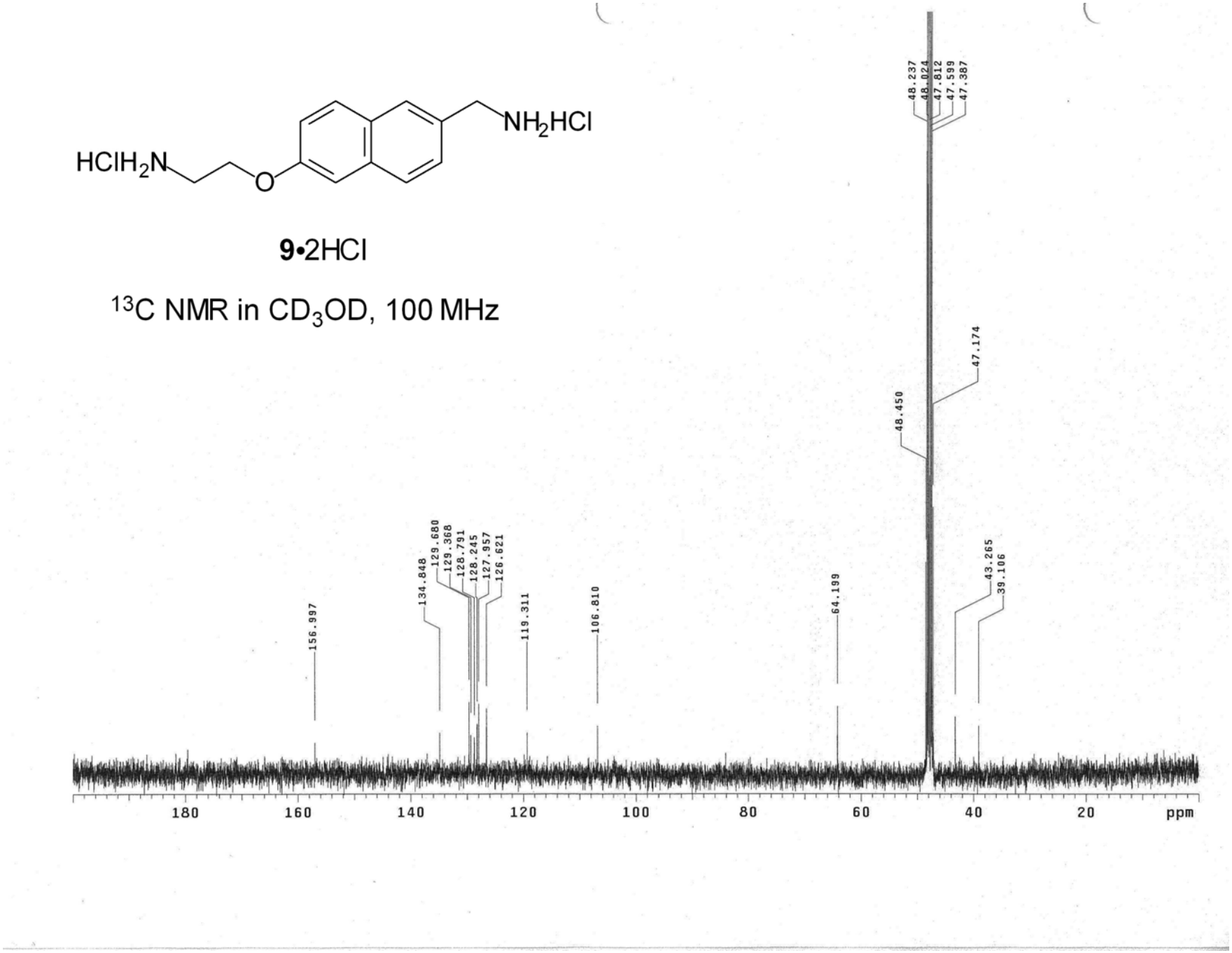
^{1}H NMR in CD_3OD, 400 MHz

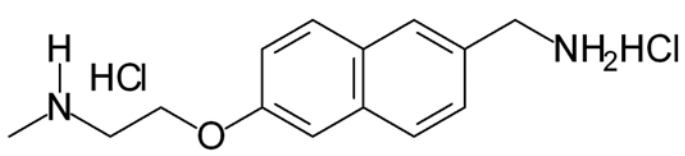

HO
O
NH2HCl
7•HCl
13C NMR in CD3OD, 100 MHz
48.267
48.055
47.880
47.842
47.630
47.417
48.480
47.197
43.326
158.006
135.038
129.406
129.012
128.215
127.828
126.385
119.691
106.385
69.482
60.450
180
160
140
120
100
80
60
40
20
ppm



9•2HCl

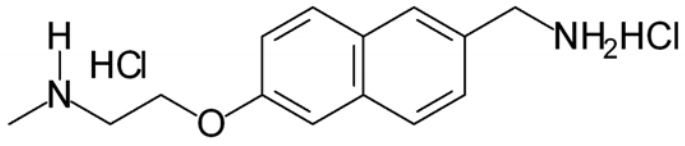
^{1}H NMR in CD_3OD, 400 MHz


HClH2N
O
NH2HCl
9•2HCl
13C NMR in CD3OD, 100 MHz
48.237
48.024
47.812
47.599
47.387
47.174
48.450
156.997
134.848
129.680
129.368
128.791
128.245
127.957
126.621
119.311
106.810
64.199
43.265
39.106
180
160
140
120
100
80
60
40
20
ppm



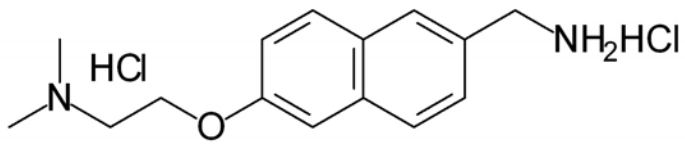
10•2HCl

^{1}H NMR in CD_3OD, 400 MHz



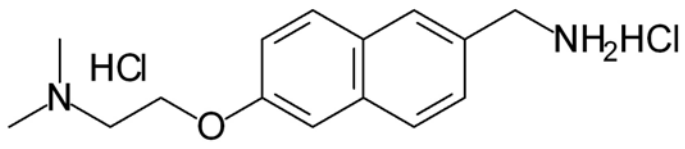
10•2HCl

^{13}C NMR in CD_3OD, 100 MHz



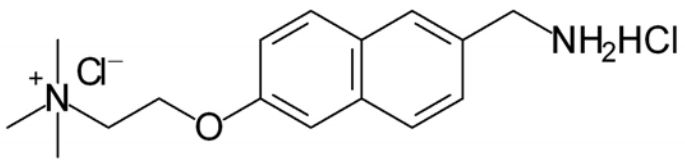
11•2HCl

^{1}H NMR in CD_3OD, 400 MHz



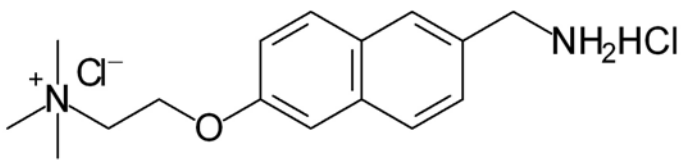
11•2HCl

^{13}C NMR in CD_3OD, 100 MHz



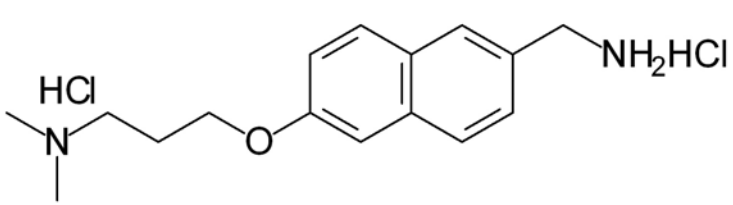
12 $Cl^{-}\bullet HCl$

^{1}H NMR in CD_3OD, 400 MHz



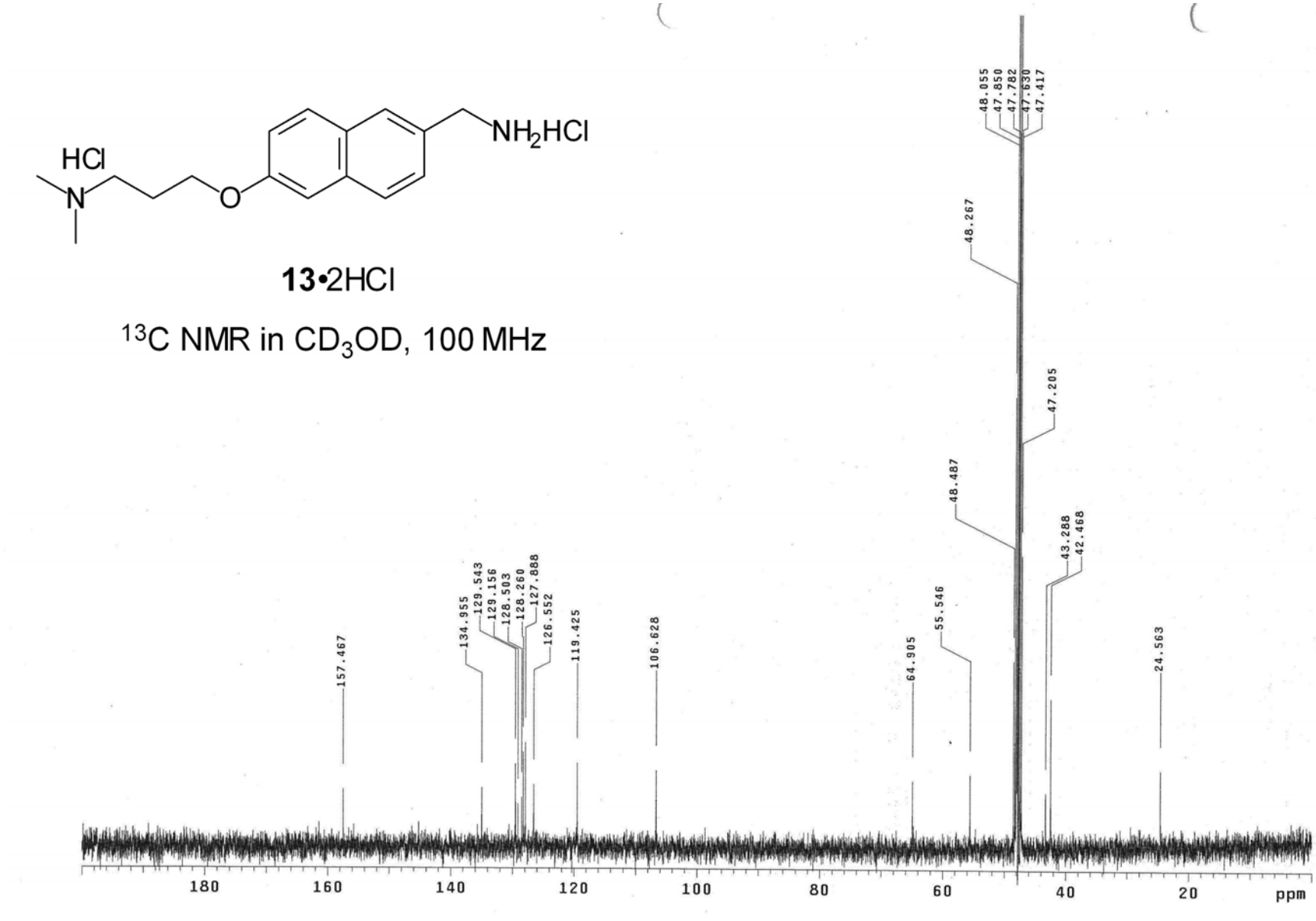
12 ·Cl⁻•HCl

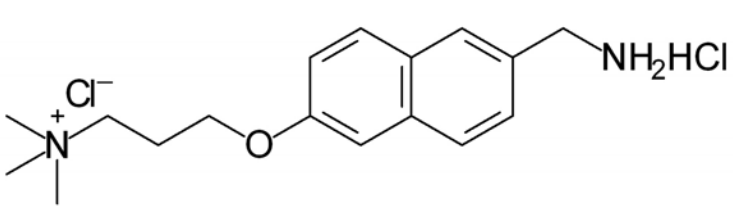
^{13}C NMR in CD_3OD, 100 MHz



13•2HCl

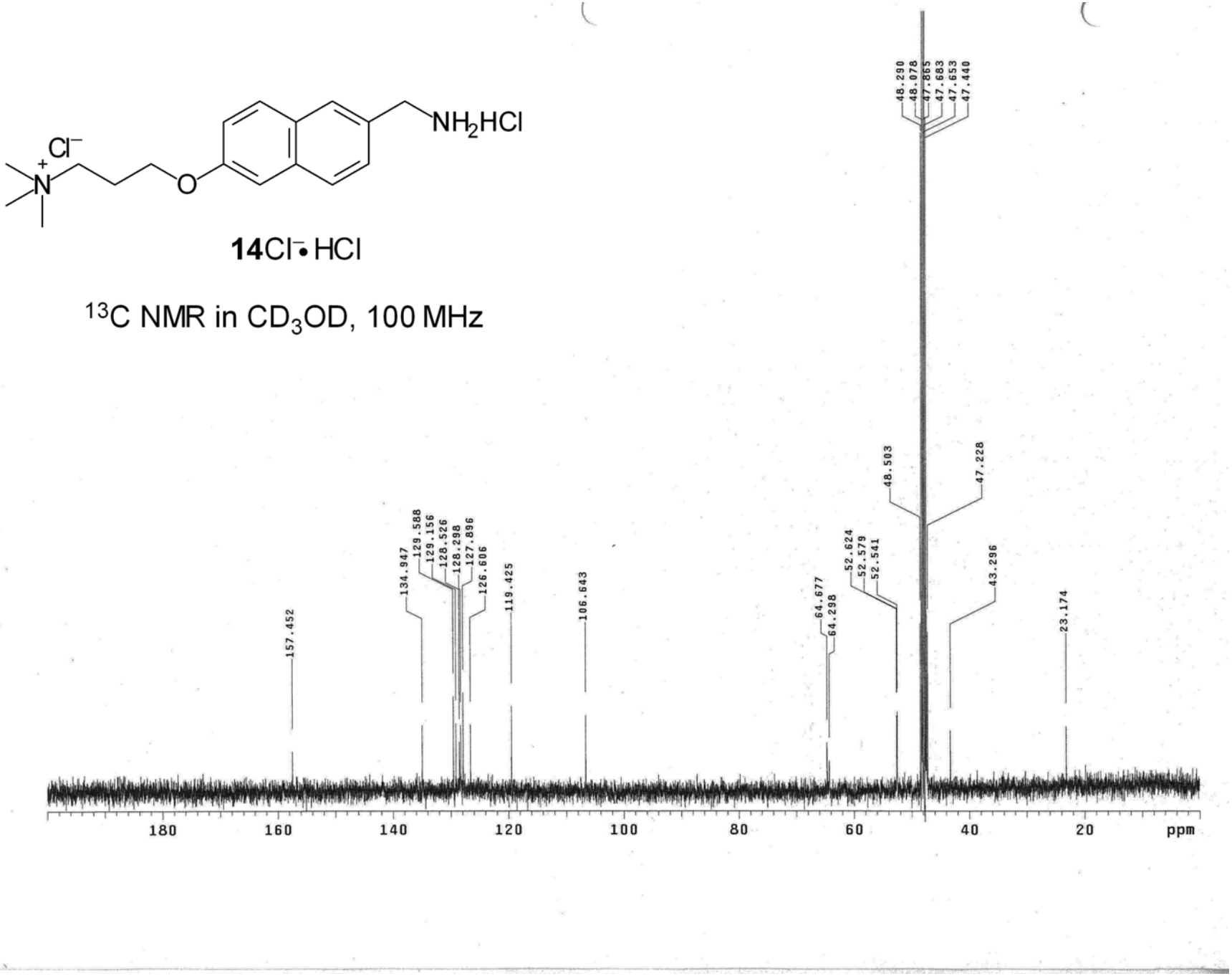
^{1}H NMR in CD_3OD, 400 MHz

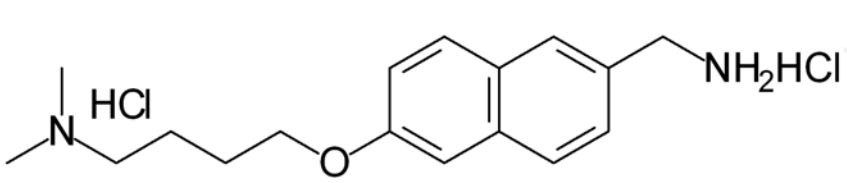

HCl
N
O
NH2HCl
13•2HCl
13C NMR in CD3OD, 100 MHz
48.055
47.850
47.782
47.630
47.417
48.267
47.205
48.487
43.288
42.468
157.467
134.955
129.543
129.156
128.503
128.260
127.888
126.552
119.425
106.628
64.905
55.546
24.563
180
160
140
120
100
80
60
40
20
ppm



14Cl⁻• HCl

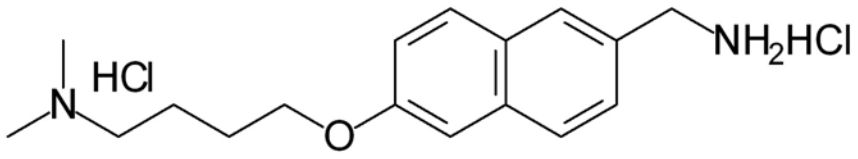
^{1}H NMR in CD_3OD, 400 MHz


Cl⁻
N⁺
O
NH2HCl
14Cl⁻• HCl
13C NMR in CD3OD, 100 MHz
48.290
48.078
47.865
47.653
47.440
48.503
47.228
157.452
134.947
129.588
129.156
128.526
128.298
127.896
126.606
119.425
106.643
64.677
64.298
52.624
52.579
52.541
43.296
23.174
180
160
140
120
100
80
60
40
20
ppm



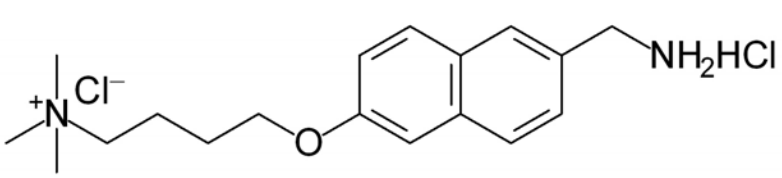
15•2HCl

^{1}H NMR in CD_3OD, 400 MHz



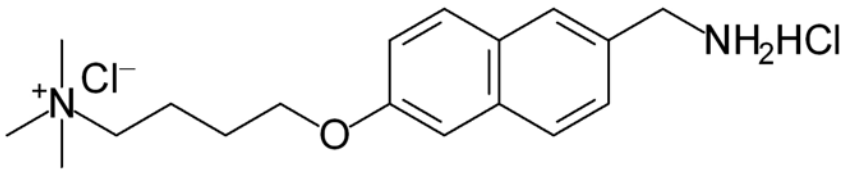
15•2HCl

^{13}C NMR in CD_3OD, 100 MHz



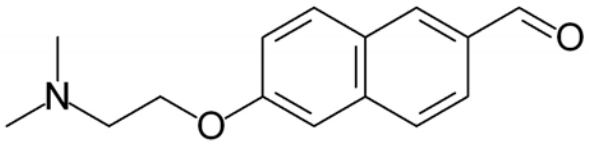
16Cl^{-} • HCl

^{1}H NMR in CD_3OD, 400 MHz



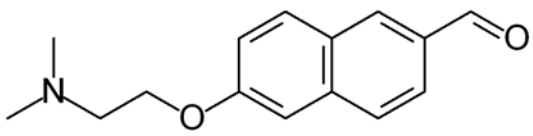
16Cl^{-}• HCl

^{13}C NMR in CD_3OD, 100 MHz



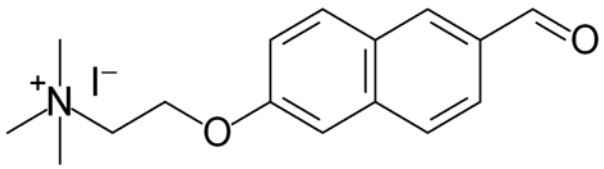
17

^{1}H NMR in $CDCl_3$, 400 MHz



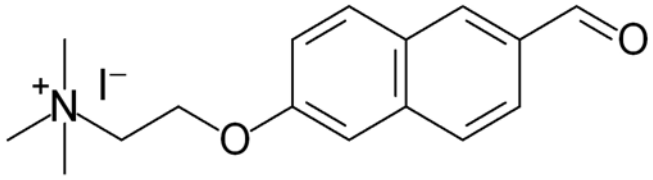
17

^{13}C NMR in $CDCl_3$, 100 MHz



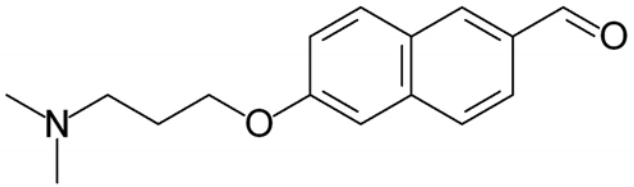
18 I^-

^1H NMR in CD_3OD, 400 MHz



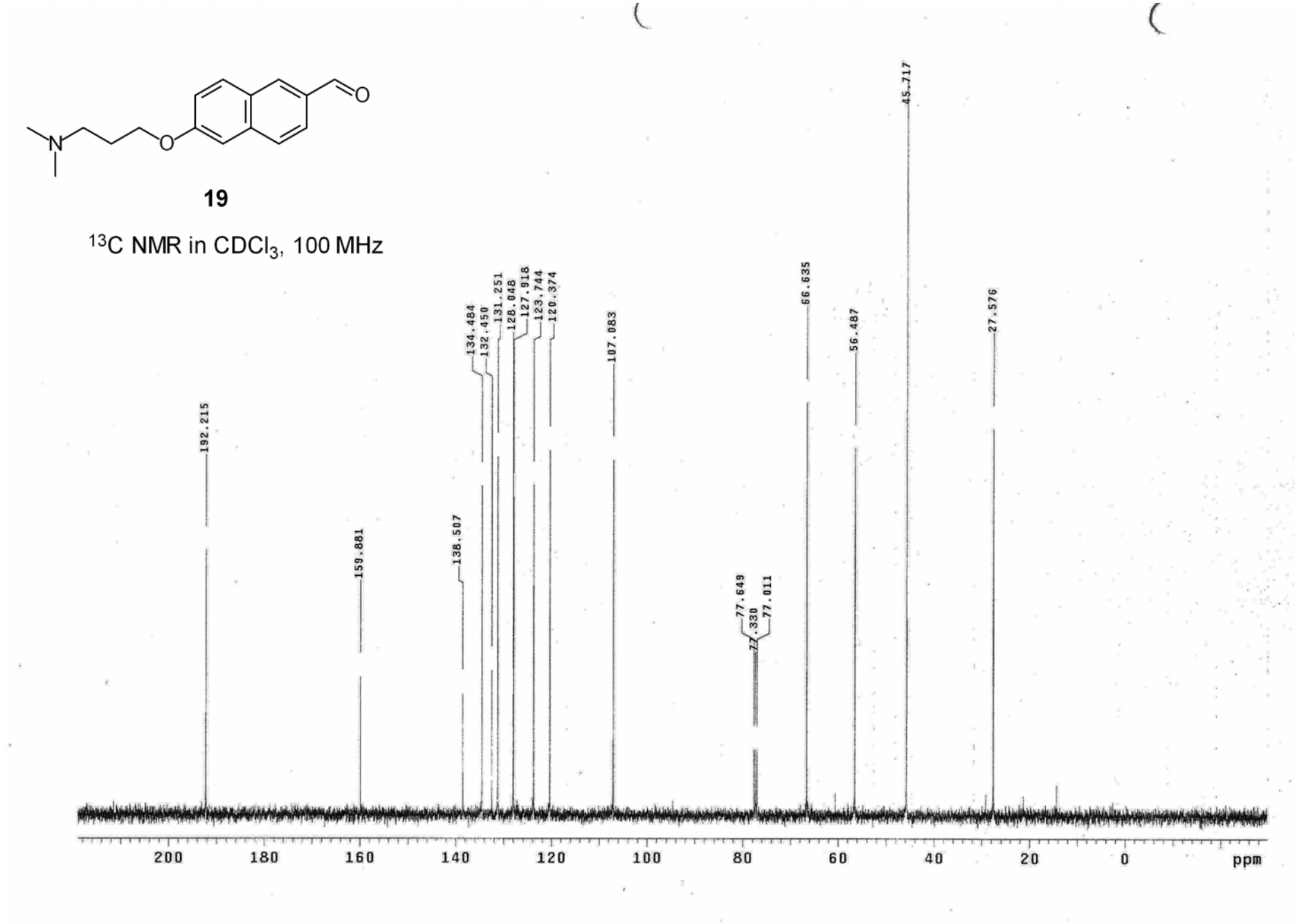
18 I^-

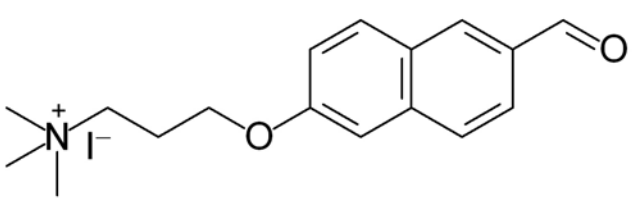
^{13}C NMR in CD_3OD, 100 MHz



19

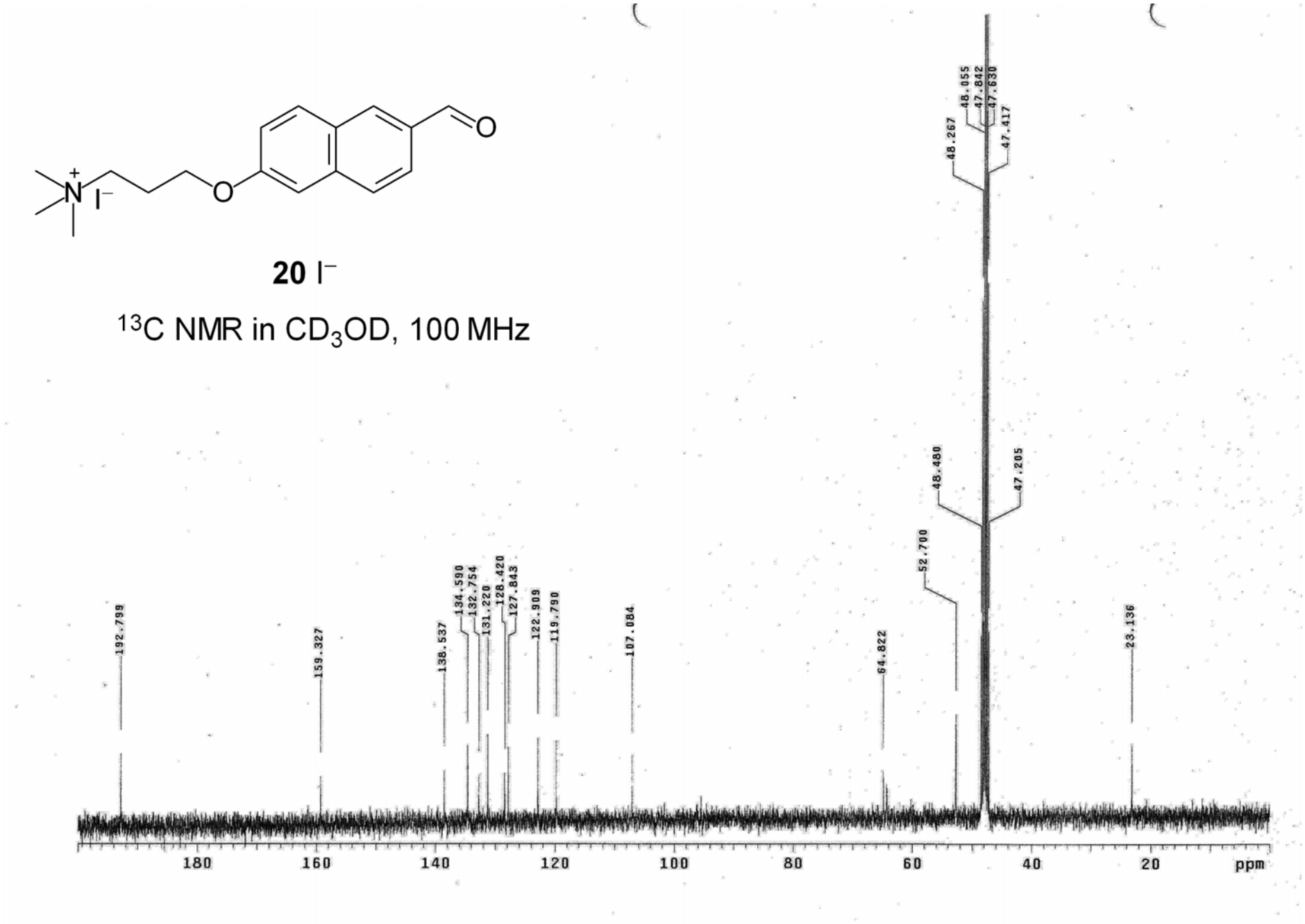
^{1}H NMR in $CDCl_3$, 400 MHz

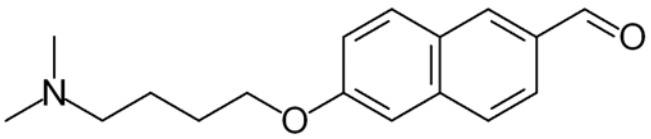

19
^{13}C NMR in $CDCl_3$, 100 MHz
192.215
159.881
138.507
134.484
132.450
131.251
128.048
127.918
123.744
120.374
107.083
77.649
77.330
77.011
66.635
56.487
45.717
27.576
200
180
160
140
120
100
80
60
40
20
0
ppm



20 I^-

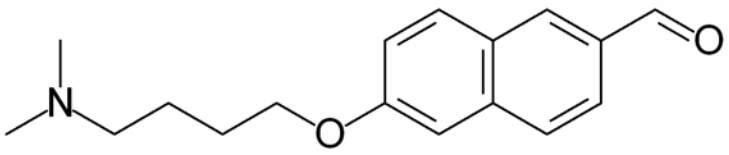
^1H NMR in CD_3OD, 400 MHz


20 I⁻
13C NMR in CD3OD, 100 MHz
192.799
159.327
138.537
134.580
132.754
131.220
128.420
127.843
122.909
119.790
107.084
64.822
52.700
48.480
48.267
48.055
47.842
47.630
47.417
47.205
23.136
180
160
140
120
100
80
60
40
20
ppm



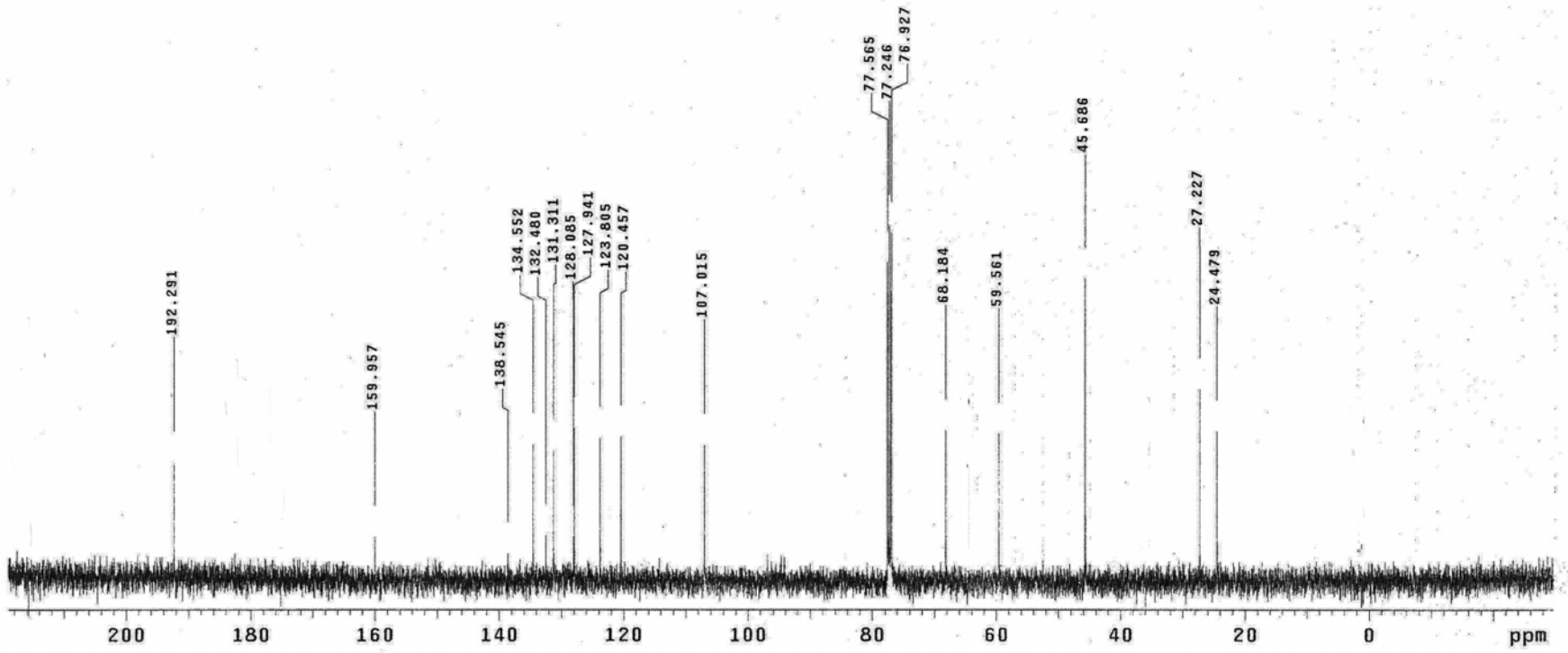
21

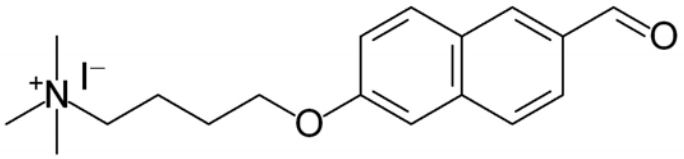
^{1}H NMR in $CDCl_3$, 400 MHz



21

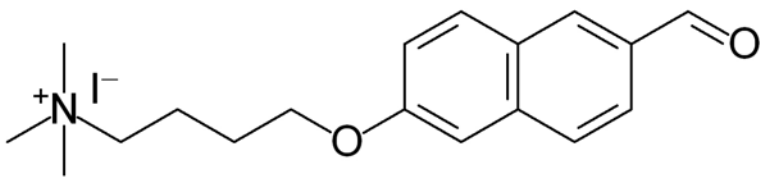
^{13}C NMR in $CDCl_3$, 100 MHz





22 I^-

^1H NMR in CD_3OD, 400 MHz



22 I^-

^{13}C NMR in CD_3OD, 100 MHz