Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Unsymmetrical PEG-substituted tris(triazolyl)amines as bi-functional surfactants for copper-catalyzed aerobic oxidation of alcohols in water

Vasut Nakarajouyphon,[†] Thanthapatra Bunchuay,[†] Naoto Yoshinari,[§] Takumi Konno,[§] Preeyanuch Sangtrirutnugul[†,*]

[†]Center of Excellence for Innovation in Chemistry (PERCH-CIC), Department of Chemistry, Faculty of Science, Mahidol University, Bangkok, 10400, Thailand

[§]Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

* Corresponding author.

* Email: preeyanuch.san@mahidol.edu

Table of Contents

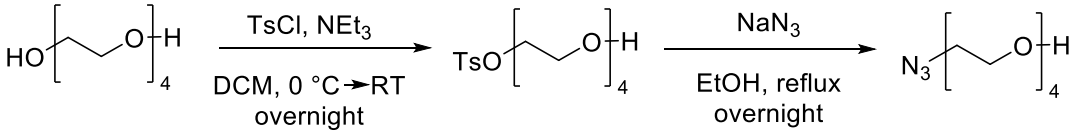
Contents Page

Fluorescence measurements. Fluorescence measurements used to investigate the critical micelle concentrations (CMC) of the surfactants were performed on FluoroMax 4+ Horiba spectrofluorometer. Fluorescence emission spectra of the pyrene probe were recorded at 25 °C using the excitation wavelength of 333 nm, with the excitation and emission slit width of 1.5 nm. A stock solution of 5.0 mM surfactant with 1.5 μM pyrene was prepared by dissolving 0.125 mmol of a surfactant in 10 mL of water and mixing with 75 μL of the pyrene stock solution (0.50 mM in ethanol), followed by sonication. The volume of the solution was then adjusted to 25.0 mL by adding water. Then, the stock surfactant solution with pyrene was diluted with water to various concentrations to measure the critical micelle concentrations.

Dynamic light scattering measurements. The size and distribution of sample aggregates were determined using the Zetasizer Nanoseries model S4700 (Malvern Instruments Corporation) laser light scattering system under the condition He-Ne laser (λ = 632.8 nm) at 25 °C. The autocorrelation function is analyzed by Zetasizer software provided by Malvern, and the corresponding data are obtained. The concentration of 5.0 mM, above the critical micelle concentrations, was used for all surfactants. **NBBT550** (26.8 mg, 0.025 mmol) or **NBBT2000** (61.2 mg, 0.025 mmol) was dissolved in 2 mL and further diluted to a final concentration of 5.0 mM. All samples were filtered with a 0.45 μm nylon membrane filter before measurements.

Transmission electron microscopy. TEM images of micelles were obtained from JEOL JEM-ARM200F (JEOL Co., Ltd. Tokyo, Japan) operated at 200 kV. Prior to analysis, surfactants were negatively stained with 1% phosphotungstic acid in water following this method: a solution containing 5–10 mM of a surfactant were dropped onto Formvar/carbon film coated on 300 mesh copper grid. After 3 min, the droplet was blotted off with filter paper to remove excess liquid. A drop of 1% phosphotungstic solution (PTA) was added on a separate petri dish. Then, the grid was gently brought to contact with a drop of 1% PTA. After 2 minutes, the excess liquid was blotted off with filter paper and open air-dried before subjected to TEM analysis.

Synthesis of PEG200-N_3

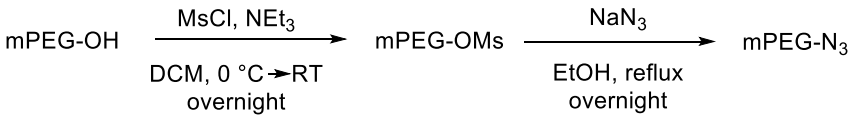


Scheme S1. Synthetic route of **PEG200-N_3**.

PEG200-N_3 was synthesized according to the literature with a slight modification.[1] To a mixture of **PEG200-OTs** [2] (5.9 g, 17 mmol) and NaN_3 (2.8 g, 42 mmol) was added 130 mL of EtOH and the solution was refluxed for overnight under N_2. After that, the reaction was cooled to room temperature and ethanol was removed under vacuum using a rotary evaporator, leaving colorless liquid, which was dissolved in 30 mL water and extracted with 3 x 50 mL of EtOAc. The organic

phase was collected, dried using anhydrous Na_2SO_4, and filtered. The filtrate was evaporated to afford **PEG200-N_3** as light yellow oil in 35% yield (1.3 g, 5.9 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (t, *J* = 4.2 Hz, 2H, N_3-C*H*$_2$-), 3.67 (m, 10H, -O-C*H*$_2$C*H*$_2$-O-), 3.60 (t, *J* = 4.3 Hz, 2H, N_3-CH_2-C*H*$_2$-), 3.39 (t, *J* = 5.0 Hz, 2H, C*H*$_2$-OH). FT-IR (cm^{-1}): 2106 (-N_3).

Synthesis of azido-functionalized methoxypolyethylene glycol (mPEG550-N_3, mPEG2000-N_3)



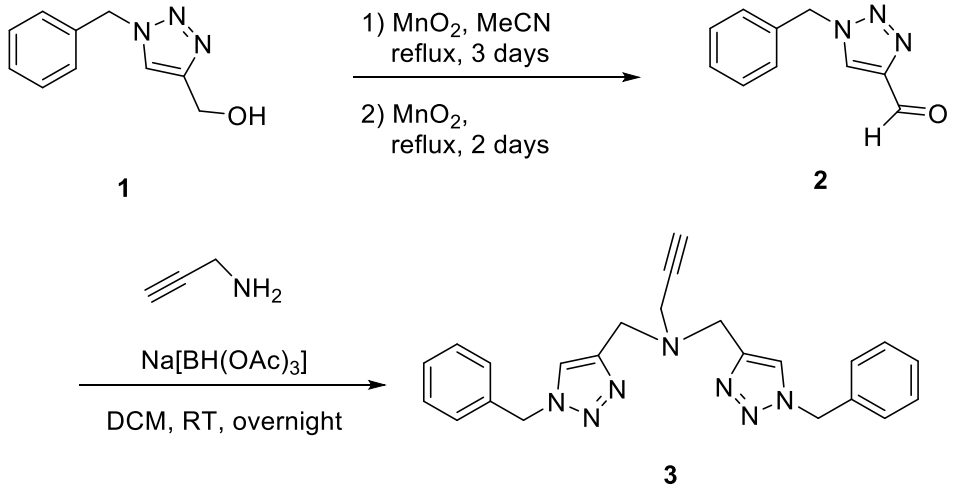
Scheme S2. Synthetic route of **mPEG550-N_3** and **mPEG2000-N_3**.

mPEG550-OMs was synthesized according to the literature with a slight modification.[3] Under N_2, mPEG550 (8.0 g, 14.5 mmol) was dissolved in 100 mL anhydrous CH_2Cl_2. At 0 °C, to the CH_2Cl_2 solution of mPEG550 was added NEt_3 (3.0 mL, 22 mmol), followed by dropwise addition of the 20 mL anhydrous CH_2Cl_2 solution of methanesulfonyl chloride (MsCl, 1.5 mL, 18.9 mmol). After the addition was completed, the reaction mixture was allowed to warm to room temperature and kept stirred under N_2 for 19 h. Then, the solution was washed with water (100 mL), dried with anhydrous Na_2SO_4, and dried *in vacuo* to afford **mPEG550-OMs** as light yellow oil in 100% yield (9.3 g, 14.5 mmol). The product was used in the next step without further purifications. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (t, *J* = 4.5 Hz, 2H, MsO-C*H*$_2$-), 3.74–3.52 (m, O-C*H*$_2$C*H*$_2$-O), 3.35 (s, 3H, O-C*H*$_3$), 3.06 (s, 3H, OS(=O)$_2$C*H*$_3$).

mPEG550-N_3 was synthesized according to the literature with a slight modification.[1] A mixture of **mPEG550-OMs** (9.3 g, 14 mmol) and NaN_3 (1.4 g, 22 mmol) in 200 mL absolute ethanol was refluxed for 19 h under N_2 atmosphere. After that, the reaction mixture was cooled to room temperature and all volatiles were was dried *in vacuo*. The crude product was then dissolved in 100 mL CH_2Cl_2, washed with water (100 mL) and brine (100 mL). Organic phase was collected and concentrated to *ca*. 3 mL, to which approximately 50 mL of diethyl ether was added at -14 °C to precipitate the product. Decantation at such temperature afforded **mPEG550-N_3**, which becomes colorless oil at room temperature (5.3 g, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63–3.57 (m, O-C*H*$_2$C*H*$_2$-O), 3.48 (m, 2H, N_3-C*H*$_2$-), 3.33 (m, 2H, N_3-CH_2-C*H*$_2$-), 3.31 (s, 3H, O-C*H*$_3$). FT-IR (cm^{-1}): 2102 (-N_3).

mPEG2000-OMs was prepared following the same method described above for the synthesis of **mPEG550-OMs**. The crude product was precipitated from CH_2Cl_2/diethyl ether to produce an off-white solid in 95% yield (9.5 g, 4.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (t *J* = 4.4 Hz, 2H, MsO-C*H*$_2$-), 3.72 (t, *J* = 4.4 Hz, 2H, MsO-CH_2-C*H*$_2$), 3.60 (m, O-C*H*$_2$C*H*$_2$-O), 3.33 (s, 3H, O-C*H*$_3$), 3.04 (s, 3H, OS(=O)$_2$C*H*$_3$).

mPEG2000-N_3 was prepared following the same method described for the synthesis of **mPEG550-N_3** with minor modifications. The solid from diethyl ether precipitation was filtered instead of decantation to give **mPEG2000-N_3** as a white solid in 73% yield (6.8 g, 3.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (m, O-C*H*$_2$C*H*$_2$-O), 3.37 (s, 3H, O-C*H*$_3$). FT-IR (cm^{-1}): 2104 (-N_3).



Scheme S3. Synthetic route of compound **3**.

(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (1). Compound **1** was synthesized according to the literature with a slight modification.[4] To 250 mL round-bottom flask, benzyl azide (6.8 g, 51 mmol) and propargyl alcohol (2.7 g, 49 mmol) were dissolved in 50 mL of methanol. Water bath was used to maintain the temperature of reaction flask at room temperature. To this methanol solution was added $CuSO_4 \cdot 6H_2O$ (3.0 g, 12 mmol) followed by ascorbic acid (3.9 g, 22 mmol). The reaction was then stirred at room temperature overnight, after which all volatiles were dried *in vacuo*. To the remaining blue-green liquid was added 100 mL of CH_2Cl_2 and the 100 mL of 10% NH_4OH solution of ethylenediaminetetraacetic acid (15.0 g, 49 mmol). The reaction solution was stirred for 3 h after which the organic layer was collected, dried with anhydrous Na_2SO_4, filtered, and evaporated. The off-white solid was obtained as the product **1** (5.9 g, 61 %yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H, *H*-triazole), 7.37–7.26 (m, 5H, Ar-*H*), 5.51 (s, 2H, Ph-C*H*$_2$-N), 4.76 (s, 2H, triazole-C*H*$_2$-OH).

1-benzyl-1*H*-1,2,3-triazole-4-carbaldehyde (2). Compound **2** was synthesized according to the literature with a slight modification.[5] First, manganese oxide (10 g, 11.5 mmol) was oven dried at 200 °C for 12 h before adding into a 30 mL CH_3CN solution of **1** (1.6 g, 8.7 mmol). The reaction mixture was refluxed for 3 d after which another 10 g of oven-dried MnO was added and the reflux continued. After 2 d, manganese oxide was filtered out using zeolite and the filtrate was vacuum dried. The product was dissolved in 20 mL of CH_2Cl_2 and passed through a short silica plug using CH_2Cl_2 as an eluent (200 mL). After evaporation, **2** was obtained as a white solid in 74% yield

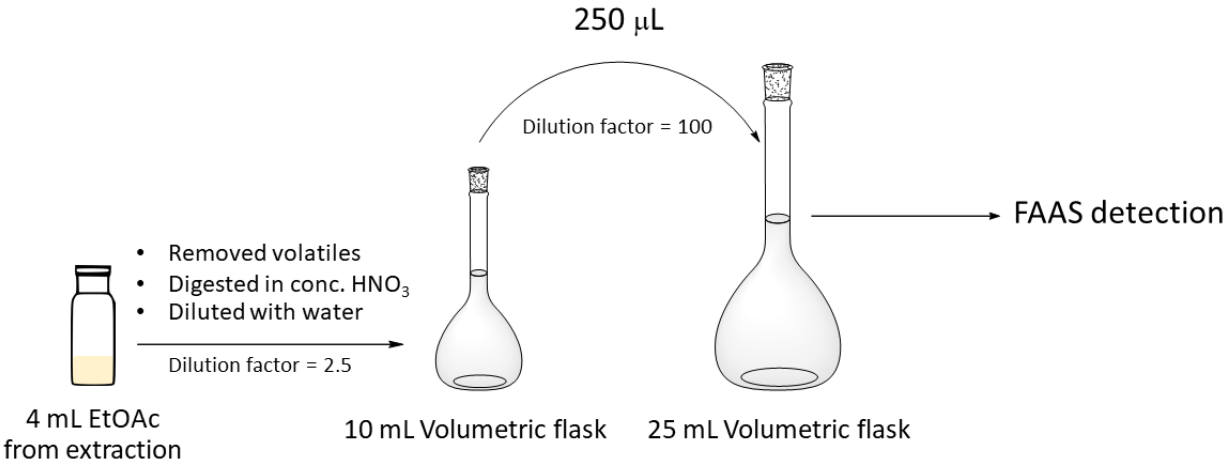
(1.2 g, 6.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H, C*H*O), 7.98 (s, 1H, *H*-triazole), 7.41–7.30 (m, 5H, Ar-*H*), 5.59 (s, 2H, Ph-CH_2-N).

***N,N*-bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)prop-2-yn-1-amine (3)**. Compound **3** was prepared following the literature method with slight modifications.[6] To a 30 mL CH_2Cl_2 solution of **2** (1.1 g, 6.4 mmol) was added propargylamine (0.17 g, 3.1 mmol). Then, $Na(OAc)_3BH$ (1.9 g, 9.0 mmol) was slowly added in portion over a course of 1 h and the reaction was left stirred at room temperature. After 19 h, 20 mL of a 2.0 M aqueous NaOH solution was added and the reaction mixture was vigorously stirred for 20 min, after which the organic layer was washed with water (50 mL) and brine (50 mL). Evaporation of the organic layer resulted in a yellow solid. Crystallization in THF/diethyl ether gave **3** as a white solid in 74% yield (0.90 g, 2.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 2H, *H*-triazole), 7.36–7.24 (m, 10H, Ar-*H*), 5.49 (s, 4H, Ar-CH_2-N), 3.81 (s, 4H, triazole-CH_2-N), 3.33 (d, J = 2.5 Hz, 2H, N-CH_2-C≡CH), 2.22 (t, J = 2.4 Hz, 1H, C≡C-*H*).

Table S1. Copper concentration in EtOAc phase from reusability study.

Run	Absorbance of Cu[a]	Cu concentration in 4 mL EtOAc extracts (ppm)
1	0.0102	32
2	0.0124	39
3	0.0112	35

[a] Measured by flame atomic absorption spectroscopy (FAAS)



Scheme S4. Preparation procedure for FAAS.

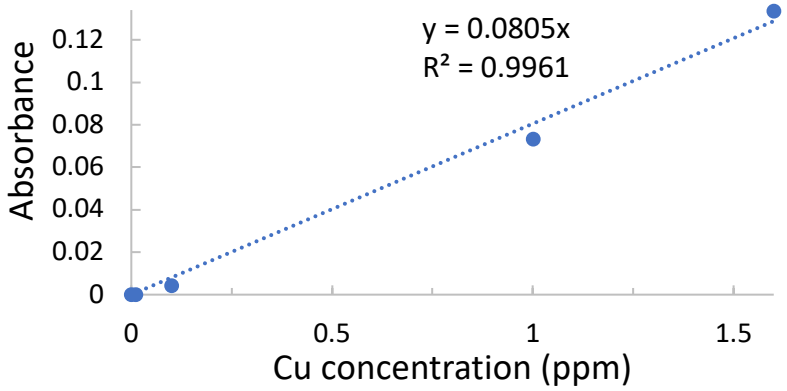


Figure S1. 5-point calibration curve of Cu from flame atomic absorption measurement.

Calculation for leached Cu ions after the 1st run of the reusability test

$$Y = 0.0805 * X$$

$$\text{Mean of absorbance} = 0.0805 * \text{Cu concentration}$$

0.0102 = 0.0805 * Cu concentration
Cu concentration = 0.127 Cu ppm

Cu concentration in 25 mL volumetric flask = 0.127 Cu ppm

Cu concentration in 10 mL volumetric flask = 0.127 Cu ppm * Dilution factor
= 0.127 Cu ppm * 100
= 12.7 Cu ppm

Cu concentration in 4 mL EtOAc from extraction = 12.7 Cu ppm * Dilution factor
= 12.7 Cu ppm * 2.5
= 32 Cu ppm

UV-Vis spectrophotometry titrations

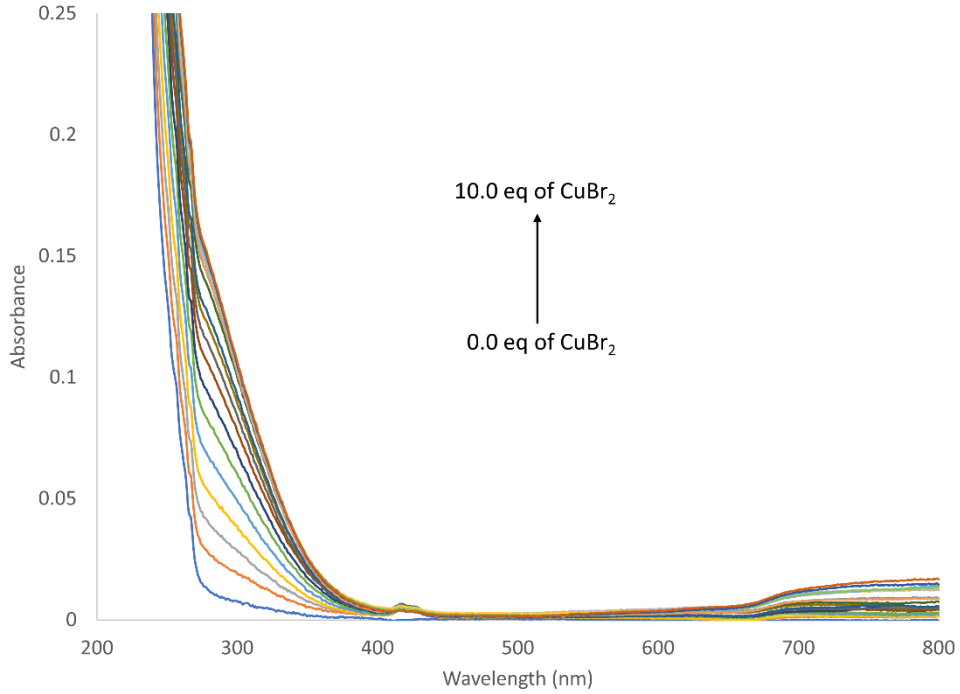


Figure S2. Absorbance spectra of $CuBr_2$ at 0.0–10.0 equivalents in 1.0 x 10^{-4} M **NBBT550** (aq.)

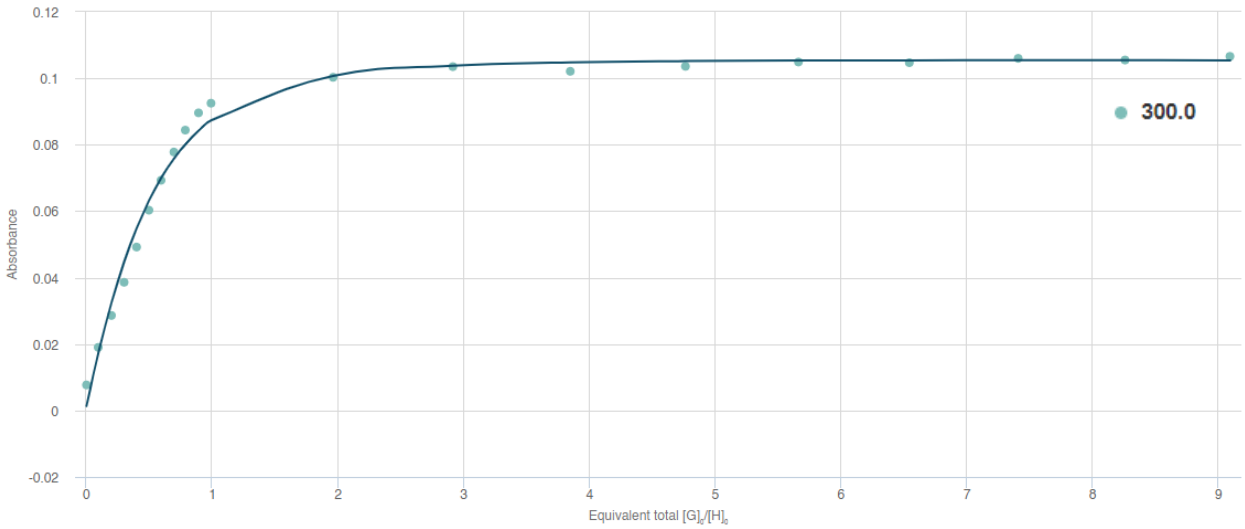


Figure S3. Binding isotherms from UV-Vis titrations of **NBBT550** with $CuBr_2$. The solid symbols represent experimental data at wavelength of 300 nm and solid lines represent the fitted binding isotherm. The graph was generated from the online program "BindFit" using UV 2:1, the Nelder-Mead method.[7]

Table S2. Summary of BindFit analysis from UV-Vis titrations between **NBBT550** and $CuBr_2$

Stoichiometry		**K**	**K error (%)**			**Covariance**
1:1		999650.32	75.86			0.00454657
Stoichiometry	**Mode**	**K_{11}**	**K_{12}**	**K_{11} error (%)**	**K_{12} error (%)**	**Covariance**
1:2	Full	3.2746×10^{14}	2.9428×10^{13}	8.26088×10^{7}	8.26088×10^{7}	0.00259787
	Non-Cooperative	6.6294×10^{20}		9.49670×10^{9}		0.00317552
	Additive	1240647.65	17.9683	90.1844	1.85224×10^{2}	0.00445804
	Statistical	2140995.77		1.04534×10^{3}		0.25272907
Stoichiometry	**Mode**	**K_{11}**	**K_{21}**	**K_{11} error (%)**	**K_{12} error (%)**	**Covariance**
2:1	Full	2.5740×10^{8}	9.8494×10^{6}	2.31062×10^{3}	2.31776×10^{3}	0.00094446
	Non-Cooperative	19647.89	4911.75	6.74797		0.01093699
	Additive	451502.07	884.44	49.2042	33.8284	0.00159911
	Statistical	25145.87	6286.25	7.79523		0.01105765

Results for 2:1 stoichiometry statistical model:
http://app.supramolecular.org/bindfit/view/7ca73e4b-d1a9-4221-af55-bdfeac4081e8

Results for 2:1 stoichiometry non-cooperative model:
http://app.supramolecular.org/bindfit/view/18586ecf-58e6-4f83-be9b-b9b8252f04ff

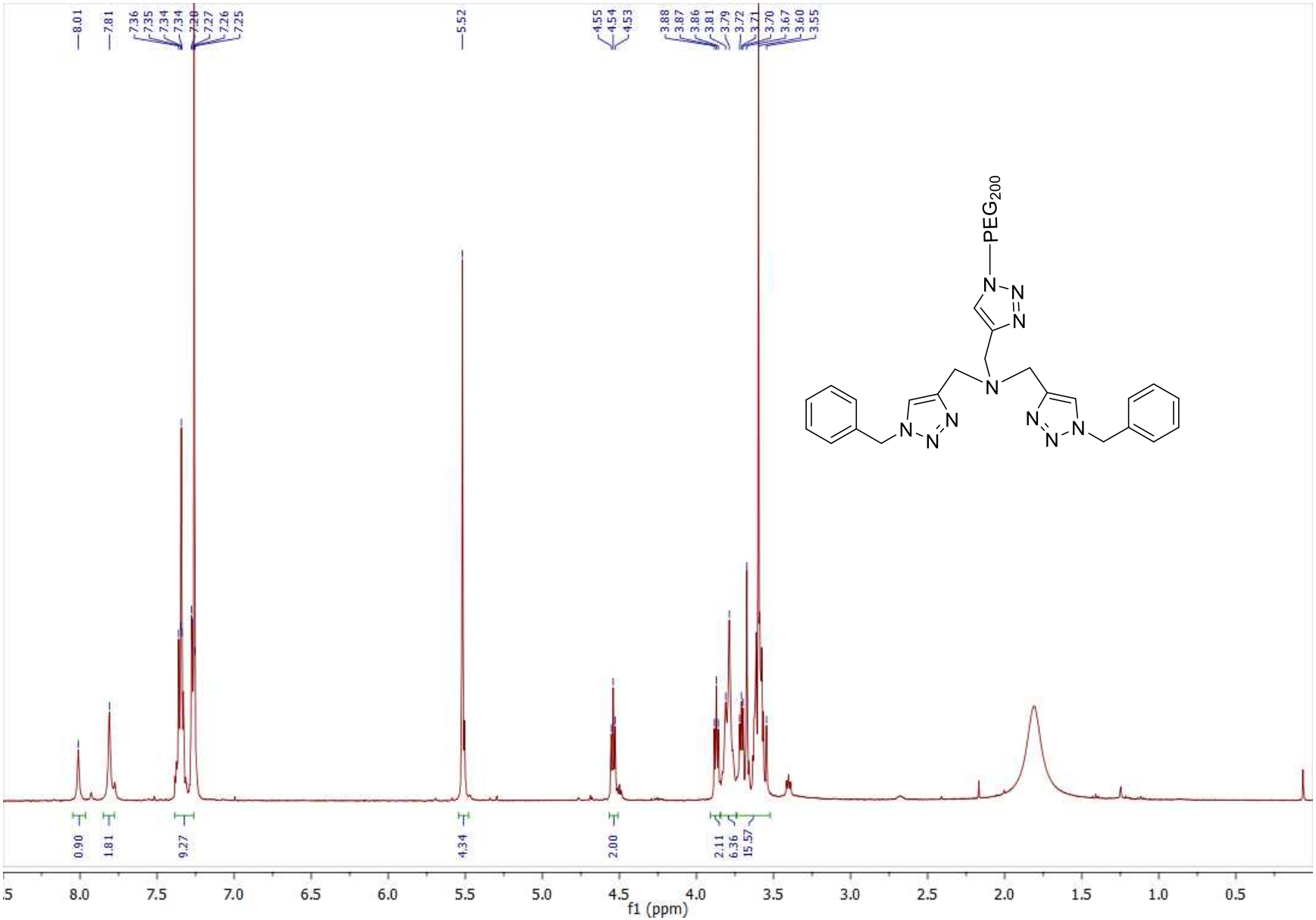


Figure S4. ^{1}H NMR (400 MHz) spectrum of **NBBT200-OH** in $CDCl_3$.

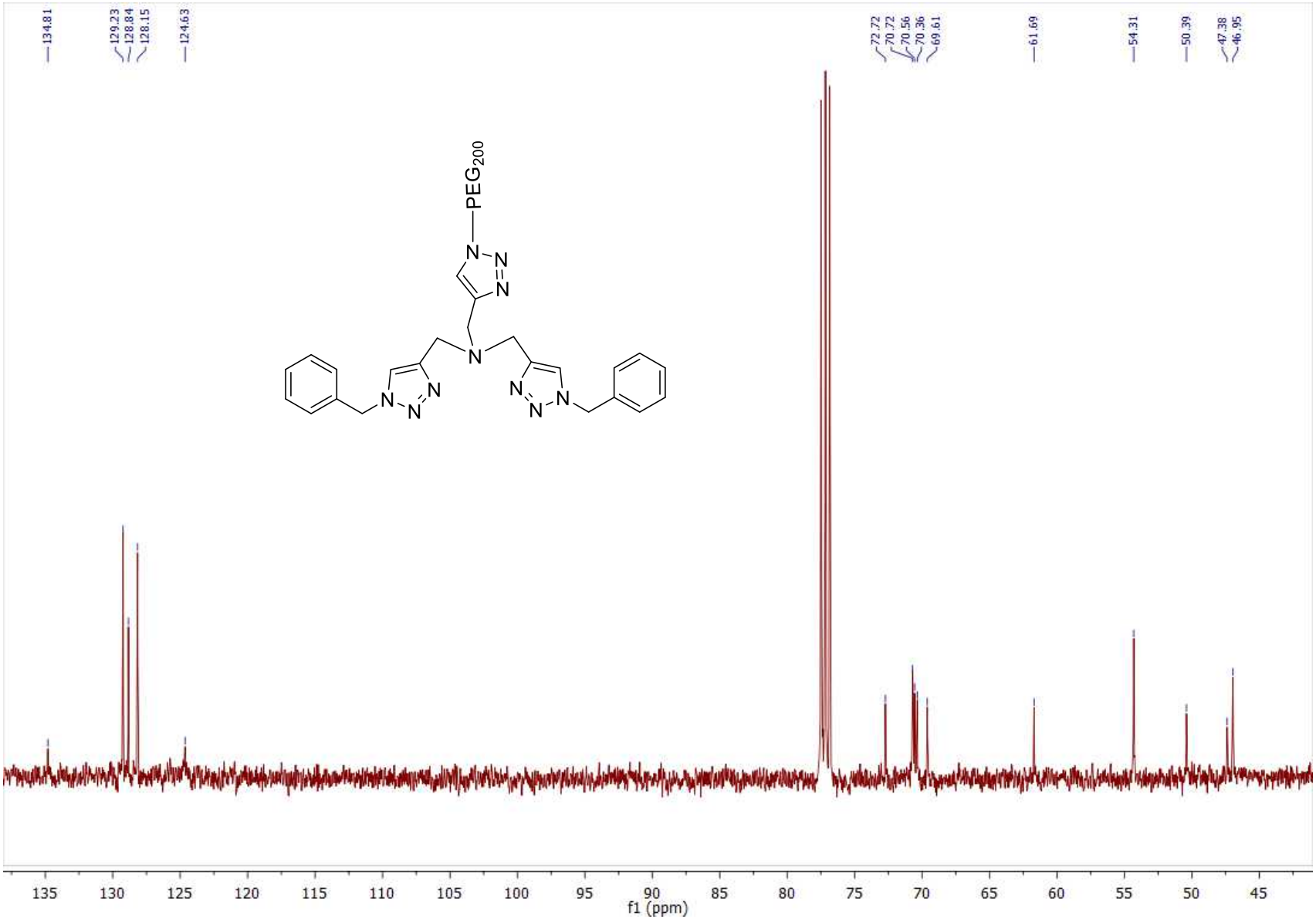


Figure S5. $^{13}C\{^{1}H\}$ NMR (101 MHz) spectrum of **NBBT200-OH** in $CDCl_3$.

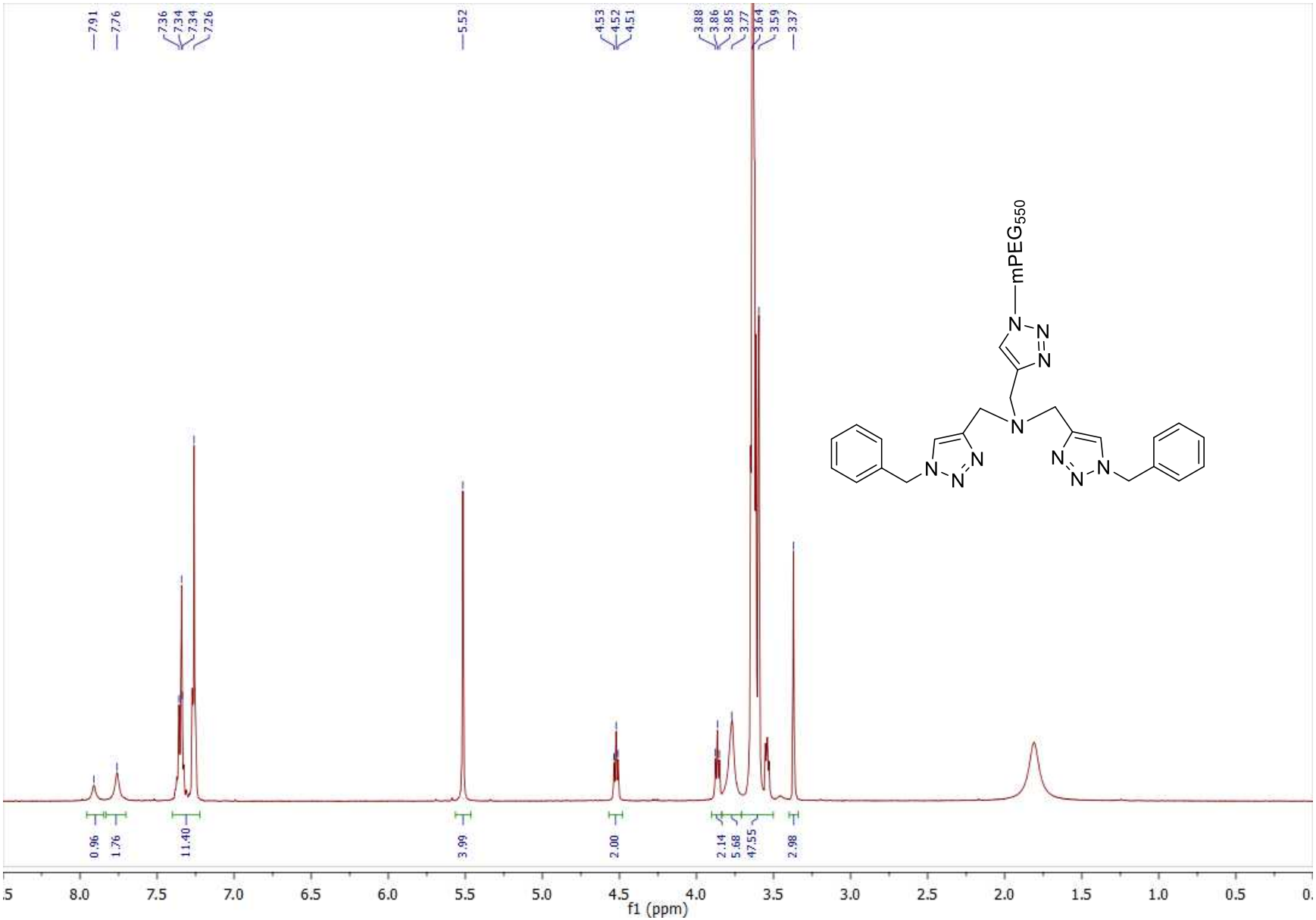


Figure S6. ^{1}H NMR (400 MHz) spectrum of **NBBT550** in $CDCl_3$.

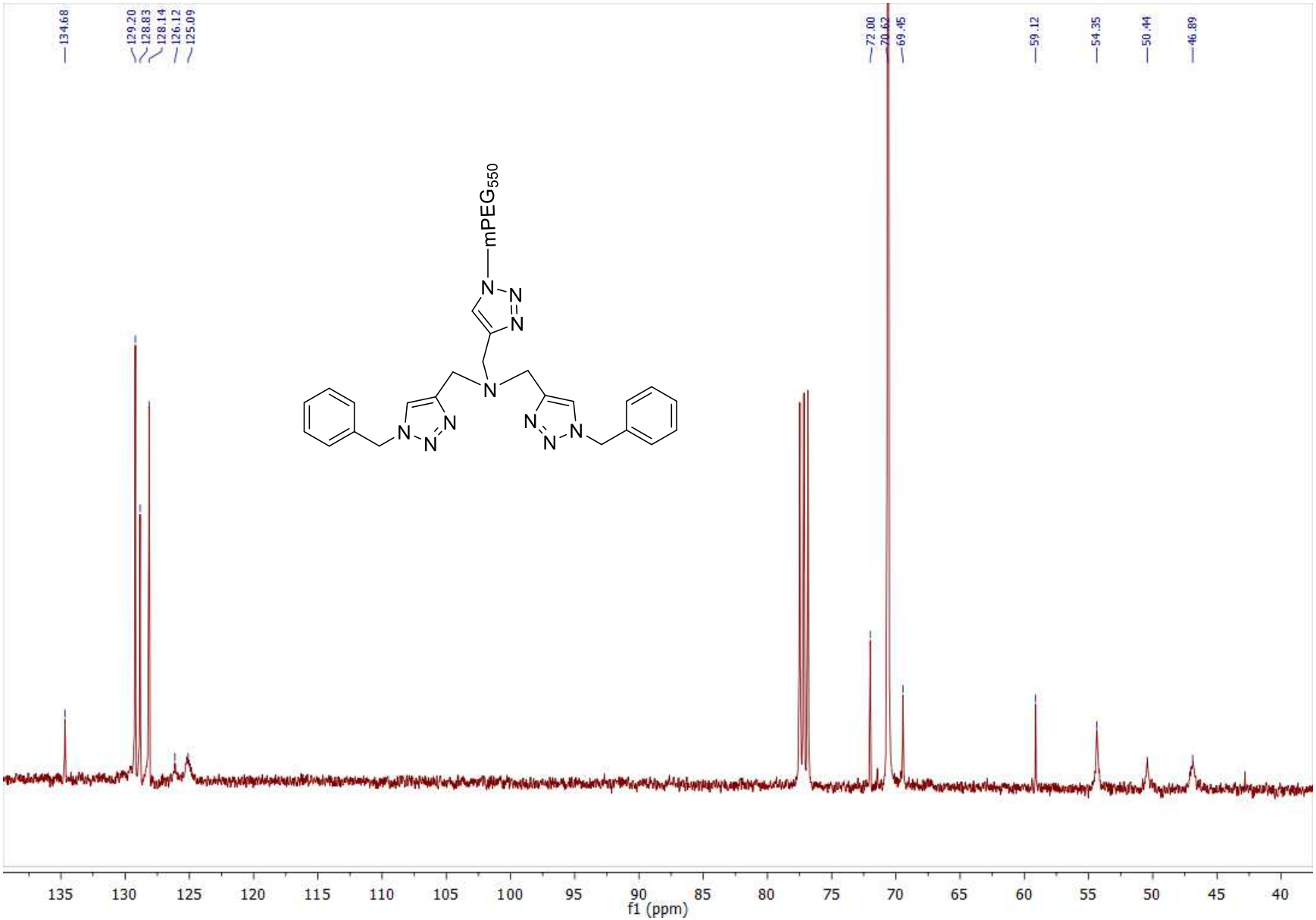


Figure S7. $^{13}C\{^{1}H\}$ NMR (101 MHz) spectrum of **NBBT550** in $CDCl_3$.

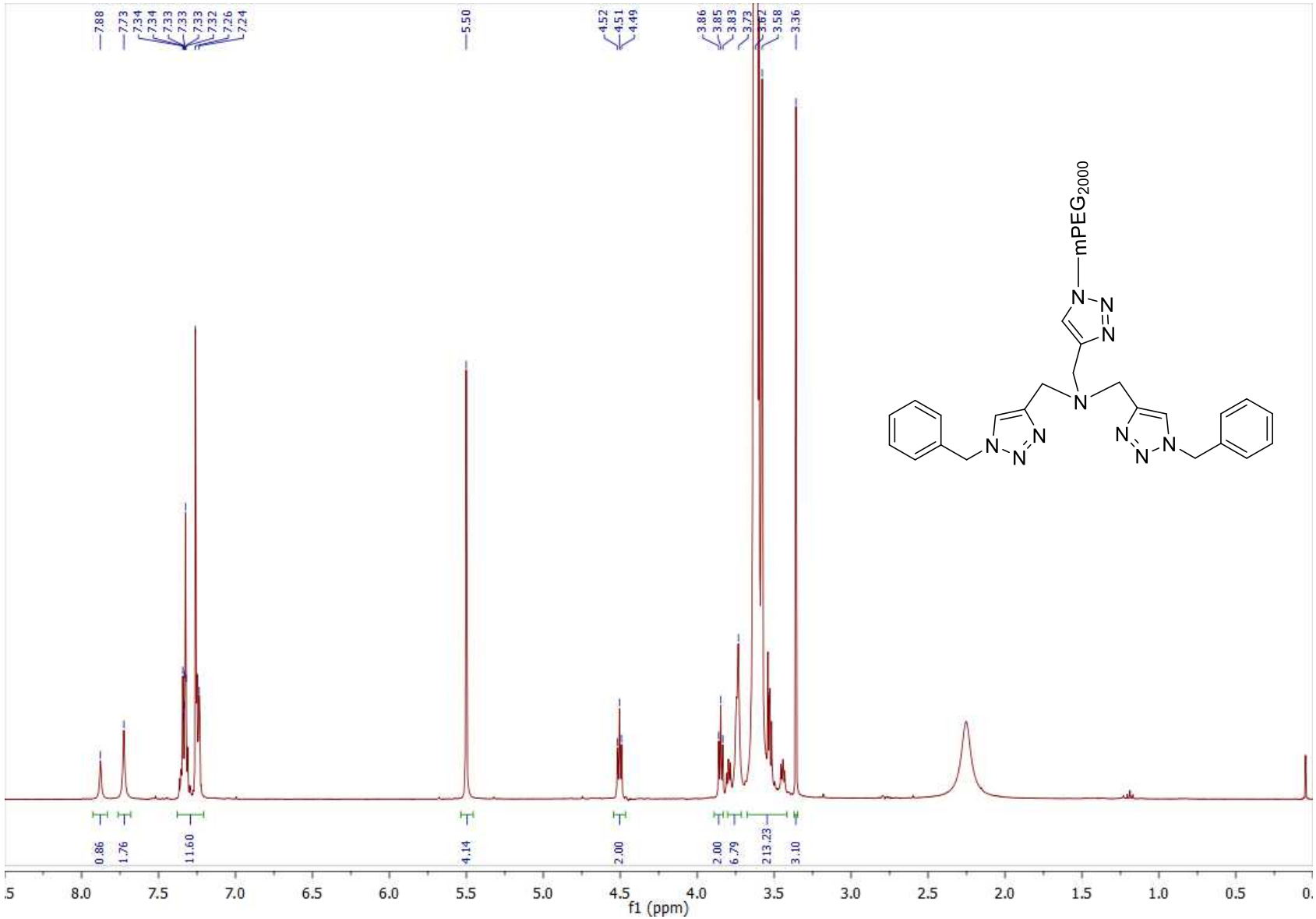


Figure S8. ^{1}H NMR (400 MHz) spectrum of **NBBT2000** in $CDCl_3$.

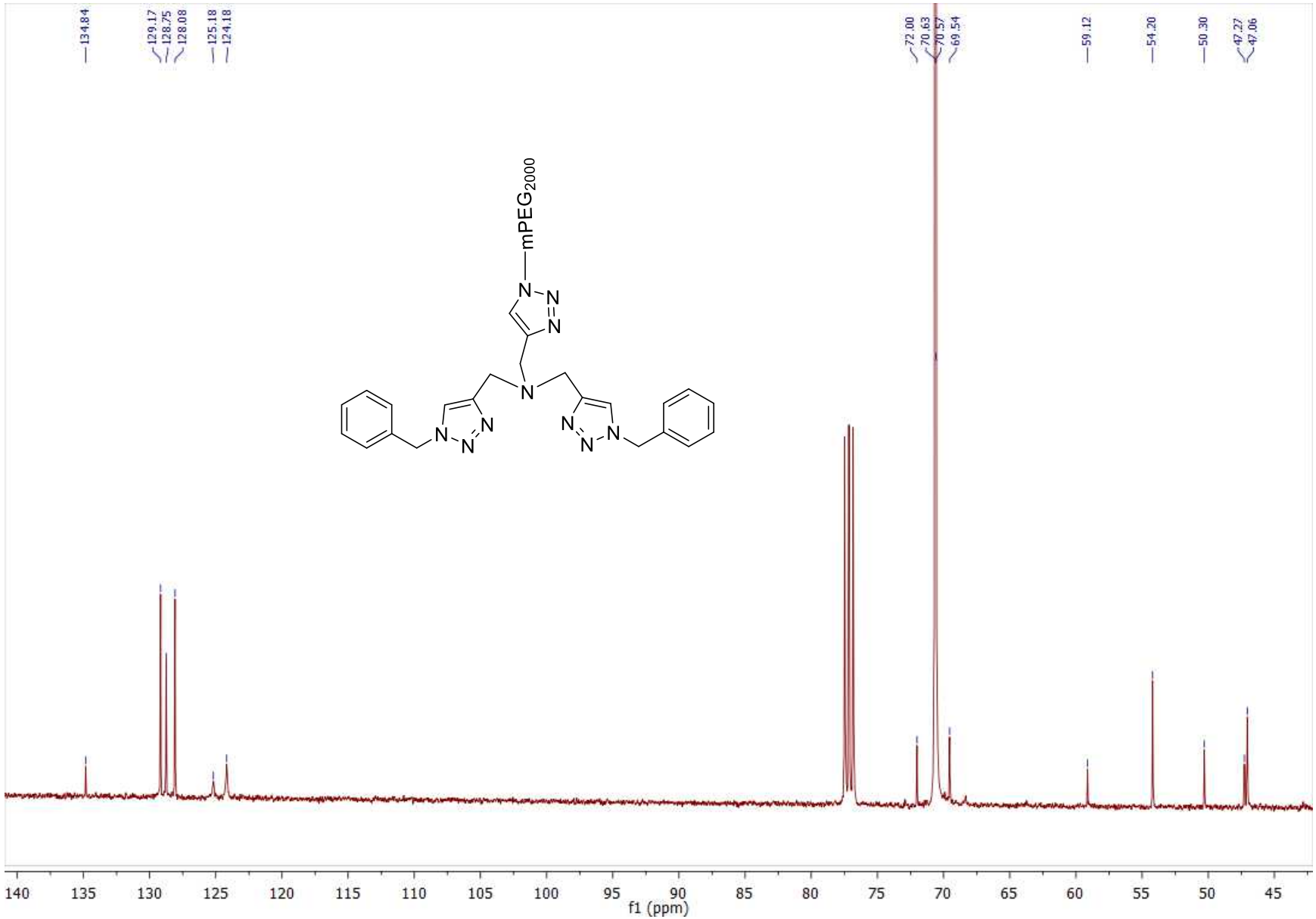


Figure S9. $^{13}C\{^{1}H\}$ NMR (101 MHz) spectrum of **NBBT2000** in $CDCl_3$.

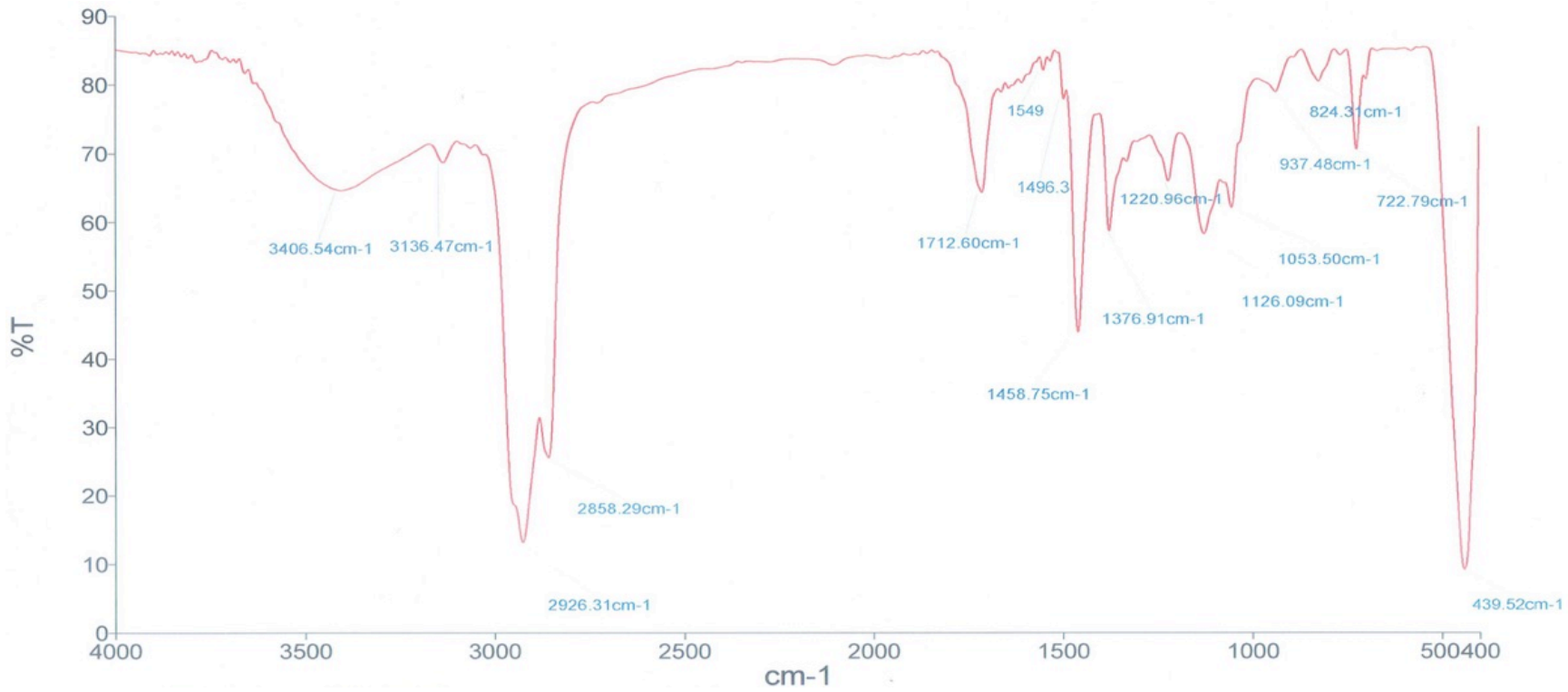


Figure S10. FT-IR spectrum of **NBBT200-OH**.

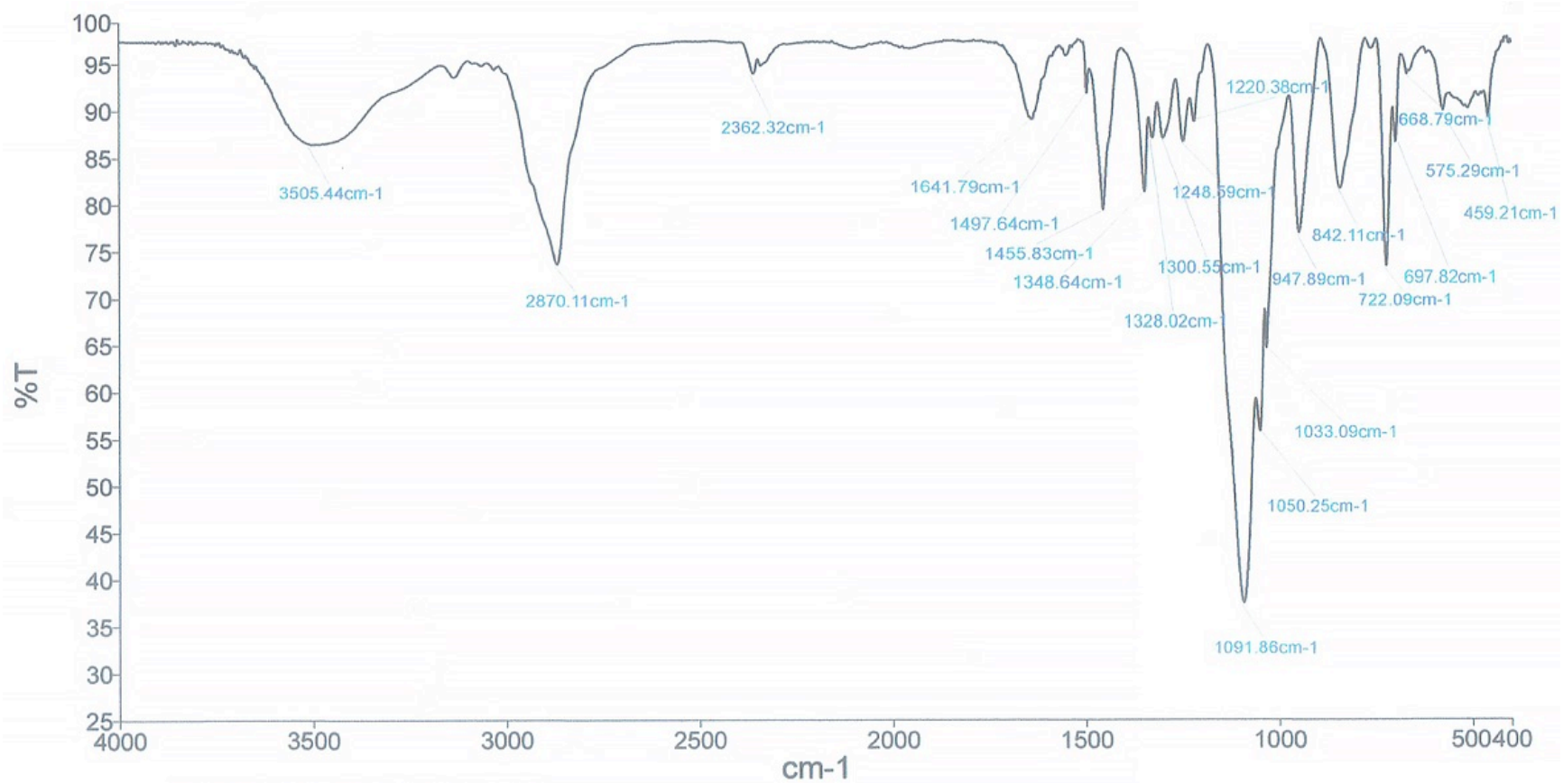


Figure S11. FT-IR spectrum of **NBBT550**.

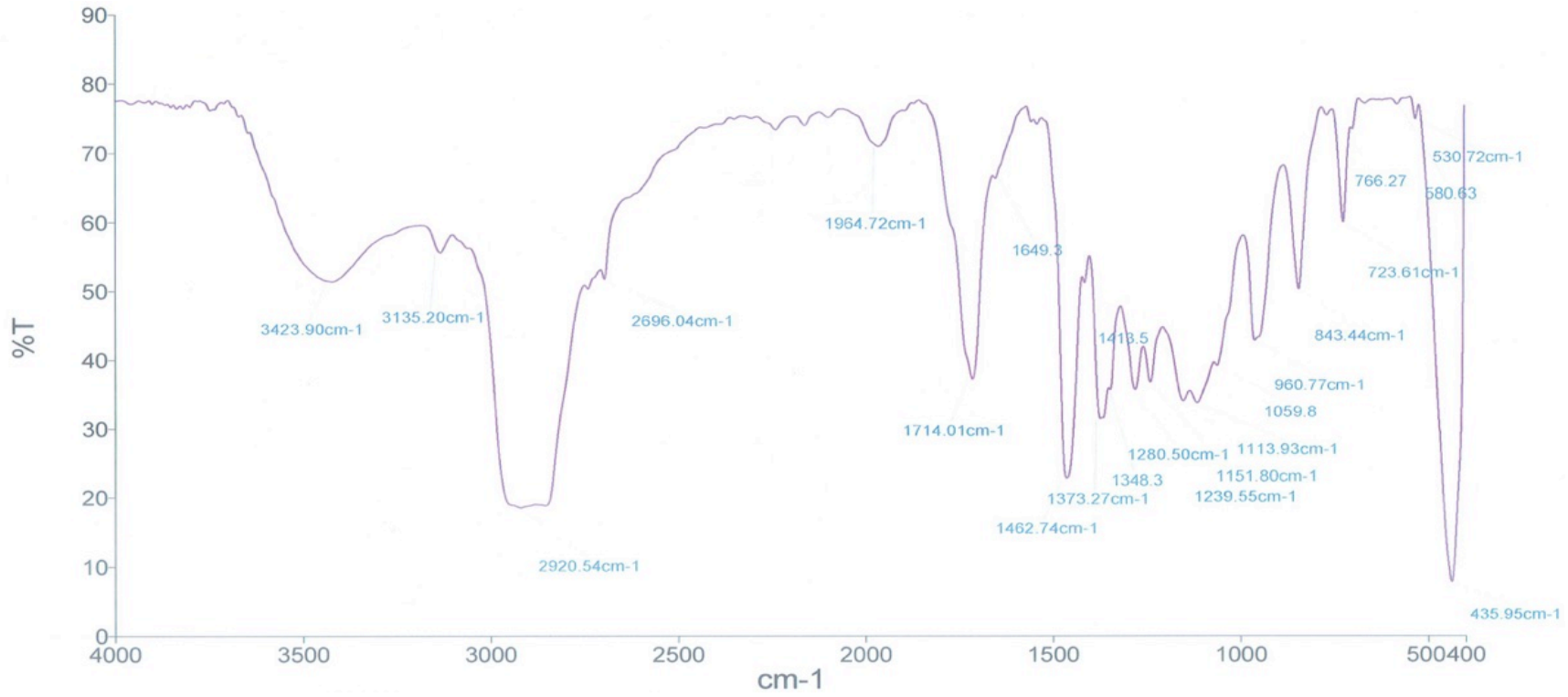


Figure S12. FT-IR spectrum of **NBBT2000**.

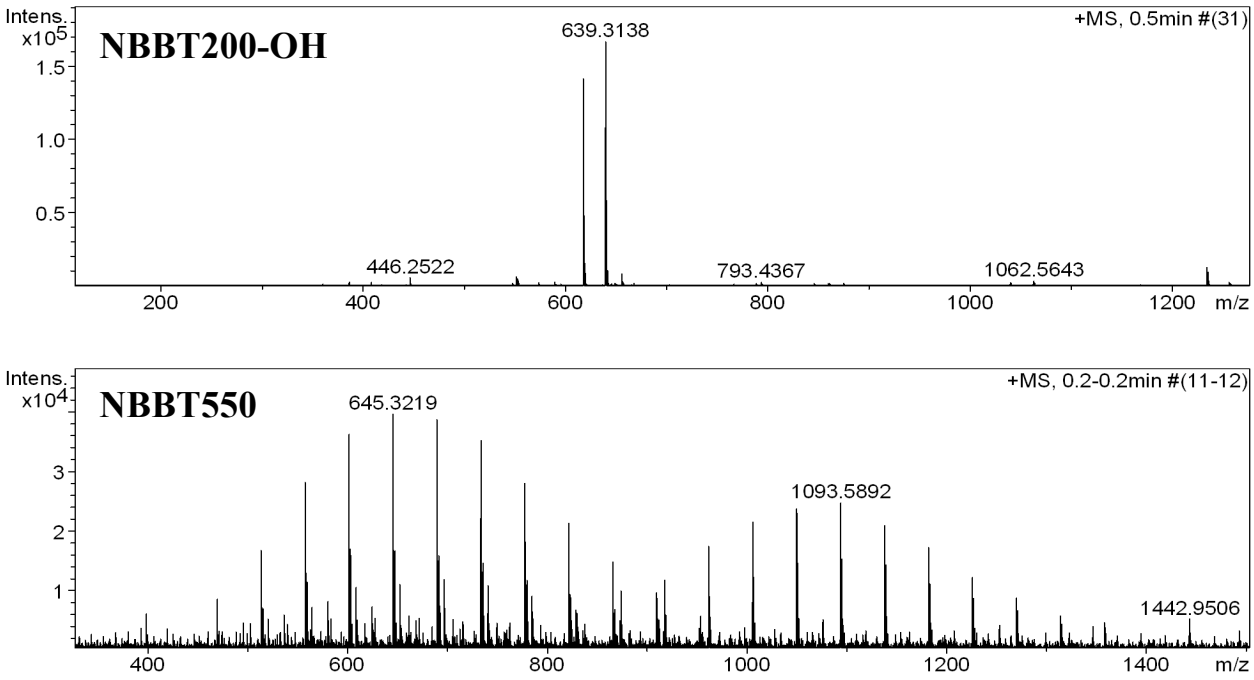


Figure S13. ESI-MS spectra of **NBBT200-OH** and **NBBT550**.

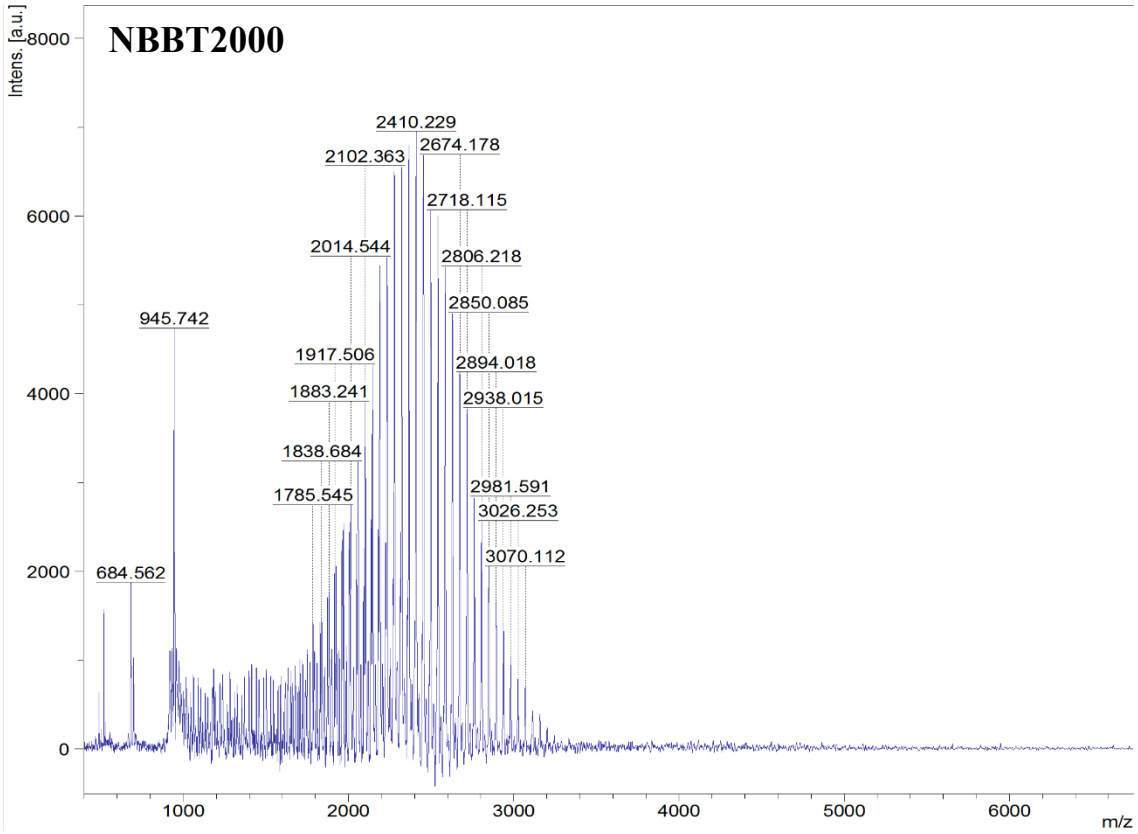


Figure S14. MALDI-TOF mass spectra of **NBBT2000**.

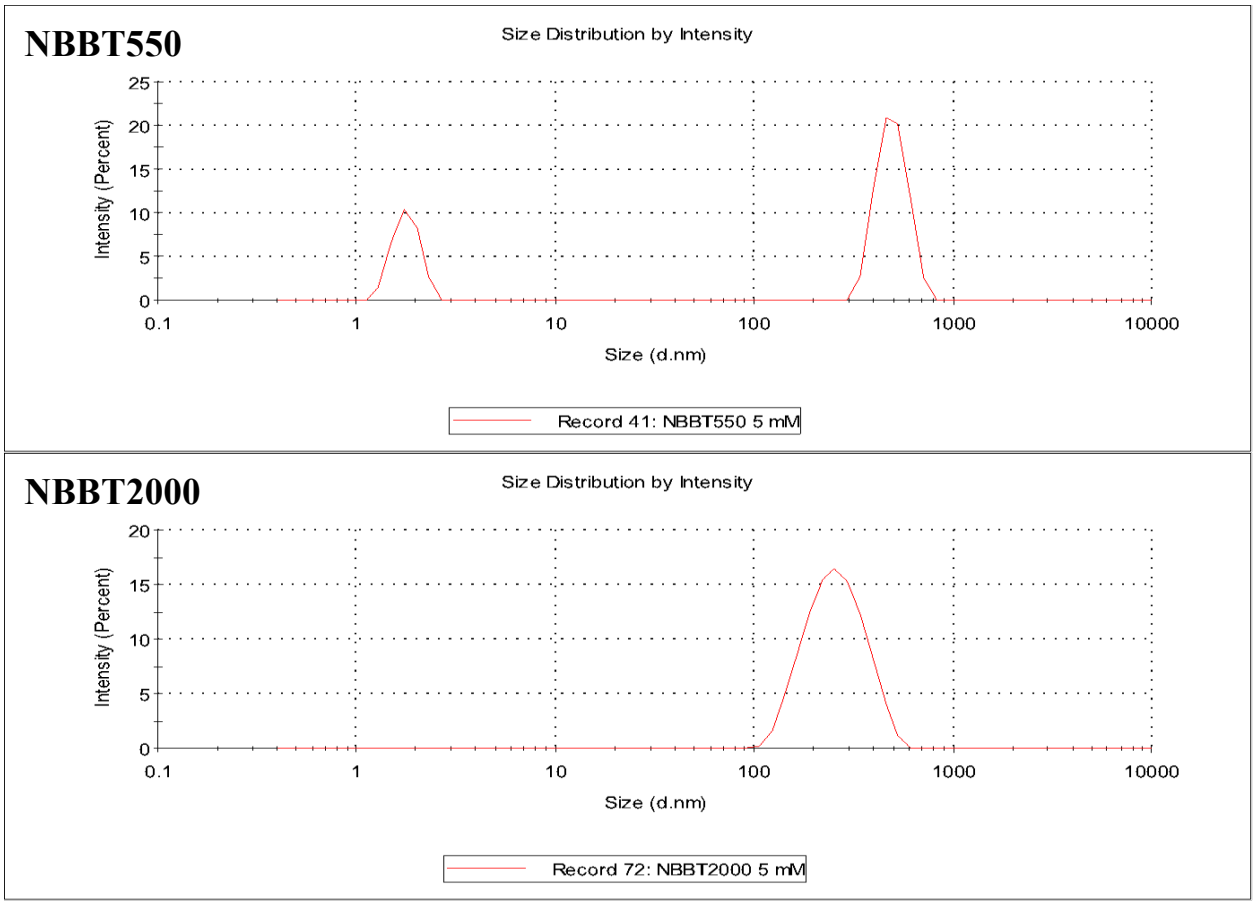


Figure S15. Size distribution of **NBBT550** and **NBBT2000** by DLS measurements.

Selected examples of GC chromatograms

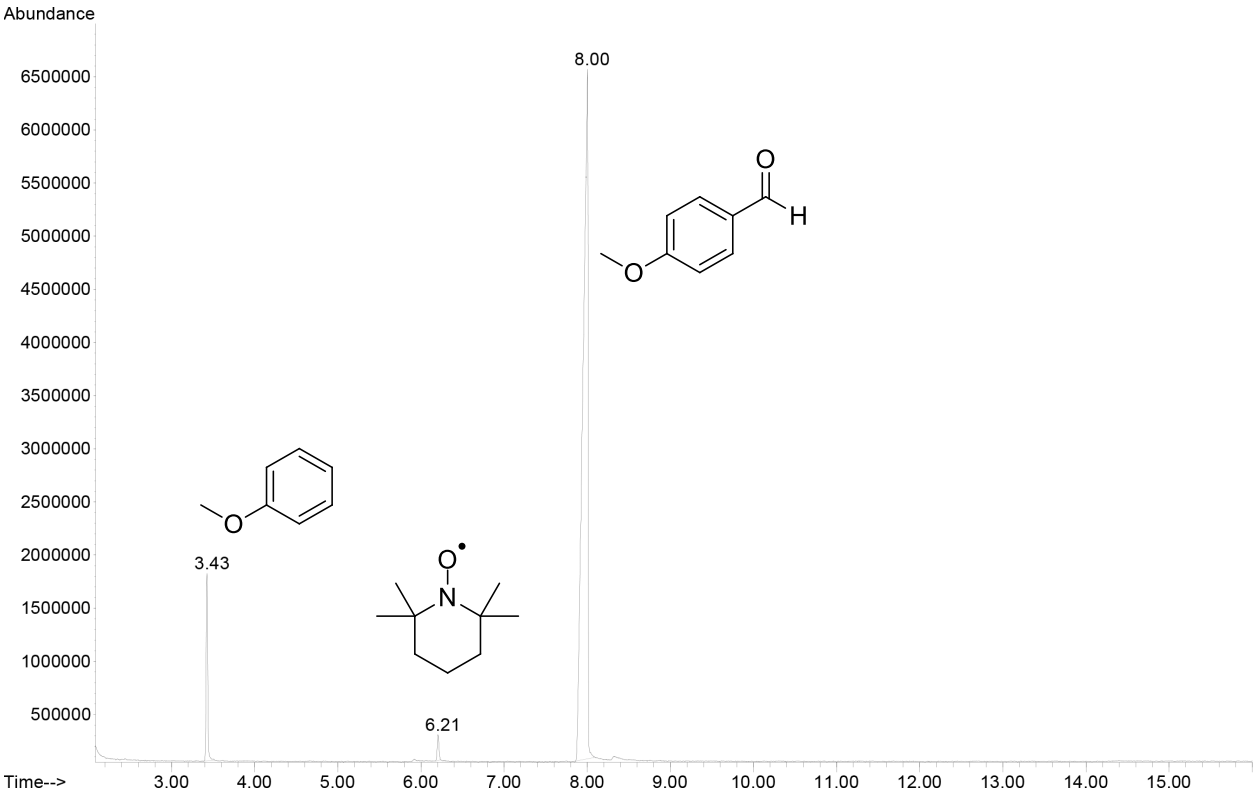


Figure S16. Chromatogram of 4-methoxybenzyl alcohol oxidation catalyzed by **NBBT550**.

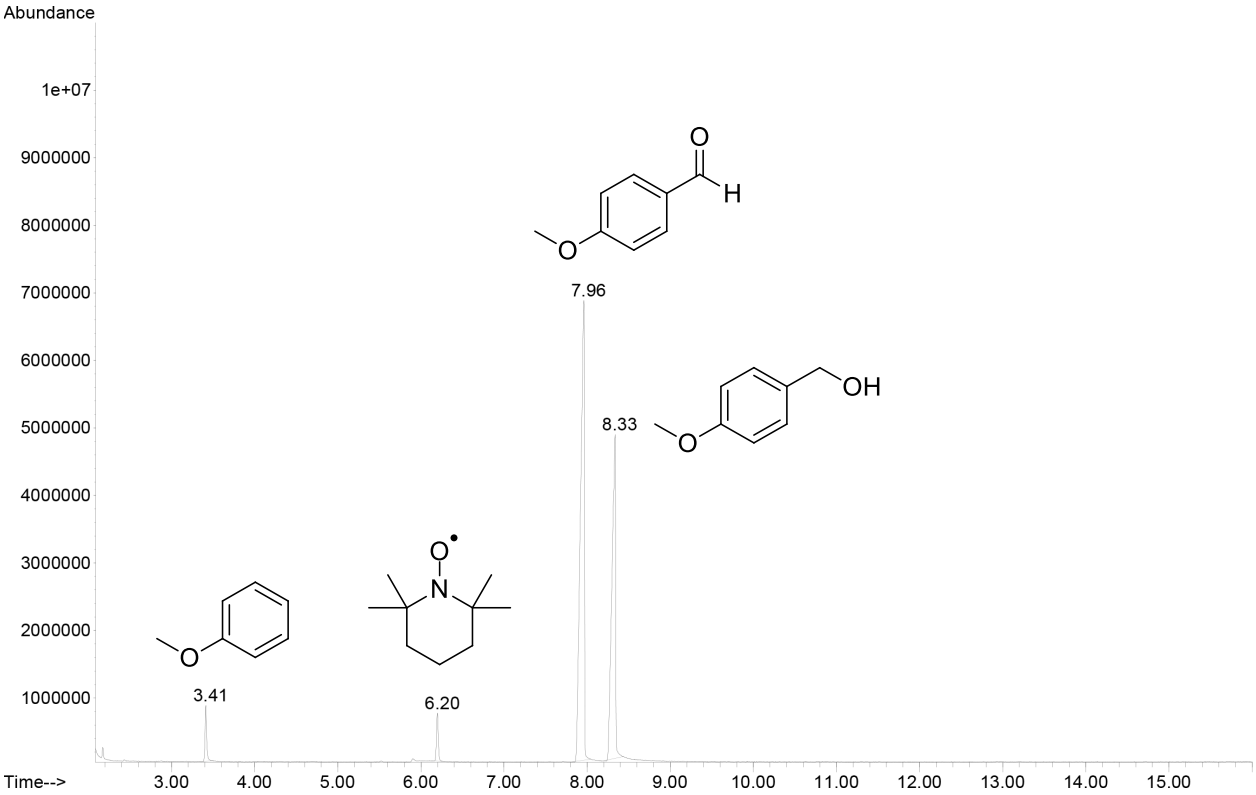


Figure S17. Chromatogram of 4-methoxybenzyl alcohol oxidation catalyzed by CuBr.

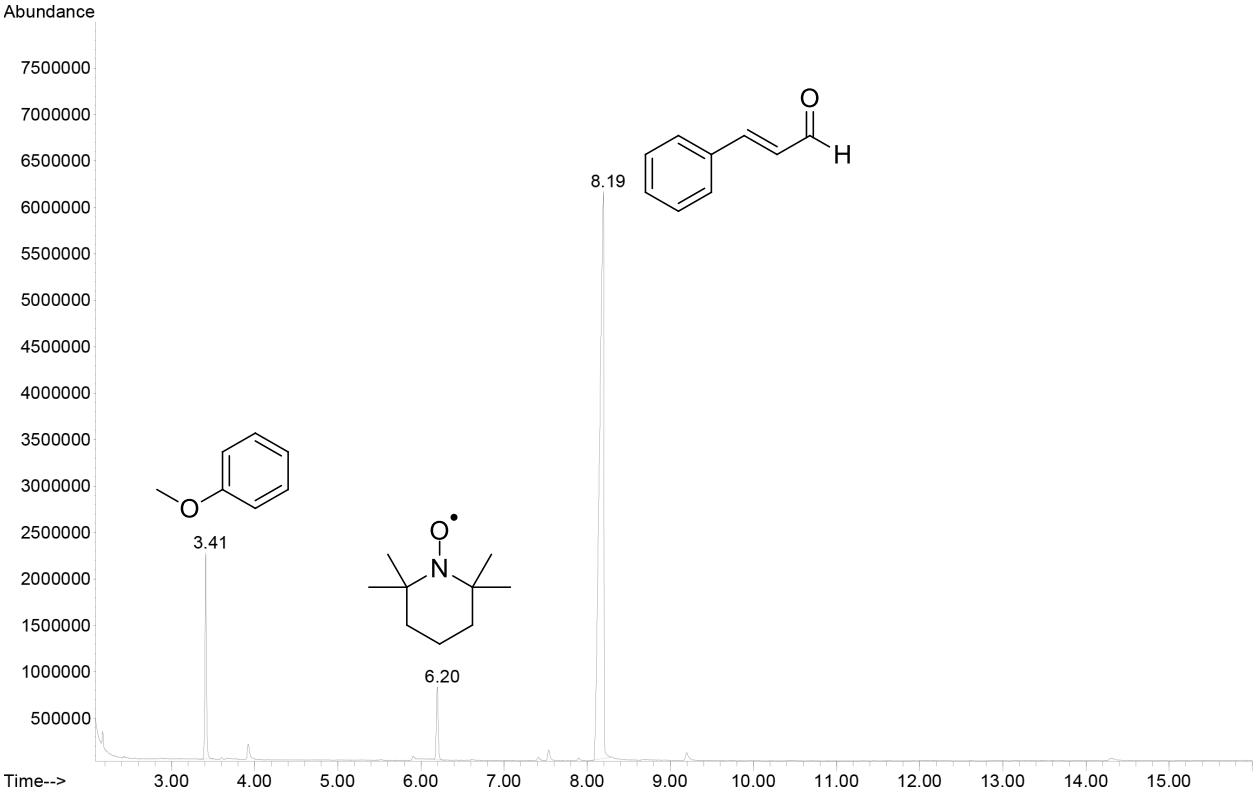


Figure S18. Chromatogram of cinnamyl alcohol oxidation catalyzed by **NBBT550**.

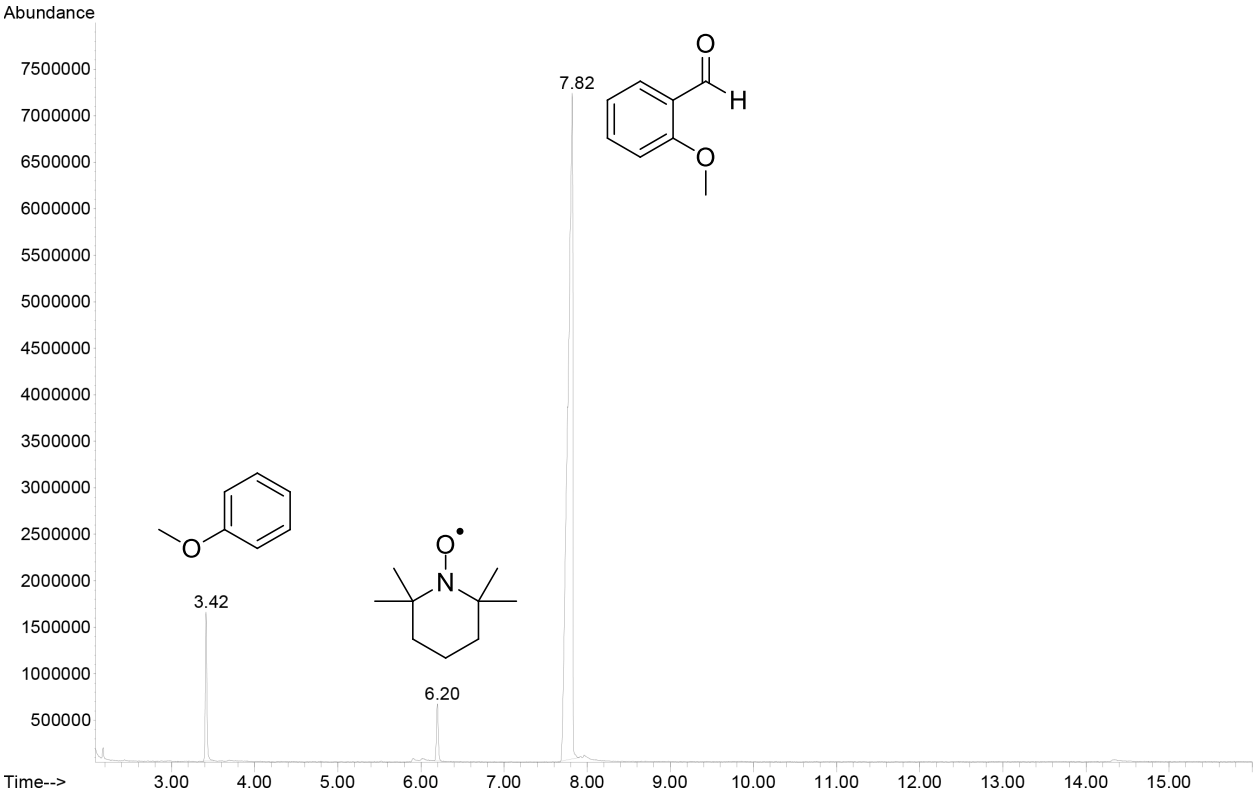


Figure S19. Chromatogram of 2-methoxybenzyl alcohol oxidation catalyzed by **NBBT550**.

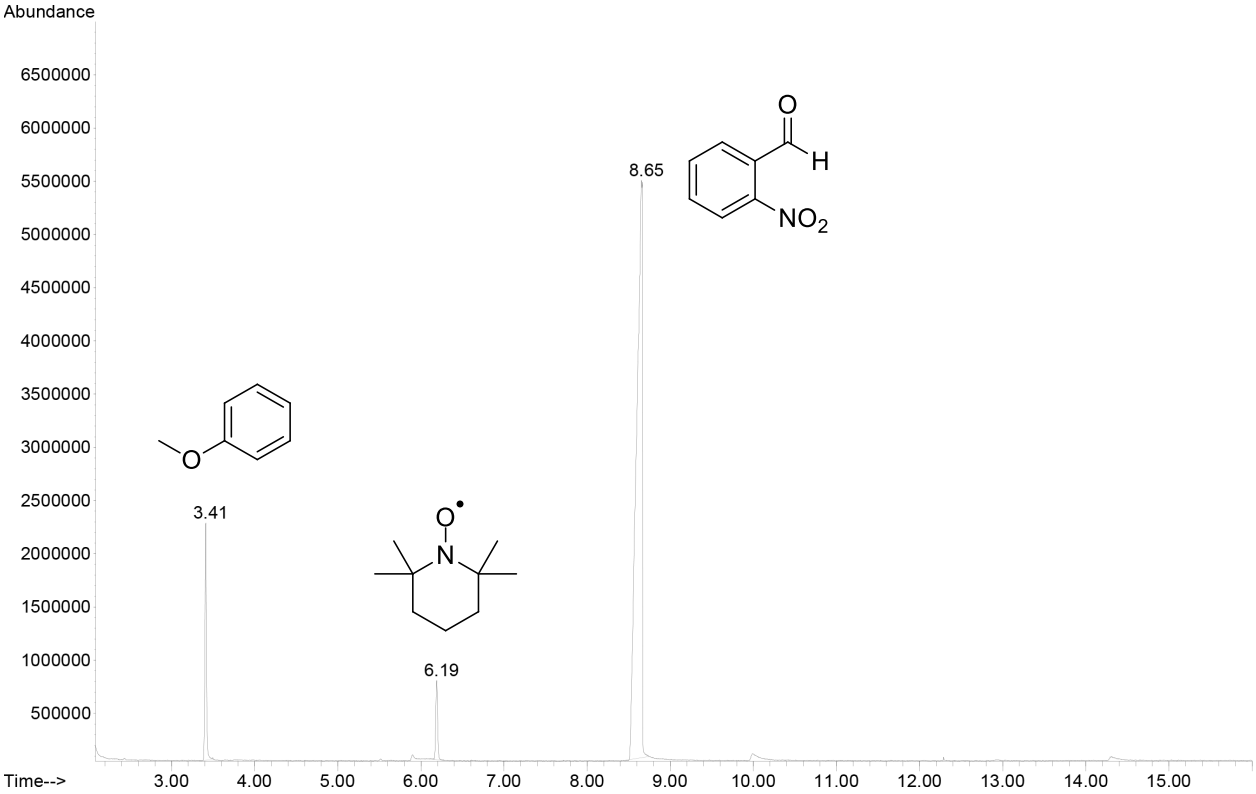


Figure S20. Chromatogram of 2-nitrobenzyl alcohol oxidation catalyzed by **NBBT550**.

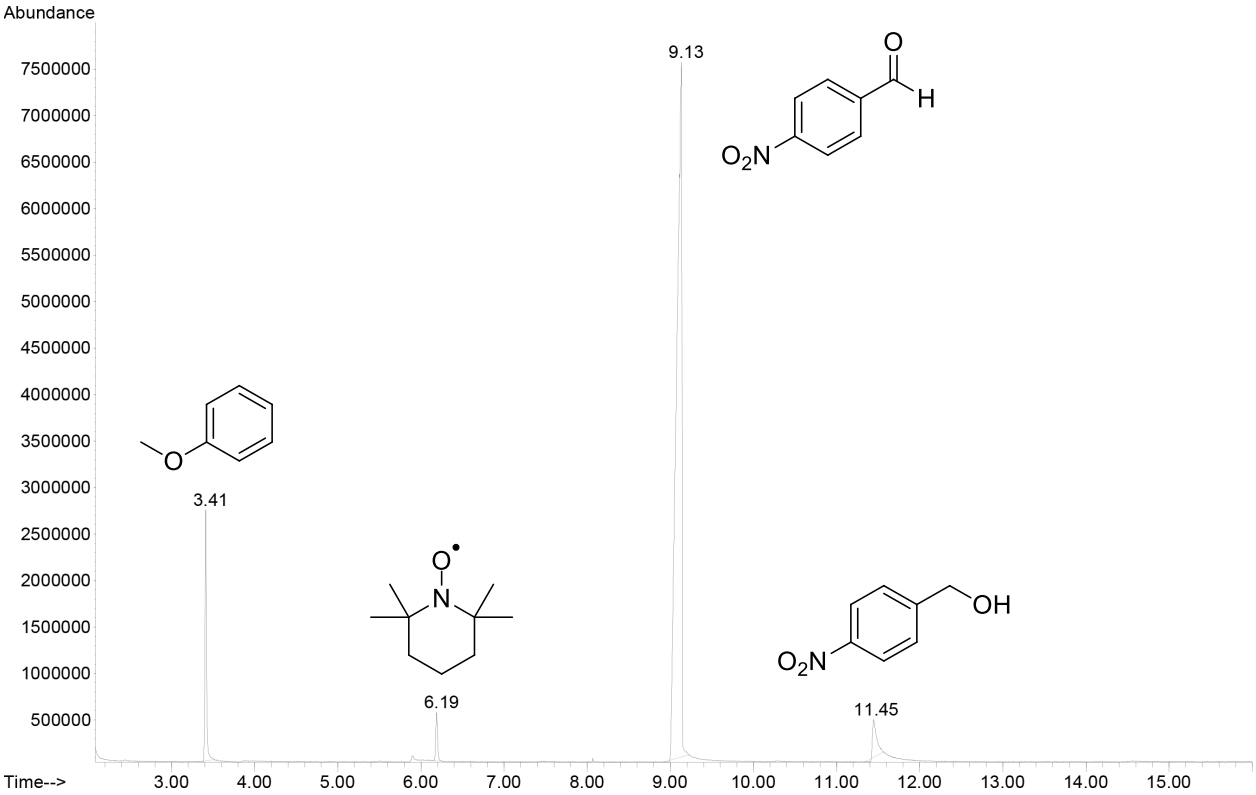


Figure S21. Chromatogram of 4-nitrobenzyl alcohol oxidation catalyzed by **NBBT550**.

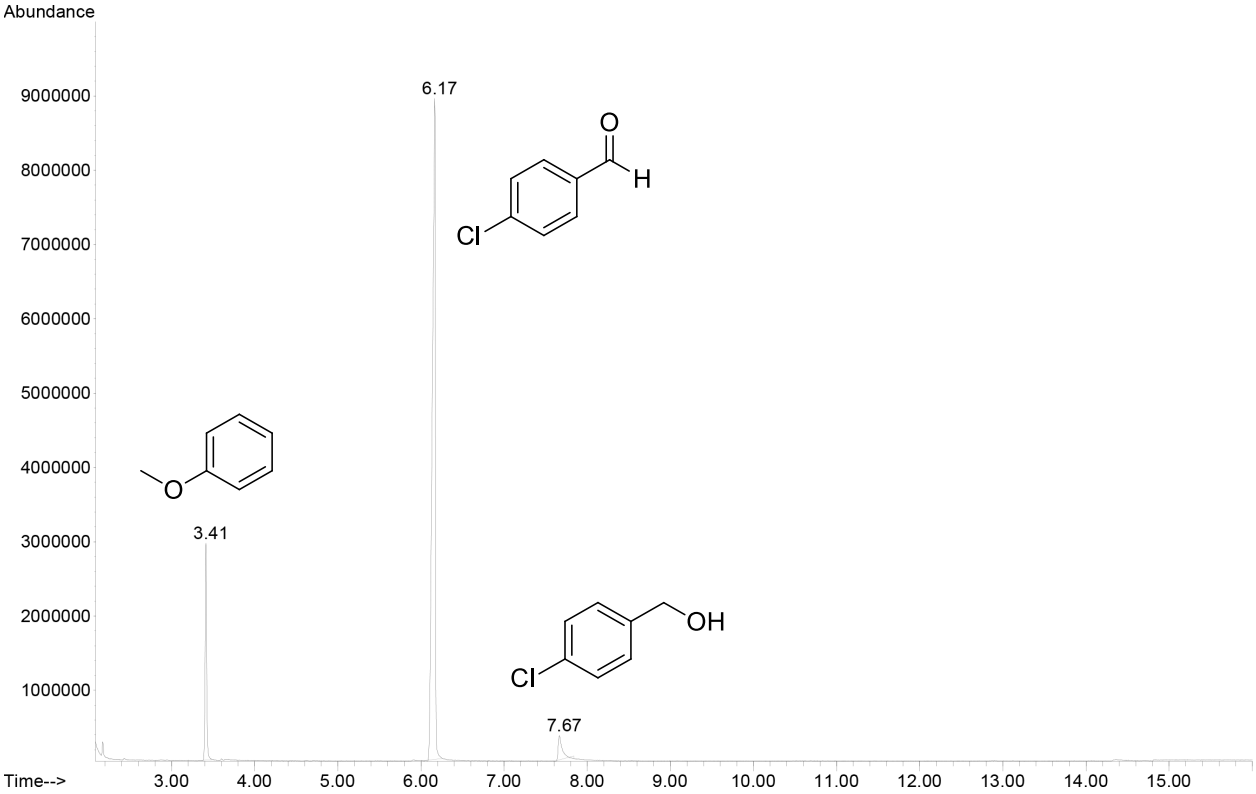


Figure S22. Chromatogram of 4-chlorobenzyl alcohol oxidation catalyzed by **NBBT550**.

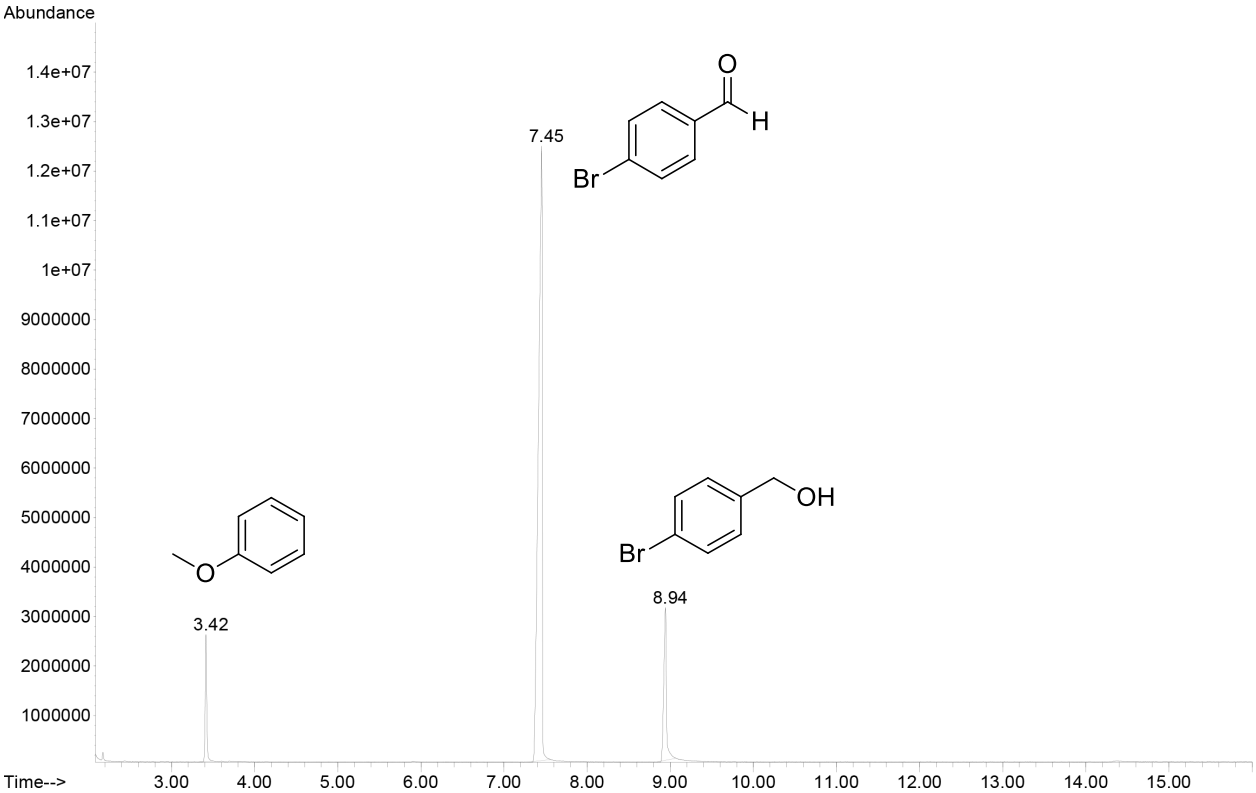


Figure S23. Chromatogram of 4-bromobenzyl alcohol oxidation catalyzed by **NBBT550**.

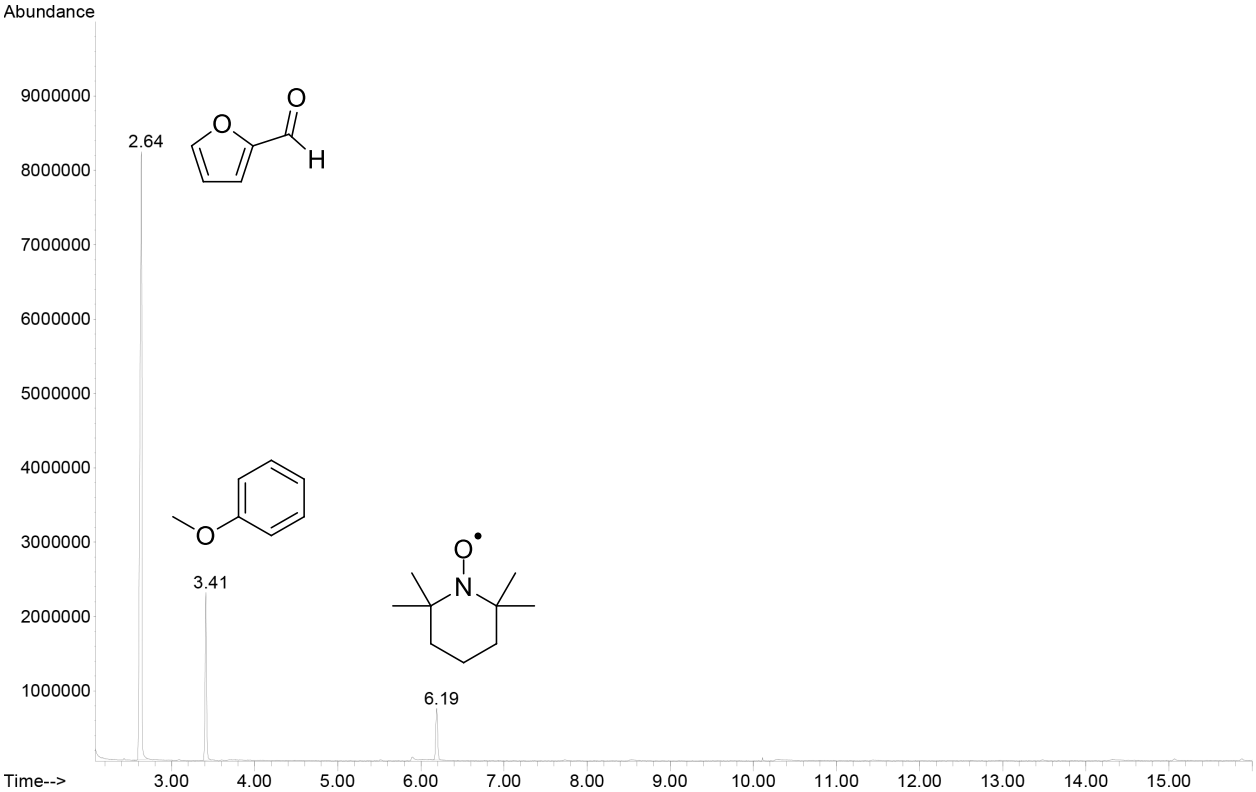


Figure S24. Chromatogram of furfuryl alcohol oxidation catalyzed by **NBBT550**.

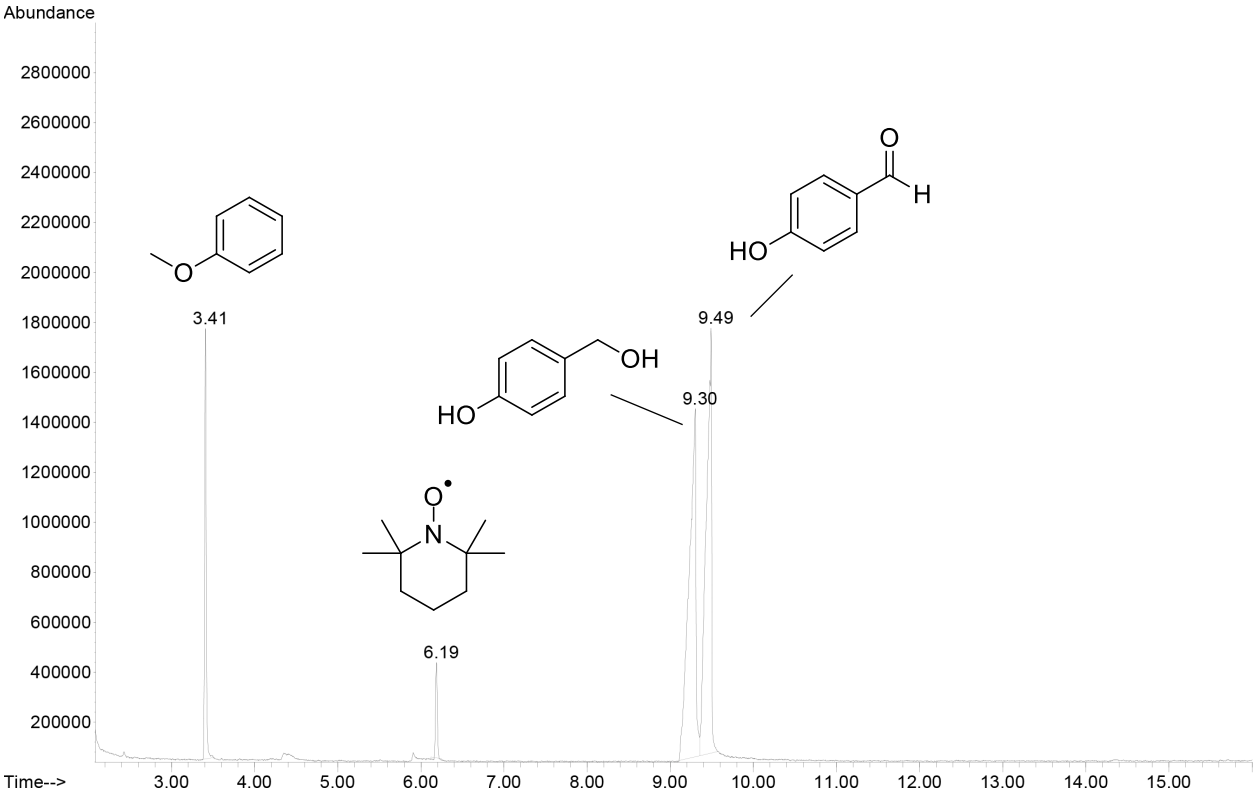


Figure S25. Chromatogram of 4-hydroxybenzyl alcohol oxidation catalyzed by **NBBT550**.

References

1. Semple, J. E.; Sullivan, B.; Vojkovsky, T.; Sill, K. N., Synthesis and facile end-group quantification of functionalized PEG azides. *Journal of Polymer Science Part A: Polymer Chemistry* **2016,** *54* (18), 2888-2895.
2. Chirkin, E.; Muthusamy, V.; Mann, P.; Roemer, T.; Nantermet, P. G.; Spiegel, D. A., Neutralization of Pathogenic Fungi with Small-Molecule Immunotherapeutics. *Angewandte Chemie International Edition* **2017,** *56* (42), 13036-13040.
3. O'Driscoll, L. J.; Welsh, D. J.; Bailey, S. W. D.; Visontai, D.; Frampton, H.; Bryce, M. R.; Lambert, C. J., Reversible Thermal Switching of Aqueous Dispersibility of Multiwalled Carbon Nanotubes. *Chemistry – A European Journal* **2015,** *21* (10), 3891-3894.
4. Presolski, S. I.; Hong, V.; Cho, S.-H.; Finn, M. G., Tailored Ligand Acceleration of the Cu-Catalyzed Azide−Alkyne Cycloaddition Reaction: Practical and Mechanistic Implications. *J. Am. Chem. Soc.* **2010,** *132* (41), 14570-14576.
5. Song, H.; Rogers, N. J.; Brabec, V.; Clarkson, G. J.; Coverdale, J. P. C.; Kostrhunova, H.; Phillips, R. M.; Postings, M.; Shepherd, S. L.; Scott, P., Triazole-based, optically-pure metallosupramolecules; highly potent and selective anticancer compounds. *Chemical Communications* **2020,** *56* (47), 6392-6395.
6. Chan, T. R.; Fokin, V. V., Polymer-Supported Copper(I) Catalysts for the Experimentally Simplified Azide–Alkyne Cycloaddition. *QSAR & Combinatorial Science* **2007,** *26* (11-12), 1274-1279.
7. "BindFit v0.5 | Supramolecular," can be found at http://supramolecular.org.