**Electronic Supplementary Information**

# Switchable nanoparticle for programmed gene-chem delivery with enhanced neuronal recovery and CT imaging for neurodegenerative disease treatment

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## Experimental Section

*Materials and Reagents*. 2-(N,N'-dimethylamino) ethyl methacrylate (DMAEMA, 98%), tert-butyl bromoacetate were from Alfa Aesar. 4-Cyano-4-(thiobenzoythio) pentanoic acid was from J&K Sientific Ltd. CPP B6 was purchased from GL Biochem Ltd. Co (Shanghai, China). Curcumin (CUR) was obtained from Melonepharma (Dalian, China). 2,2'-Dicyano-2,2'-azopropane (AIBN) was purchased from Aladdin Industrial Corporation. 3-(4,5-Dimethylthiazol-2-thiazolyl)-2,5-diphenyltetrazolium bromide (MTT) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were obtained from Sigma Aldrich. Cy5-labeled siSNCA (Cy5-siSNCA, antisense strand[1], 5'-UGCUCCUCCAACAUUUGUCTT-3'), negative control siSNCA (siNonsense, antisense strand, 5'-GACAAAUGUUGGAGGAGCATT-3') were synthesized by GenePharma company (Suzhou, China).

*Synthesis and purification of CB-tBu monomer*. CB-tBu was synthesized according to the method reported in our laboratory. Briefly, tert-butyl bromoacetate (6.49 mL) was added dropwise to acetonitrile containing DMAEMA (5.36 mL). The reaction mixture was stirred under nitrogen protection at 50 ºC for 24 h. The white precipitate was purchased by washed with 50 mL of diethyl ether. The product was then dried under reduced pressure to obtain the final CB-tBu monomer, yield 83.9%. $^1$H NMR (600 MHz, DMSO-d6, δ): 6.08 (s, 1H, -CH=C$CH_3$-), 5.78 (s, 1H, -CH=C$CH_3$-), 4.55 (t, 2H, -O$CH_2$-), 4.50 (s, 2H, -N$CH_2$COO- ), 3.95 (t, 2H, -O$CH_2$-), 3.30 (s, 6H, -N($CH_3$)$_2$-), 1.91 (s, 3H, $CH_2$=C$CH_3$-), 1.48 (s, 9H, -C($CH_3$)$_3$).

*Synthesis and purification of PCB-tBu.* PCB-tBu was synthesized by the reversible addition-fragmentation chain transfer polymerization (RAFT). 4-Cyano-4-(thiobenzoythio) pentanoic acid (38.5 mg), AIBN (azodiisobutyronitrile, 6.4 mg) and CB-tBu (136.1 mg) were dissolved in the methanol, and then they were added to a clean and dry schlenk flask. The system was degassed by three freeze-pump-thaw cycles and recharged with nitrogen. The reaction mixture was stirred for 24 h at 60 ºC. The impurities and unreacted monomers were removed by dialyzing in a Cellu SepH1-membrane (MWCO 1000) against ethanol and deionized water for 48 h and lyophilized to obtain the final product 101.0 mg PCB-tBu. $^1$H NMR (600 MHz, DMSO-d6, δ): 8.06 (t, 2H, Ar H), 7.83 (t, 1H, Ar H) 7.64 (d, 2H, Ar H), 4.55 (m, 20H, -O$CH_2$-), 4.50 (m, 20H, -N$CH_2$COO-), 3.95 (m, 20H, -O$CH_2CH_2$N-), 3.30 (m, 60H, -N($CH_3$)$_2$-), 1.93 (m, 20H, -C$CH_3$-), 1.48 (m, 90H, -C($CH_3$)$_3$), 1.17 (m, 30H, -$CH_2$-C-). The molecular weight (Mw) of PCB-tBu was calculated by gel permeation chromatography (GPC). The GPC was using DMF as a solvent. The injection volume was 50.00 μL and the run time was 45.00 min.

*Synthesis and purification of thiol-functionalized PCB-tBu (PCB-tBu-HS).* The end of PCB-tBu RAFT chain transfer agent was a thioester group, which was transformed to thiol-functionalized PCB-tBu via aminolysis. Briefly, PCB-tBu (44.85 mg) and N, N-dimethylformamide (10 mL) were added a 25 mL round-bottomed flask equipped with a magnetic stir bar. The mixture was stirred until a homogeneous solution was obtained. To this solution propylamine was added as a solution in N, N-Dimethylformamide

(5 mL). The resulting solution was stirred at room temperature for 5 h. Subsequently, the solution was loaded to a dialysis bag and dialyzed against water for 48 h. 29.5 mg crude product was isolated by lyophilization. $^1$H NMR (600 MHz, DMSO-d6, δ): 7.44 (s, 1H, HS-), 4.55 (m, 20H, -$OCH_2$-), 4.50 (m, 20H, -$NCH_2COO$-), 3.95 (m, 20H, -$OCH_2CH_2N$-), 3.30 (m, 60H, -$N(CH_3)_2$-), 1.93 (m, 20H, -$CCH_3$-), 1.48 (m, 90H, -$C(CH_3)_3$), 1.17 (m, 30H, -$CH_2$-C-).

*Synthesis and purification of curcumin-β–thiother ester prodrug (curcumin-ene).* Curcumin (3 g) was dissolved in the dried dichloromethane and triethylamine were added in the mixture for 1 h. Methacryloyl chloride (790 μL) was added dropwise in this mixture. The resulting solution was stirred at 40 ºC for 5 h. The product was purified by column chromatography with a 20:1 mixture of $CH_2Cl_2$ and ethyl acetate as eluent. After evaporation of the $CH_2Cl_2$, pure yellow powder compound was obtained. $^1$H-NMR (600 MHz, DMSO-d6, δ): 9.66 (s,1H, HO-Ar), 7.63 (d,1H, Ar-CH=CH-), 7.60-7.21 (m, 6H, Ar H), 7.17 (d, 1H, -CH=CH-Ar-), 6.96 (d, 1H, -CH=CH-Ar), 6.83 (s, 1H, -CH=CH-Ar), 6.28 (s, 1H, -CH-$CCH_3$-), 6.14 (s, 1H, -HC=CO-), 5.91 (s, 1H, -CH-$CCH_3$-) 3.84 (s, 6H, $CH_3O$-), 2.00 (s, 3H, $CH_3$-CCH2-).

*Synthesis and purification of PCB-tBu-S-curcumin.* PCB-tBu-S-curcumin was synthesized by thiol-ene click reaction of PCB-tBu-HS with curcumin-ene in the presence of radical initiator AIBN. Briefly, curcumin-ene (10 mmol), AIBN (0.6 mmol) were dissolved in DMF subsequently and added in a 25 mL round-bottomed flask equipped with a magnetic stir bar. Then, PCB-tBu-HS was added dropwise in the mixture. The system was degassed by three freeze-pump-thaw cycles and recharged with nitrogen. The reaction mixture was stirred for 24 h at 80 °C. The impurities were removed by dialyzing in a Cellu SepH1-membrane (MWCO 1000) against ethanol and deionized water for 48 h and lyophilized to obtain the final product PCB-tBu-S-curcumin, yield 31.6%. The molar ratio of PCB-tBu-S-curcumin among PCB-tBu substrate was 60%.

*Synthesis and purification of MA-PCB-tBu-S-curcumin and B6-PCB-tBu-S-curcumin.* MA-PCB-tBu-S-curcumin was synthesized via condensation of carboxyl and hydroxyl groups. Briefly, PCB-tBu-S-curcumin was activated by EDC/DMAP method in DMF. Then, mazindol (MA) was added dropwise in the mixture and stirred for 12 h at room temperature. Similarly, B6-PCB-tBu-S-curcumin was synthesized via condensation of carboxyl and amino groups. Briefly, PCB-tBu-S-curcumin was activated by EDC/NHS method in DMF. Then, cell penetrating peptides (CPP) B6 was added dropwise in the mixture and stirred for 12 h at room temperature. The MA connection rate was detected by UV-Vis absorption spectrum and CPP connection rate was detected by BCA kit.

*Synthesis and purification of MA-PCB-S*-curcumin *and B6-PCB-S*-curcumin*.* MA-PCB-tBu-S-curcumin and B6-PCB-tBu-S-curcumin were respectively dissolved in DMSO and 1.5mL trifluoroacetic acid (TFA) was added to each of these. Then, the mixtures were condensed by evaporation. At last, the condensed mixtures were redissolved in DMSO and the impurities were removed by dialyzing in a Cellu

SepH1-membrane (MWCO 1000) against ethanol and deionized water for 48 h, respectively, and lyophilized to obtain the final product. The Mw of B6-PCB-S-curcumin was calculated by GPC.

*Preparation of levodopa restored gold nanoparticles and its ion selectivity.* All glasswares were thoroughly cleaned with aqua regia ($HNO_3$/HCl, 1: 3) and rinsed extensively with Milli-Q water (resistivity: >18 MΩ·cm) prior to use. The gold nanoparticles were synthesized through levodopa mediated reduction of $HAuCl_4$. Briefly, $HAuCl_4$ solution ($2.5 \times 10^{-4}$ M, 10.0 mL), trisodium citrate ($2.5 \times 10^{-4}$ M, 10.0 mL) were mixed in a conical flask and were brought to a vigorous boil, then 0.1 M $NaBH_4$ solution was added to the solution while stirring. After 2-5 h, the seed was prepared. Meanwhile, $HAuCl_4$ solution ($2.5 \times 10^{-4}$ M, 200 mL) and CTAB (0.08 M, 6 g) were mixed and heated to clear orange color to prepare growth solution. After the preparation, growth solution (9.0 mL) and levodopa solution (0.1 M, 1.0 mL) was added quickly at once under a vigorous boil. Then the seed was added to the mixture to turn to wine red. The solution was stirred for an additional 10 min and then it was removed from heat and cooled slowly to room temperature. A dialysis membrane (MWCO: 1 kDa; pore size: ca. 1.0 nm) was used in PBS to remove any residual unreacted species. The prepared gold nanoparticle were respectively incubated with 1 mM $Na^+$, $Ca^{2+}$, $Mg^{2+}$, $K^+$, $Zn^{2+}$, $Cu^+$, $Al^{3+}$, $Cu^{2+}$, $Fe^{2+}$ and $Fe^{3+}$ for 10 min to detected the sensibility.

*Preparation and characterization of MBPCS and control groups.* MA-PCB-tBu-S-curcumin (0.3 mM), B6-PCB-tBu-S-curcumin (0.3 mM), PCB-tBu-S-curcumin (0.3 mM) and levodopa gold nanoparticles (2.3 mg/mL) were prepared in the above experiment. Then, NPs were prepared by self-assembly via ligand effect between thiother and gold nanoparticle. In detail, MA/B6-PCB-S-curcumin@GNP (MBPC), MA-PCB-S-CUR@GNPs (MPC), B6-PCB-S-CUR@GNPs (BPC), PCB-S-CUR@GNPs (PC) were self-assembled by these volume ratio (B6-PCB-tBu-S-curcumin: MA-PCB-tBu-S-curcumin: PCB-tBu-S-curcumin: levodopa gold nanoparticles = 500 μL: 500 μL: 0:1 mL; 0: 500 μL: 500 μL: 1 mL; 500 μL: 0: 500 μL: 1 mL; 0: 0: 1 mL: 1 mL). These mixtures were incubated in a shaker overnight. After 3 times centrifuging in 14000 rpm and washing, the brown precipitates were achieved and were re-suspended to achieve MBPC and control groups.

MBPC hybrid was conducted by gold nanoparticle (Au NP) with MA/B6-PCB-S-curcumin polymer via the thiother, the Au NP concentration ($C_{Au\ NP}$) was 1.15 mg/mL. MA/B6-PCB-S-curcumin polymer concentration was calculated by curcumin standard assay. Based on the UV-Vis spectrum of assembly-MBPC (Fig. 1h), the curcumin in assembly-MBPC was 0.009 μmol/mL. Therefore, the number of curcumin (Ncurcumin) was 0.009 μmol/mL. The MA/B6-PCB-S-curcumin polymer ligand number attached onto each gold nanoparticle was calculated by the Formula S2 and it was 161. From Formula S1, the number of gold atoms ($N_{Au\ atom}$) contained in a gold nanosphere with a diameter of 15 nm can be calculated as 104512. Therefore, the mass of 15 nm gold sphere ($M_{Au\ NP}$) is $2.06 \times 10^7$ g/mol (197 $N_{Au\ atom}$). Based on the UV-Vis spectrum of the mix-MBPC and assembly-MBPC, the MA/B6-PCB-S-

curcumin polymer concentration were calculated as 5.95 μg/mL and 3.32 μg/mL based on curcumin standard curve. Therefore, the efficiency of ligand exchange reactions was 55.8%. The MBPCS was prepared by adding siSNCA to the MBPC solution at various N/P ratios for 0.5 h at room temperature. The hydrodynamic size and zeta potential of NPs were measured in triplicate using a Nano Zeta Sizer (Malvern).

$$N_{\text{Au atom}} = \frac{V_{\text{Au NP}}}{V_{\text{Au atom}}} = \frac{4\pi \quad R^3}{3\ V_{\text{Au atom}}} \quad \text{(S1)}$$

$$\frac{N_{\text{curcumin}}}{N_{\text{Au NP}}} = N_{\text{curcumin}} \frac{M_{\text{Au NP}}}{C_{\text{Au NP}}} \quad \text{(S2)}$$

*Release of curcumin from MBPCS.* The curcumin release was performed in phosphate buffer solutions (PBS) with 2% SDS at pH 7.4 and $H_2O_2$ (0, 0.5 mM, 1 mM), in a time-dependence procedure. Briefly, NPs were suspended in 3 mL of the above PBS in a dialysis bag (MWCO 3500) and incubated in 20 mL of the same PBS at 37 ºC under horizontal shaking (150 rpm). At predetermined time intervals, 0.5 mL PBS were removed and the same volume of fresh solution was added. The concentration of drug in the PBS was detected using microplate reader under condition of 425 nm excitation and 530 nm emission. The weight of curcumin in each time was calculated by standard curve method. The release rate of curcumin was calculated using the formula S3 (Where M0 was the mass of curcumin in total in NPs, M1 was the mass of different time of curcumin in PBS.):

$$\text{Survival rate (\%)} == \frac{M1}{M0} * 100\% \quad \text{(S3)}$$

*Cell culture and toxicity.* SH-SY5Y cells were purchased from ATCC and the over expression of synuclein SH-SY5Y cell line was prepared. Briefly, the full-length cDNA of SNCA gene was amplified by PCR and was constructed into lentiviral vector pLV-mCherry-N at EcoRV restriction site. The lentiviral vector pLV-SNCA-mCherry was overexpressed. SH-SY5Y cells were infected with the lentiviral vector pLV-SNCA-mCherry and the corresponding empty vector, respectively, and then the SNCA gene stable overexpression cell line (SH-SY5Y/α-synuclein) was screened by puromycin. The SH-SY5Y and SH-SY5Y/α-synuclein were cultured in DMEM medium (10% fetal bovine serum). MTT method was used to measure the cytotoxicity of NPs and each NPs incubated with siRNA (NPs/siRNA). In detail, SH-SY5Y cells were cultured in 96 well plates, in each well of which 5000-10000 cells were cultured. Then each NPs were incubated with SH-SY5Y cells for 24 h, and after that 20 μL MTT (5 mg/mL in PBS) was added and then incubated for 2 h. At last, the culture in each well were poured and 100 μL DMSO were added and were shacked at low speed for 10 min to fully dissolve the crystals. The absorbance was measured at 490 nm using a Tecan microplate reader (Tecan, Switzerland).

*In vitro siRNA uptake and release measurement.* SH-SY5Y cells were cultured in 24 well plates and the cells were seeded at a density of $4 \times 10^5$ cells per well. MBPC/Cy5-siSNCA and BPC/Cy5-siSNCA (siRNA loading weight was 1 μg per well, Cy5-labeled siSNCA were incubated with cells for 0.5, 1 h, 2 h, 4 h and 8 h. All these cells were collected and detected by BD Caliburflow cytometry (BD Co., USA). The Cy5 mean fluorescence intensity (MFI) were calculated to measure the siRNA uptake. To mimetic the blood brain barrier (BBB), bEnd.3 cells were incubated in transwell. Similarly, after incubated MBPC/Cy5-siSNCA and MPC/Cy5-siSNCA with bEnd.3 cells for 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h and 12 h, and Cy5 MFI of bEnd.3 cells and SH-SY5Y cells were calculated. Then, SH-SY5Y cells were cultured in confocal well (Cellvis) and incubated with MBPC/Cy5-siSNCA (0.5 μg per well) for 1 h, 2 h, 4 h and 8 h at 37 ºC. After that, the cells were washed with PBS 3 times and replaced with lysotracker red. The cells were cultured for 30 min and then washed with PBS 3 times. After that, the cells' culture was replaced with 4% paraformaldehyde for 20 min at 37 ºC. Then, the culture was washed with PBS 3 times and replaced with DAPI and were cultured for 10 min at 37 ºC. The cells were washed with PBS and detected by confocal laser scanning microscopy (CLSM, Zeiss Co., Germany).

*In vitro pathological inhibition by NPs.* SH-SY5Y/α-synuclein cells were cultured and incubated with different NPs (PBS, free curcumin & free siSNCA, MBPC-siNC, MBPS, MBPCS) for 72 h at 37 ºC in an incubator. The cells were washed with PBS 3 times and replaced with 4% paraformaldehyde and then were washed and replaced with DAPI. At last, the cells were washed and stored in PBS. Confocal laser scanning microscopy was used to detect α-syn-mCherry (587 nm, 610 nm). Meanwhile, the cells' α-syn-mCherry protein expression was quantified by Western blot. Briefly, cells were lysed in 100 μL of lysate including PMSF and were shacked well on ice. After 14000 rpm centrifugation, the supernatant was taken for protein quantification BCA kit and boiled for 10 min at 95 ºC. The proteins were firstly resolved by SDS-polyacrylamide gel electrophoresis (SDS-PAGE), secondly transferred to polyvinylidene fluoride membranes, thirdly blocked in 5% non-fat powdered milk in PBS-T (0.5% Tween-20) and at last incubated with α-synuclein antibodies (primary antibody from AbCAM) and then with secondary antibody (from AbCAM). At last, enhanced chemiluminescence reagent (ECL) was used for protein bands detected by X-ray film.

*In vivo micro-CT imaging and ex-vivo bioluminescence imaging method.* In vivo CT imaging was obtained using Micro-CT system (Quantum FX, Caliper). Ex-vivo bioluminescence imaging was obtained using KODAK In-Vivo Imaging System FX Pro.

*Pharmacokinetics study.* PD model mice were intravenously injected with Cy5-siRNA in different formulations at the dose of 1 mg/mL. At different time points, 50-200 μL of blood was collected by eye puncture and serum was isolated. Ten microliters of serum was mixed with 90 μL lysis buffer (0.1% sodium dodecyl sulfate in phosphate-buffered saline) and incubated at 65 °C for 10 min, followed by the addition of 200 μL methanol and incubation at 65 °C for 10 min. The sample was centrifuged at 14000

rpm for 5 min and 200 μL supernatant was transferred to a 96-well plate. The fluorescence intensity of the sample was measured by a plate reader at $\lambda_{ex}$: 625 nm and $\lambda_{em}$: 670 nm. Cy5-siRNA concentration in each sample was calculated from a standard curve.

*In vivo therapy of Parkinson disease model mice.* 5 groups C57BL/6 mice (8 weeks) were treated intraperitoneally with MPTP (30 $mg \cdot kg^{-1}$) for 7 consecutive days. In the mice, 4 groups were treated with NPs (III, IV, V, VI). The rest one group mice (II) were treated with the same volume saline. In the therapy time, 4 groups were treated with different NPs by intravenous injection every three days for 10 times. We placed the mice upright on a 50 cm high pole and recorded the time they took for the entire journey to assess the movement coordination of the mice, the journey time was from the start until all the limbs of the mouse landed. Then we placed the mice in open field instrument and recorded their track of motion.

**Table S1**. The abbreviation of NPs prepared in the experiments

| Full name | Abbreviation |
|---|---|
| MA/B6-PCB-S-CUR@GNP, (MBPC@GNP) | MBPC |
| MA/B6-PCB-S-CUR@GNP/siSNCA, (MBPC@GNP/siSNCA) | MBPCS |
| MA-PCB-S-CUR@GNP/siSNCA, (MPC@GNP/siSNCA) | MPCS |
| B6-PCB-S-CUR@GNP/siSNCA, (BPC@GNP/siSNCA) | BPCS |
| PCB-S-CUR@GNP/siSNCA, (BPC@GNP/siSNCA) | PCS |
| MA/B6-PCB-S@GNP/siSNCA, (BPC@GNP/siSNCA) | MBPS |
| MA/B6-PCB-S@GNP/siNegtive Control (BPC@GNP/siNC) | MBPC-siNC |

## Supplementary Figures

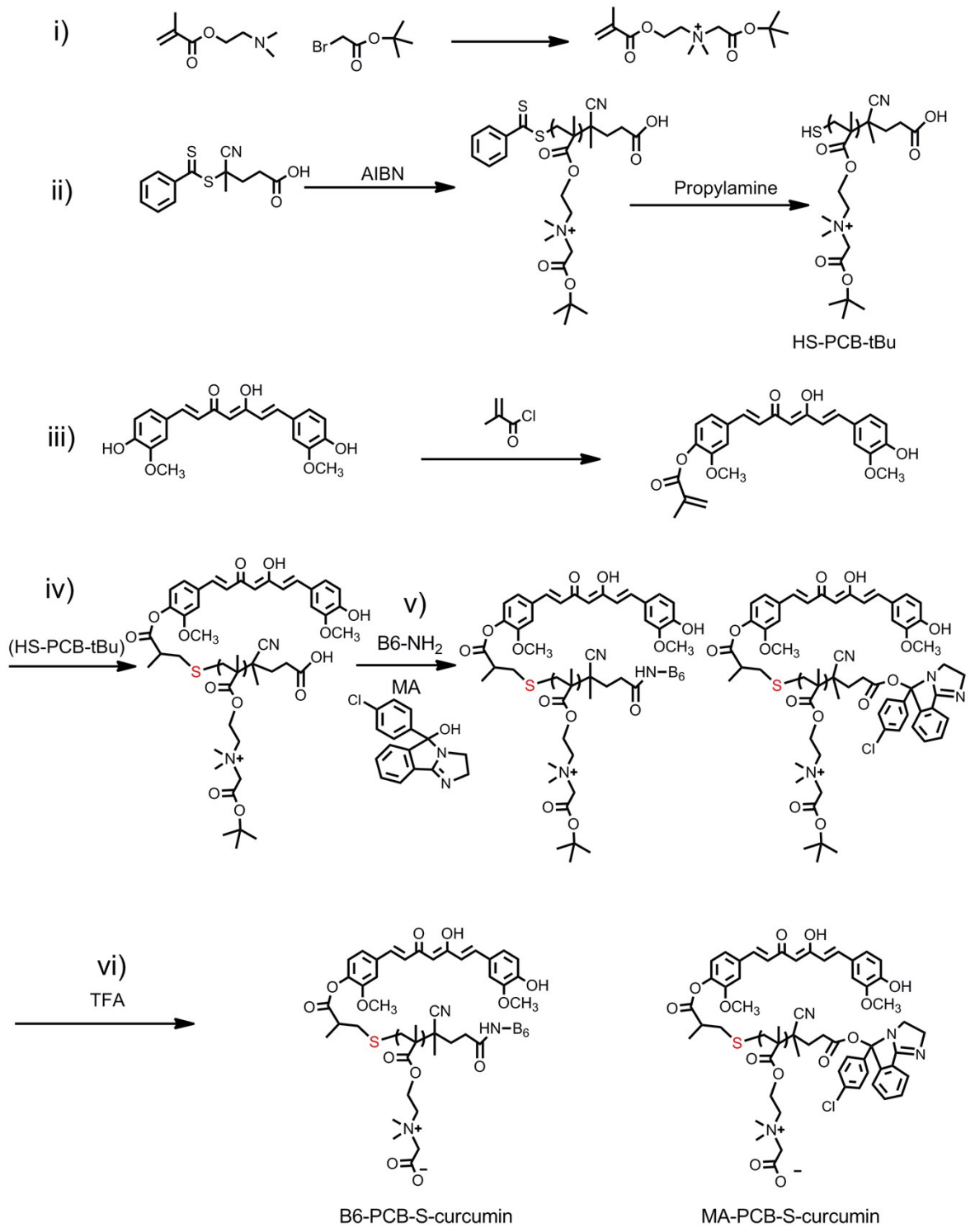


**Figure S1.** The synthetic routes of B6-PCB-S-curcumin and MA-PCB-S-curcumin polymers.

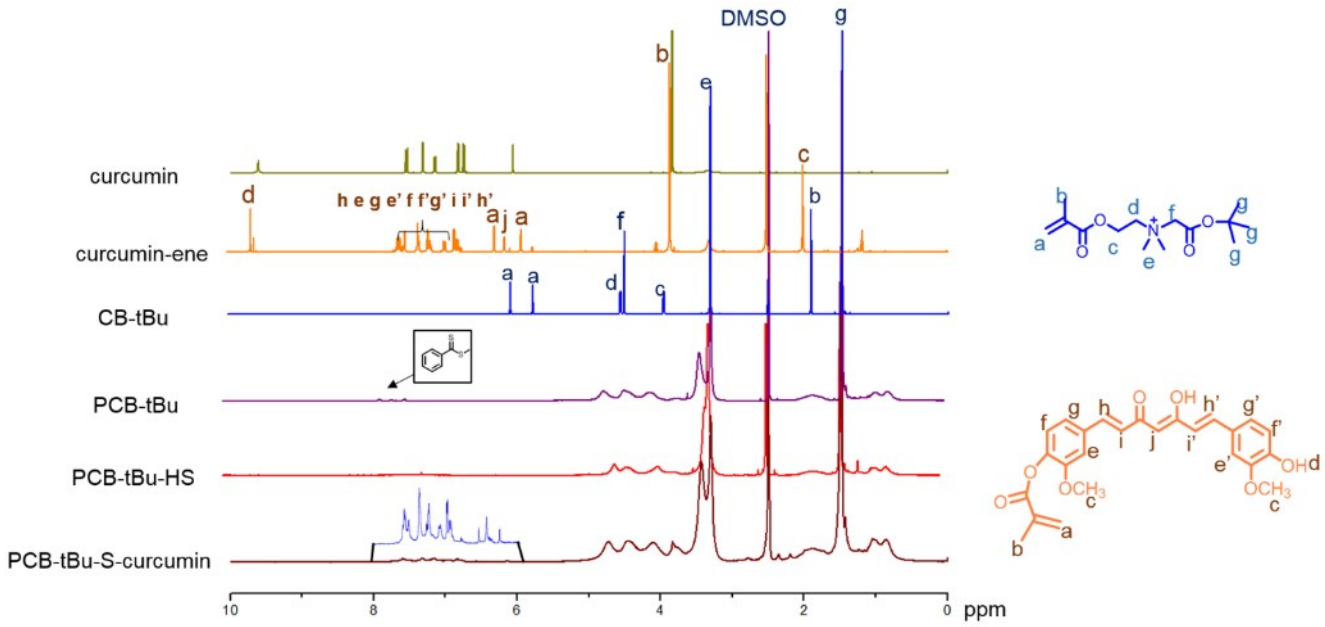


**Figure S2**. $^{1}$H NMR spectra of the curcumim, curcumin-ene prodrug (the orange molecule structure at bottom right), CB-tBu monomer (the blue molecule structure at upper right), PCB-tBu polymer, PCB-tBu-HS polymer and PCB-tBu-S-curcumin polymer.

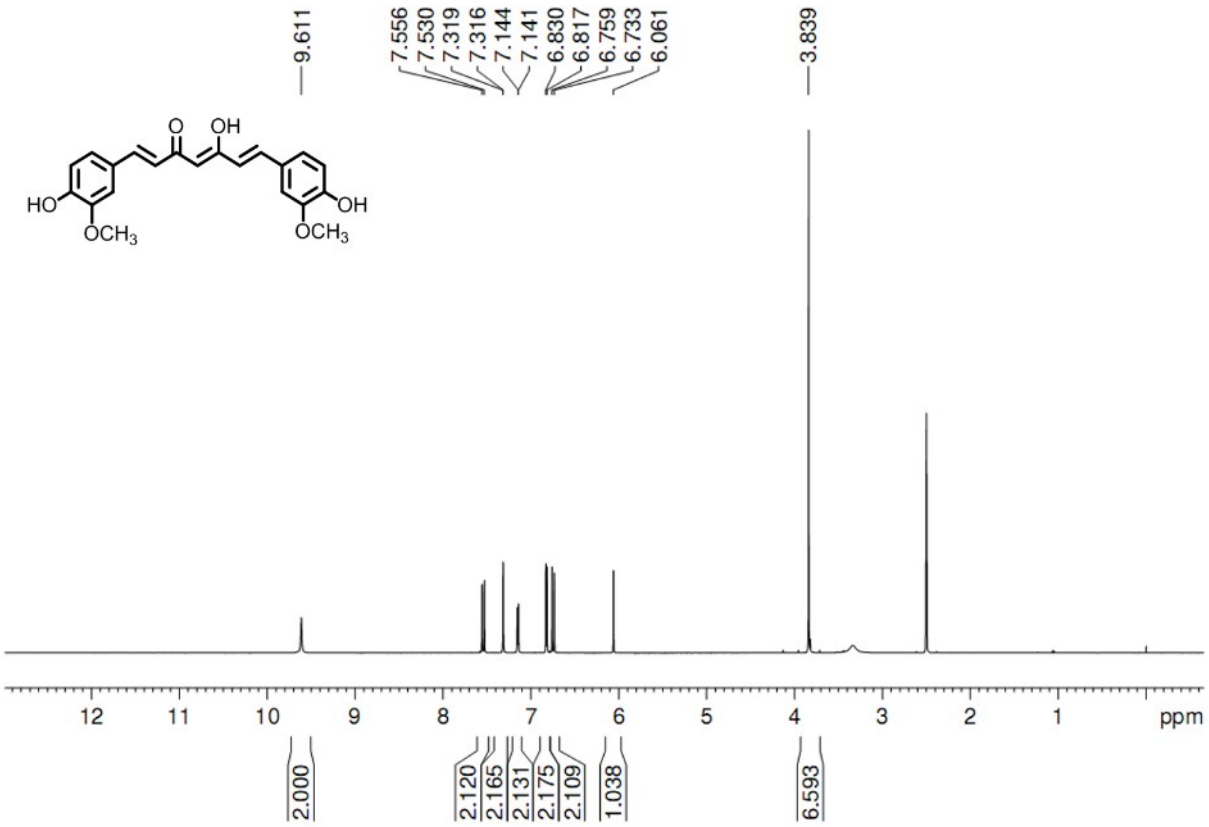


**Figure S3**. $^{1}$H NMR spectra of curcumim.

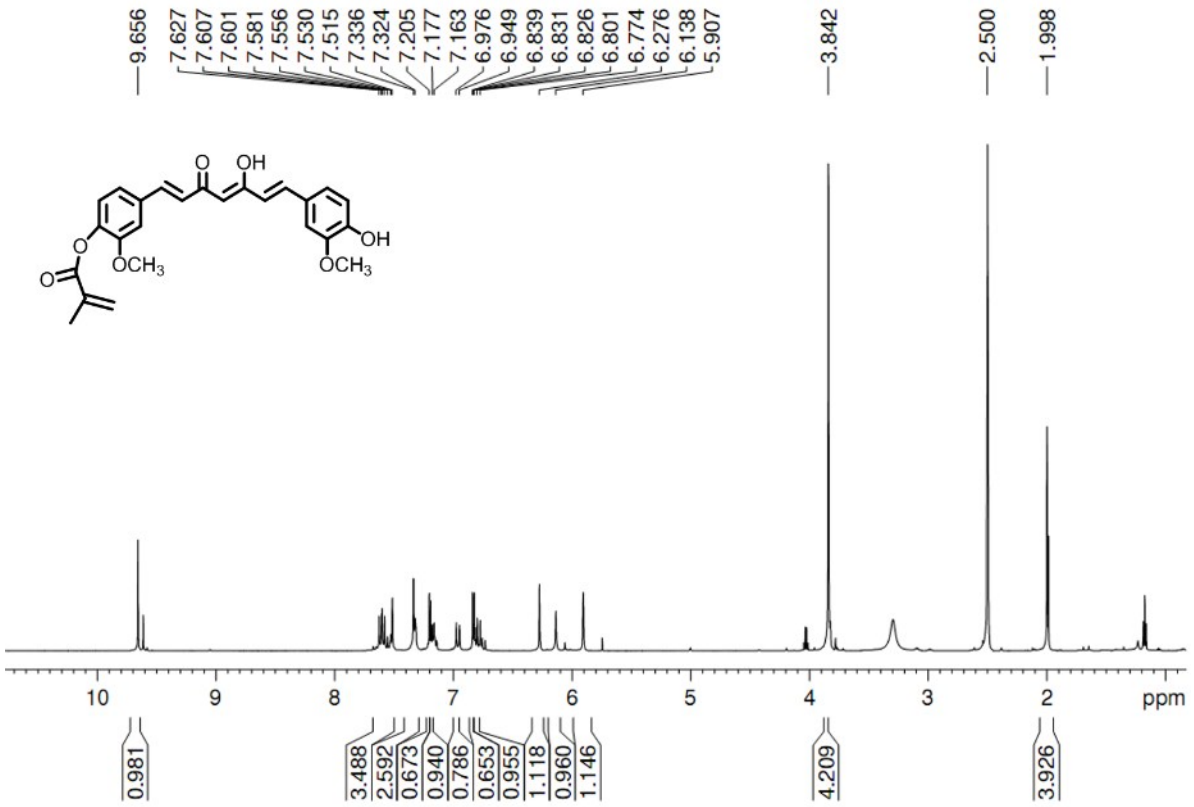


**Figure S4**. $^{1}$H NMR spectra of the curcumin-ene prodrug.

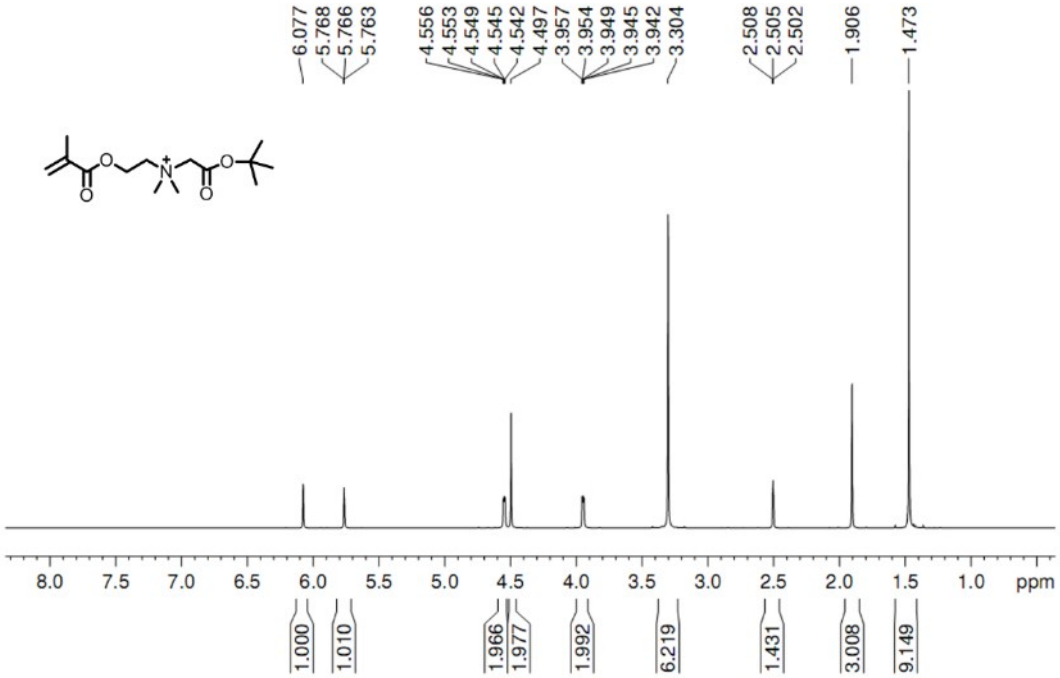


**Figure S5**. $^{1}$H NMR spectra of CB-tBu monomer.

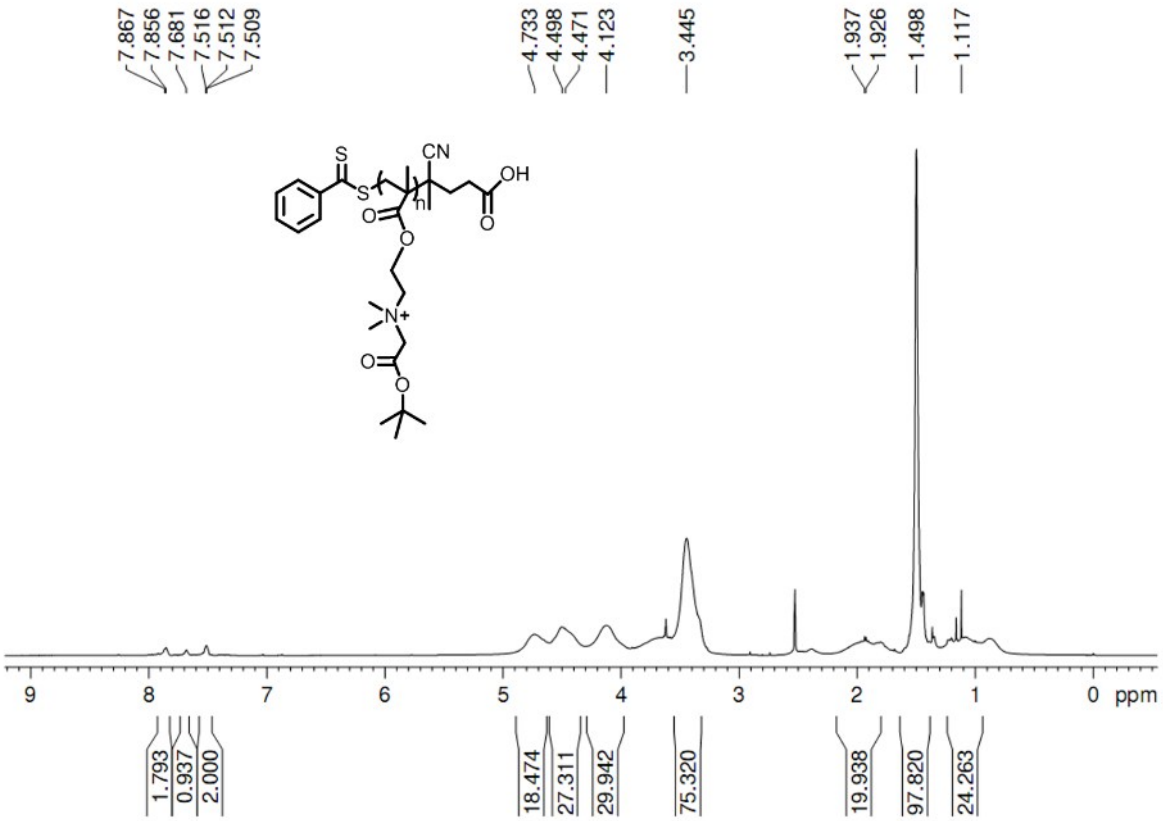


**Figure S6**. $^{1}$H NMR spectra of PCB-tBu polymer.

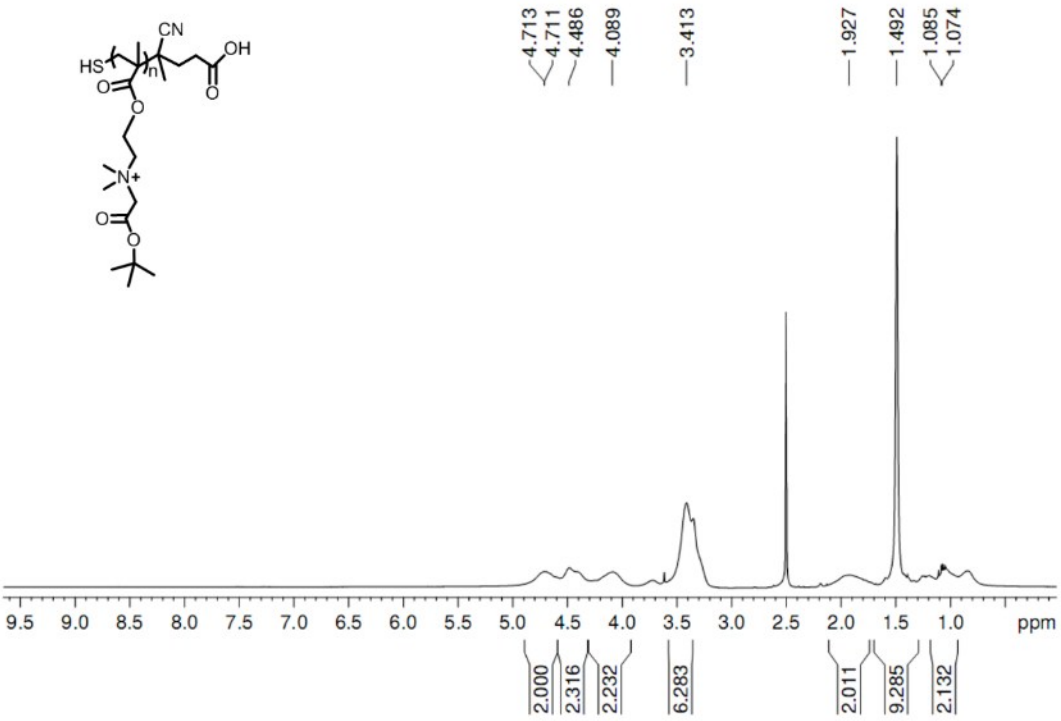


**Figure S7**. $^{1}$H NMR spectra of PCB-tBu-HS polymer.

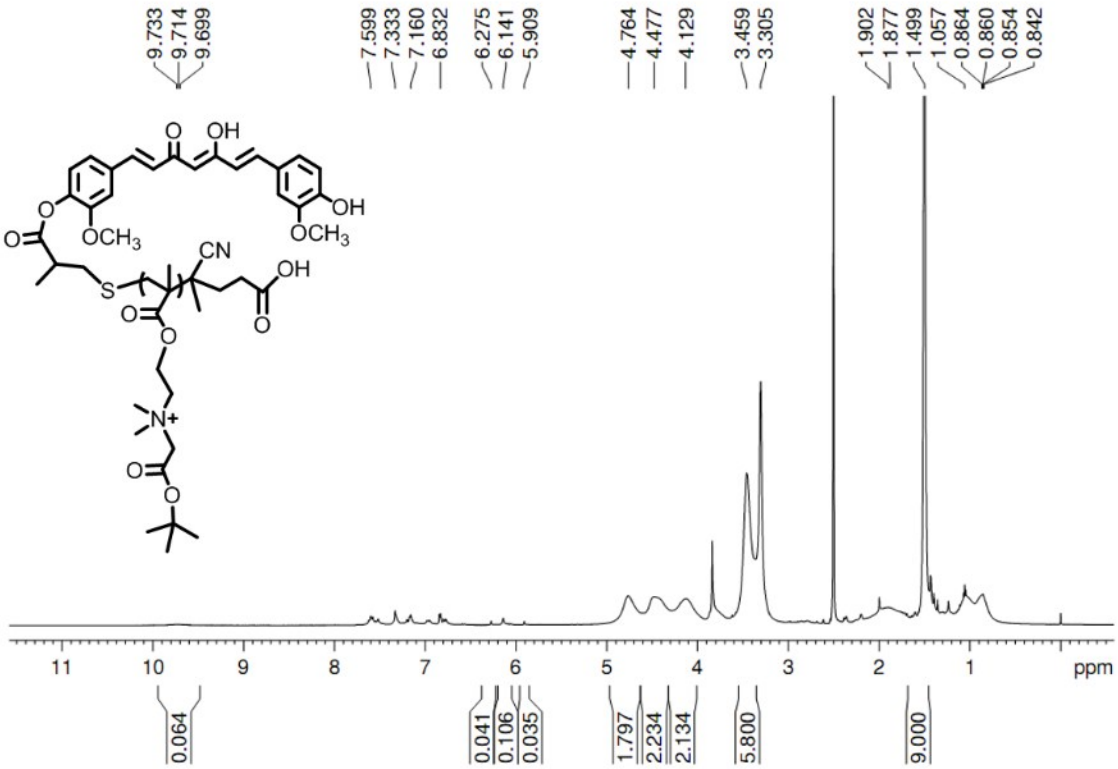


**Figure S8**. $^{1}$H NMR spectra of PCB-tBu-S-curcumin polymer.

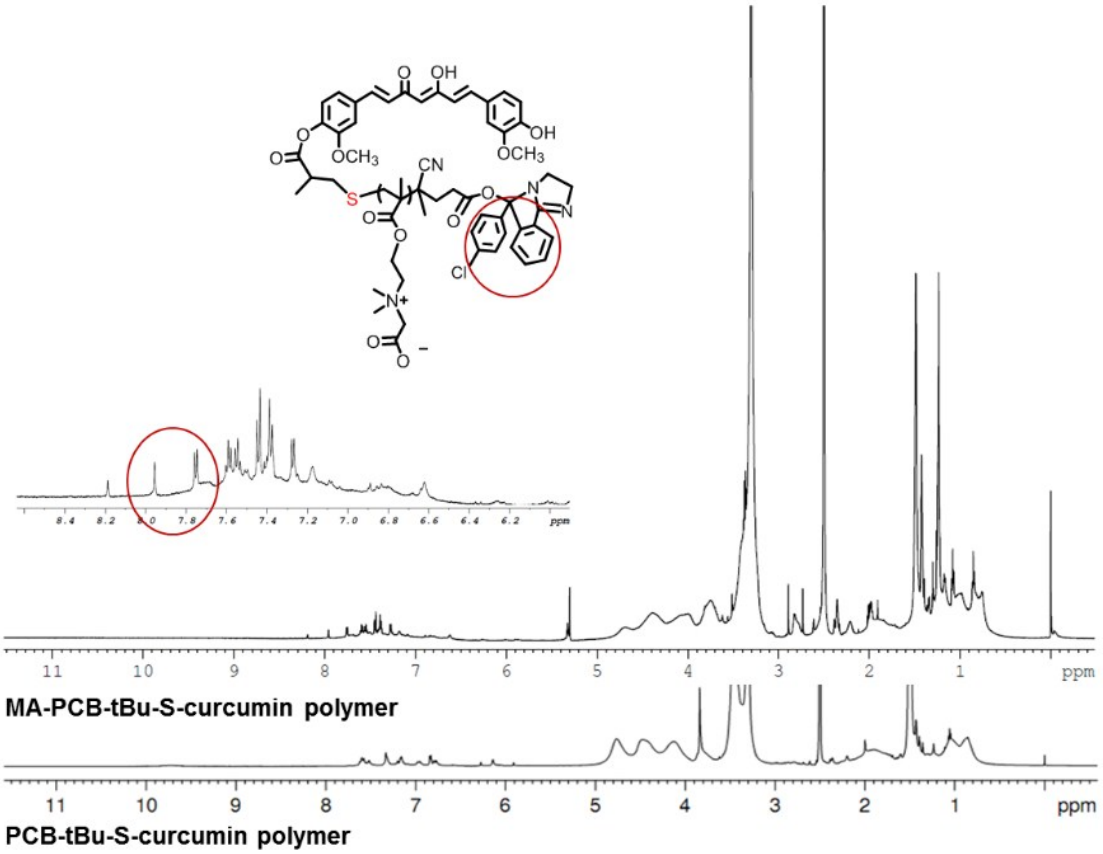


**Figure S9.** $^{1}$H NMR spectra of MA-PCB-tBu-S-curcumin polymer and the comparison with PCB-tBu-S-curcumin polymer.

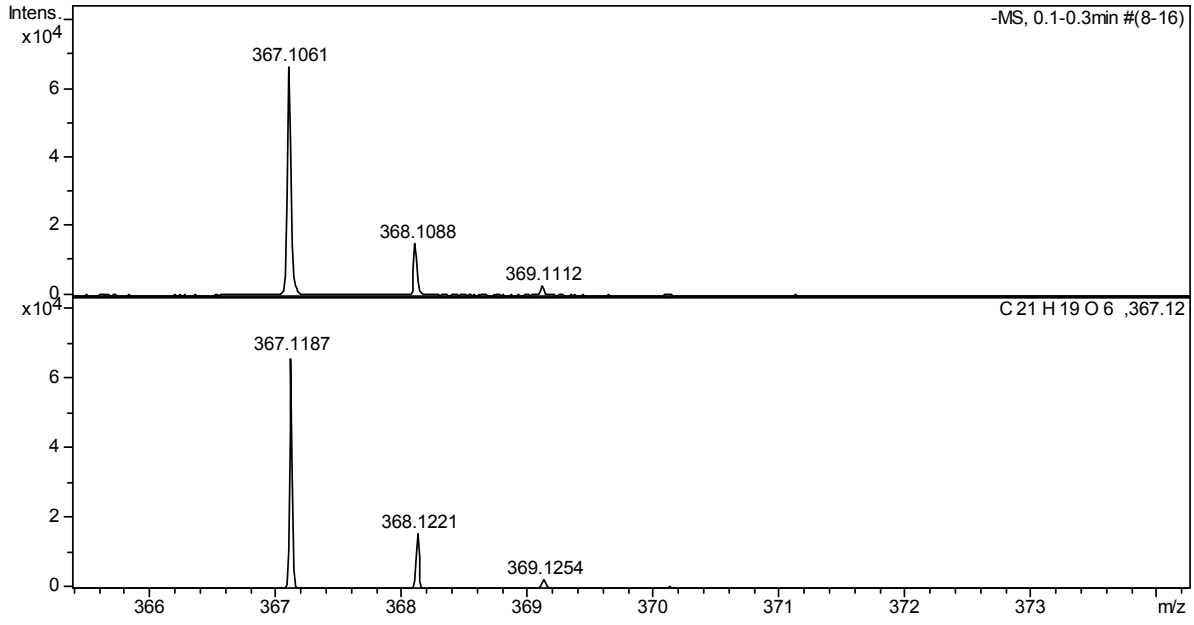


**Figure S10**. ESI-MS spectra of curcumim.

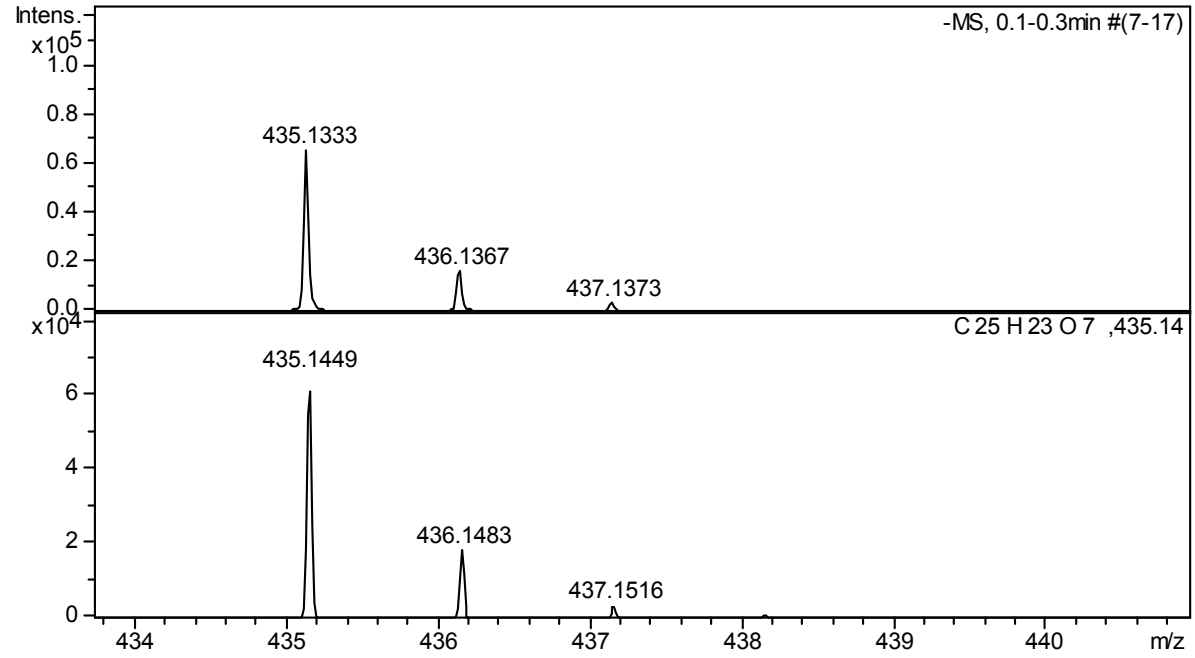


**Figure S11**. ESI-MS spectra of curcumin-ene prodrug.

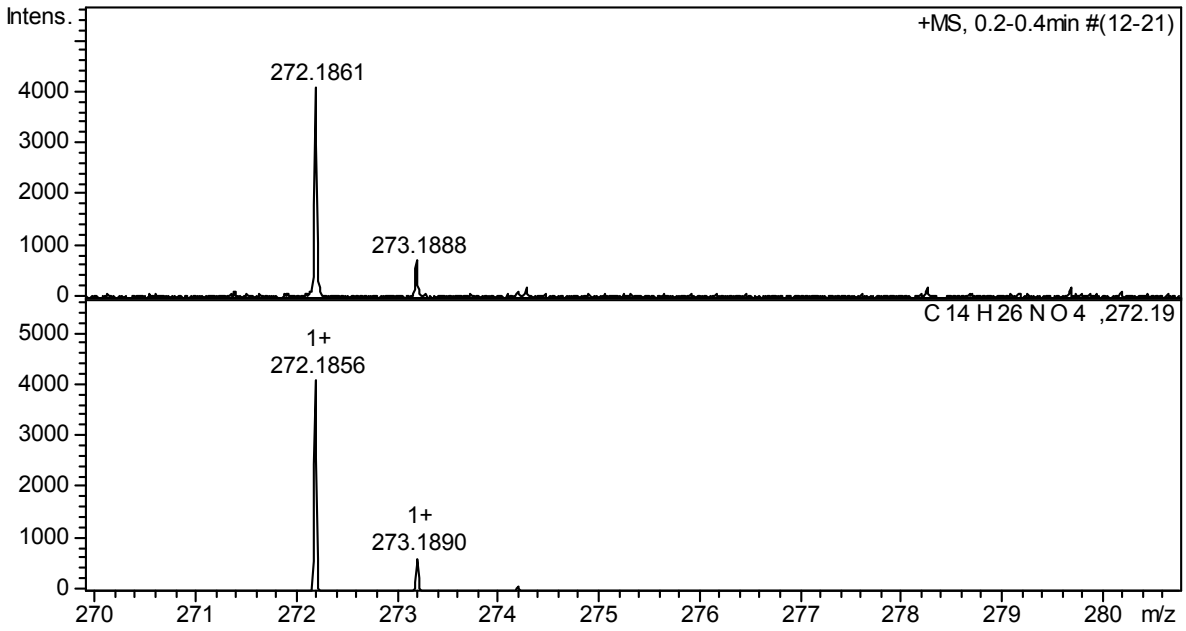


**Figure S12**. ESI-MS spectra of CB-tBu monomer.

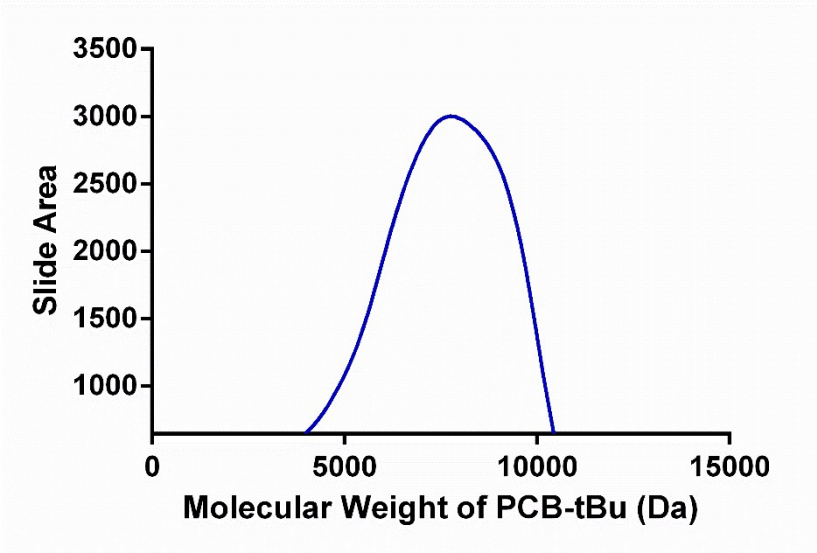


**Figure S13**. The gel permeation chromatography of PCB-tBu polymer (Mw = 7753 Da, Mw/Mn = 1.07).

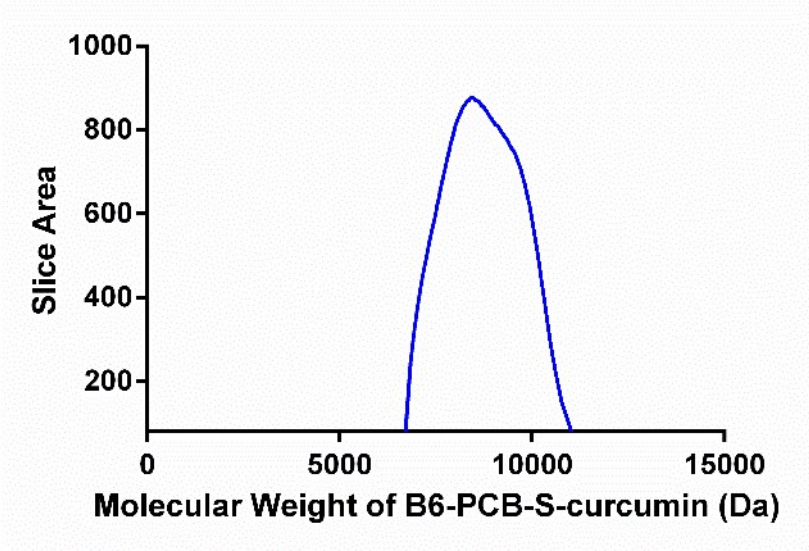


**Figure S14.** The gel permeation chromatography of B6-PCB-S-curcumin polymer (Mw = 8663 Da, Mw/Mn = 1.01).

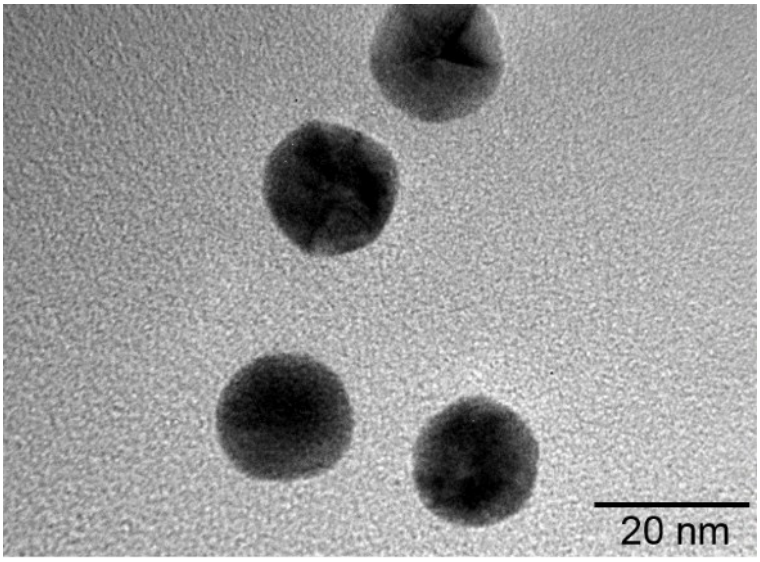


**Figure S15**. TEM image of GNPs.

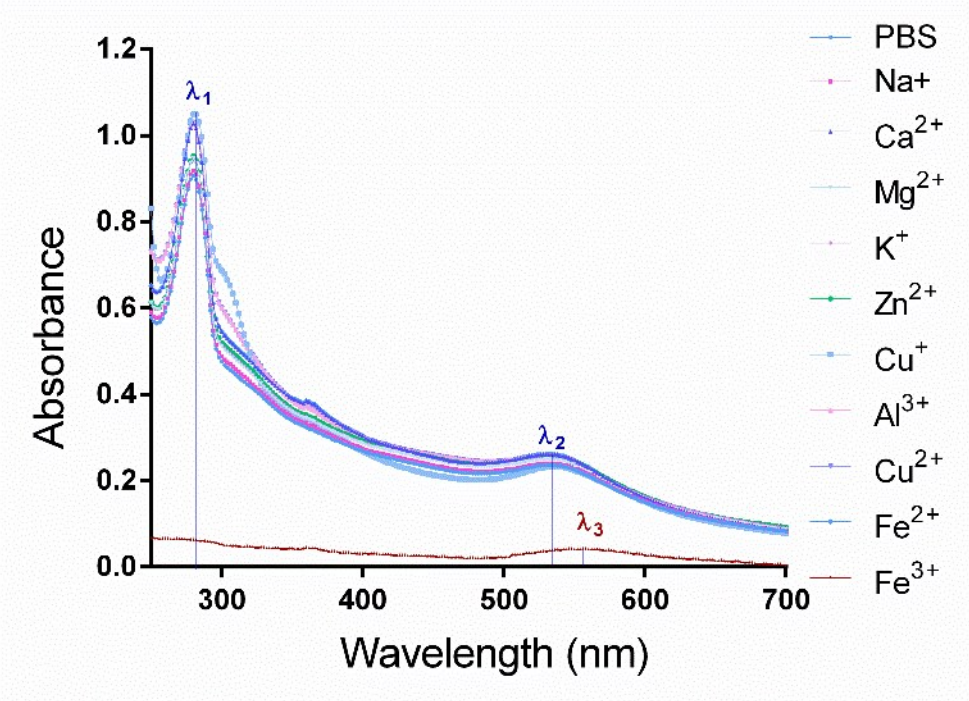


**Figure S16**. UV-Vis absorbance spectra of GNPs with different ions. ($\lambda_1$: 282 nm was the characteristic peak of levodopa-quinone; $\lambda_2$: 533 nm was the characteristic peak of gold nanoparticle; $\lambda_3$: 556 nm was the characteristic peak of changed gold nanoparticle.)

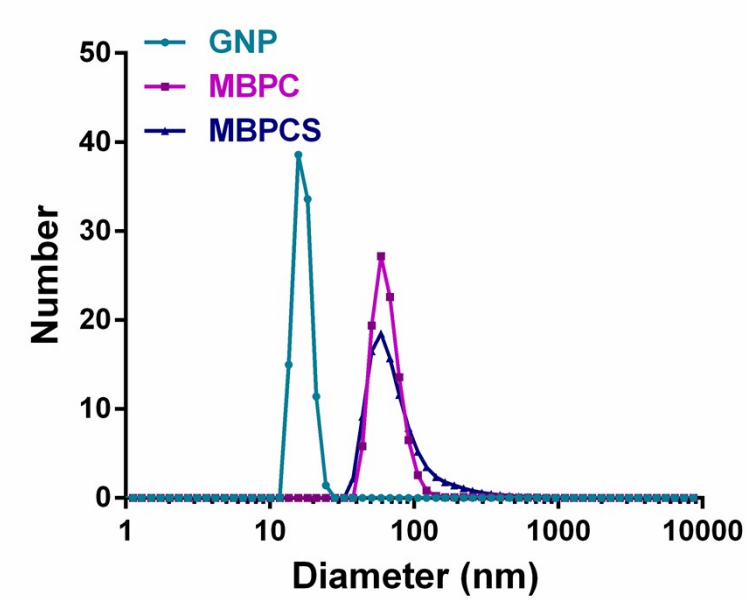


**Figure S17.** The hydrodynamic sizes of GNP, MBPC and MBPCS charactered by dynamic light scattering.

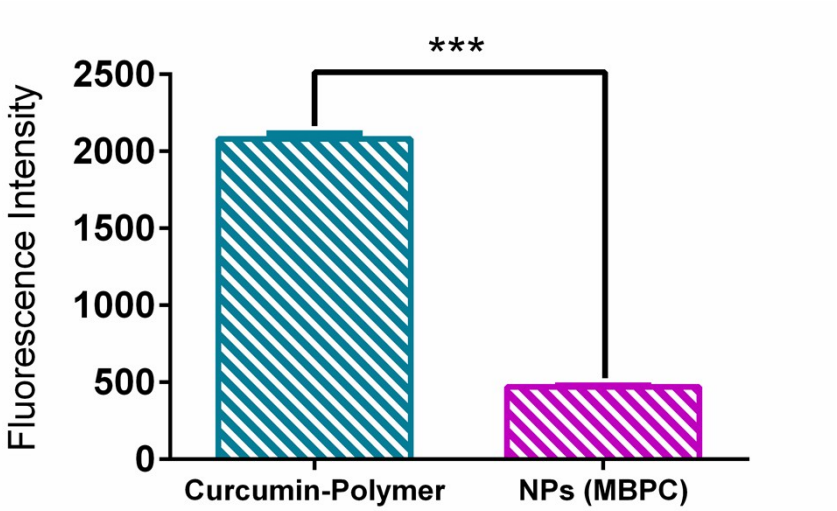


**Figure S18**. Fluorescence intensity of curcumin prodrug polymer: MA/B6-PCB-S-CUR and MA/B6-PCB-S-CUR@GNP assembled MBPC (excitation of 425 nm and emission of 530 nm).

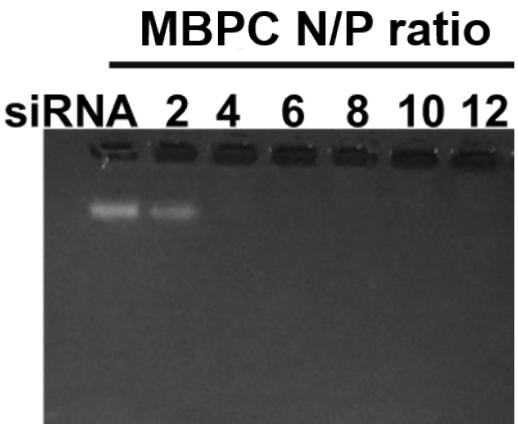


**Figure S19**. Gel retardation assay of siSNCA at various MBPC ratios.

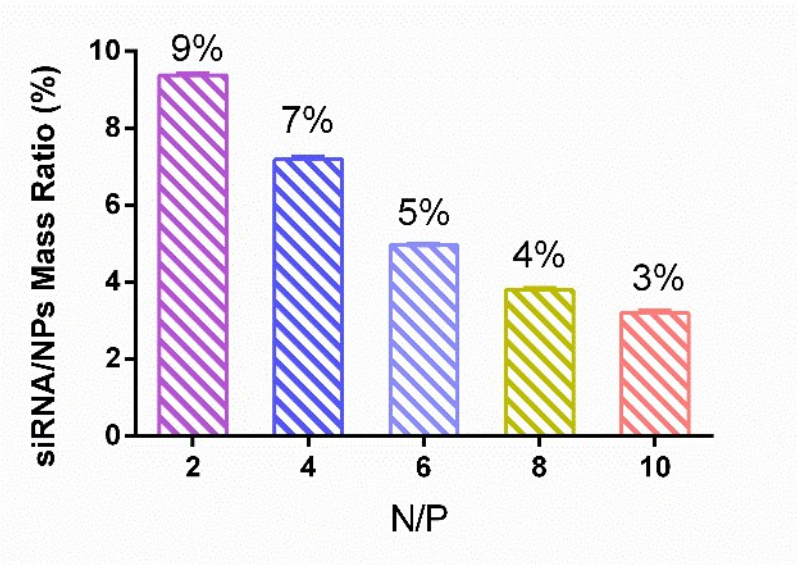


**Figure S20.** The siRNA/NPs mass ratio detected by Quant-iT RiboGreen RNA Reagent and Kit (Invitrogen).

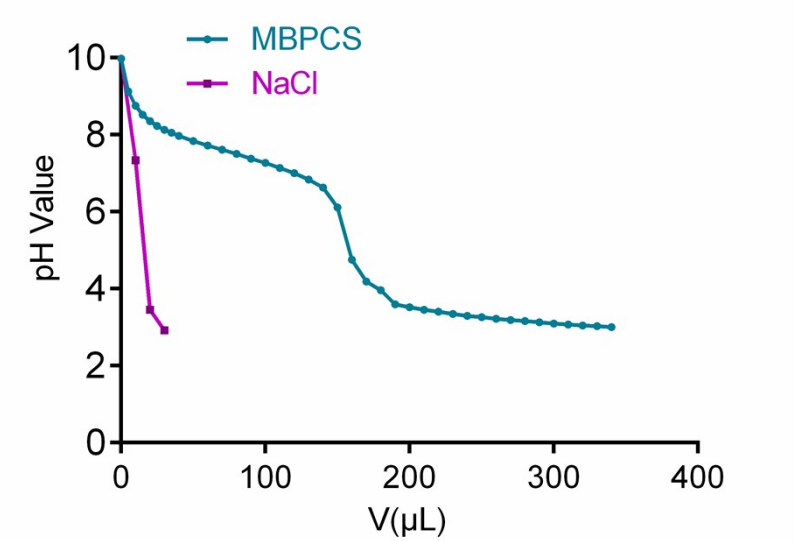


**Figure S21.** The buffer capacity NPs detected by acid-based titration in 0.01 M NaCl aqueous solution. Samples: NaCl aqueous solution; MBPCS.

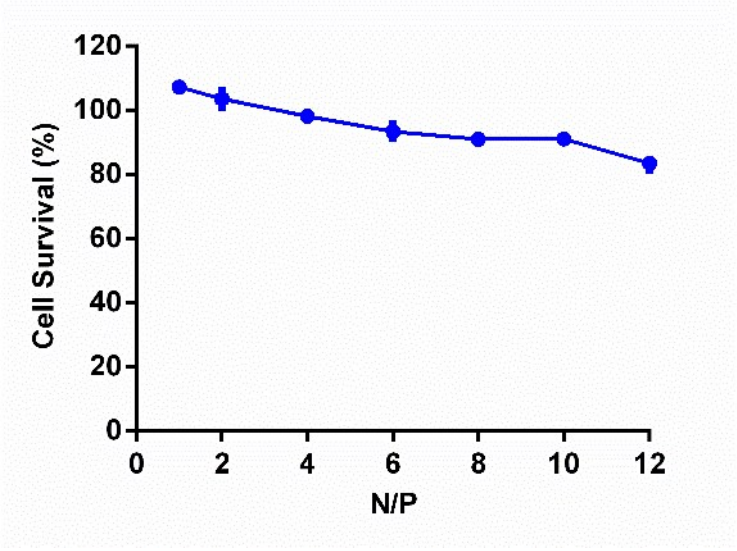


**Figure S22.** MTT assay of MBPCS from 1 to 12 N/P ratio.

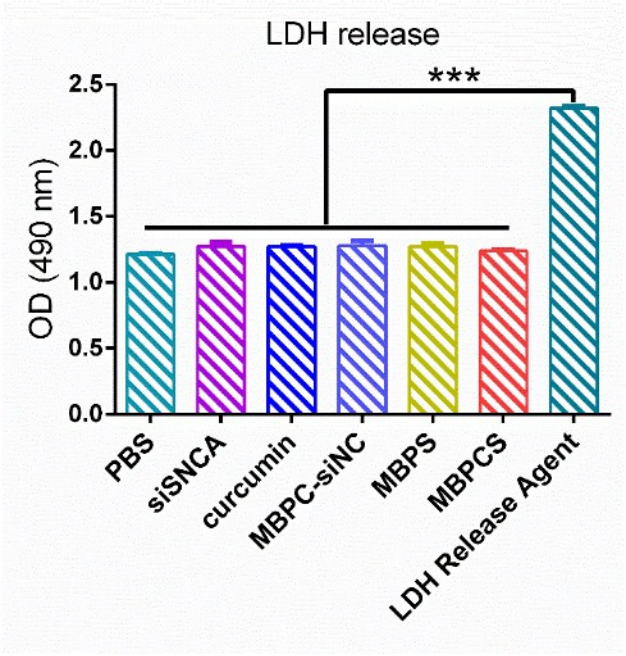


**Figure S23.** Cell damage caused by medium conditioned by medicine or nanomedicine: PBS, free gene drug siSNCA, free chemical drug curcumin, three compared NPs MBPC-siNC, MBPS, MPBCS and lactate dehydrogenase (LDH) release agent.

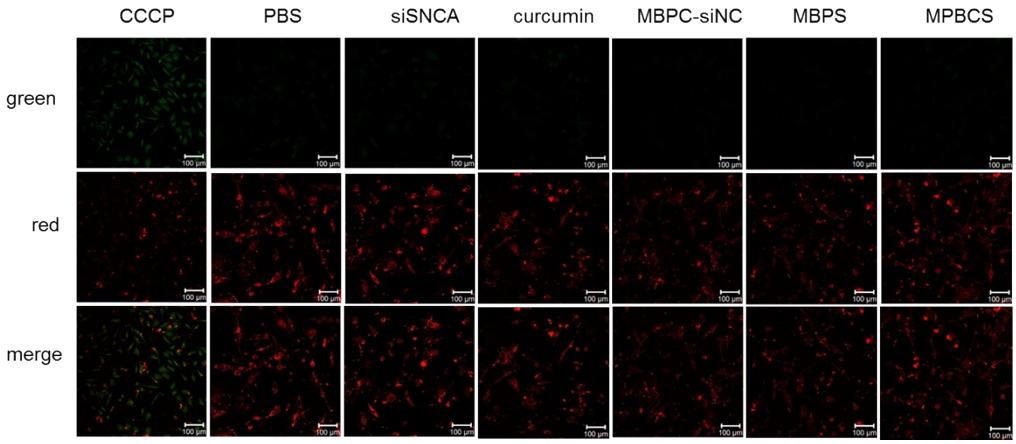


**Figure S24.** Effect of various medicine or nanomedicine on the mitochondrial membrane potential (MMP) in SH-SY5Y cells.

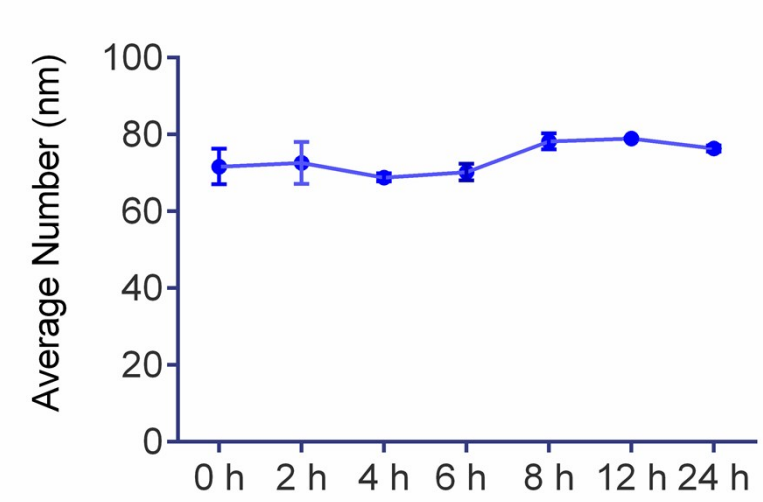


**Figure S25.** The serum stability test conducted by measuring the average diameters of MBPCS.

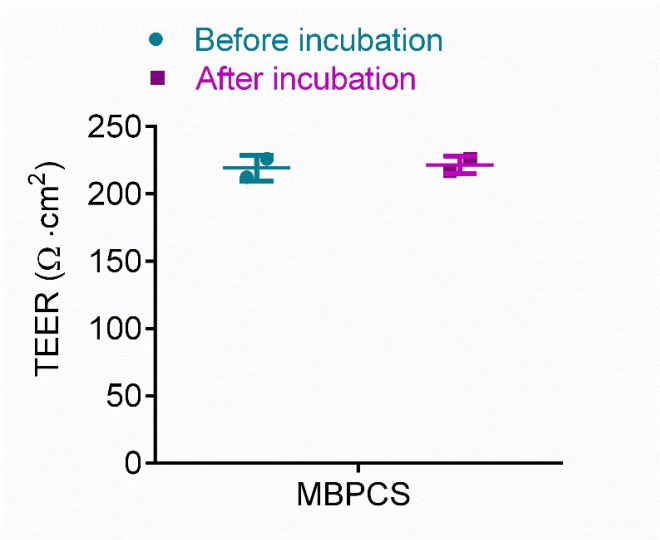


**Figure S26.** The trans epithellal electric resistance (TEER) of bEnd.3 cells in tranwell inserts before and after MBPCS incubation for 12 h.

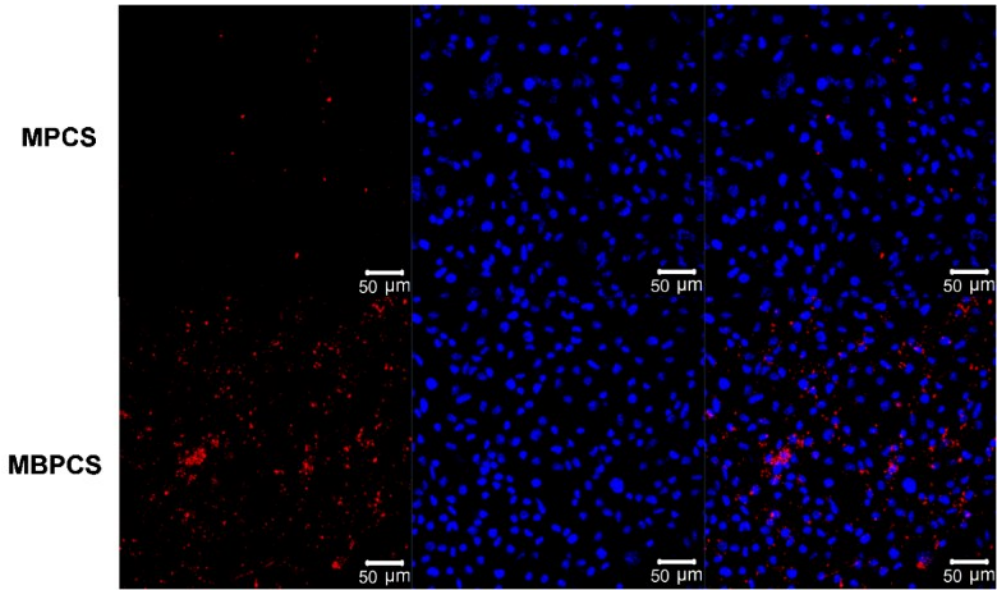


**Figure S27.** Assessment of CLSM of MPCS and MBPCS in SH-SY5Y cells after incubation in transwell for 2 h (Cy5-siRNA: red; DAPI: blue).

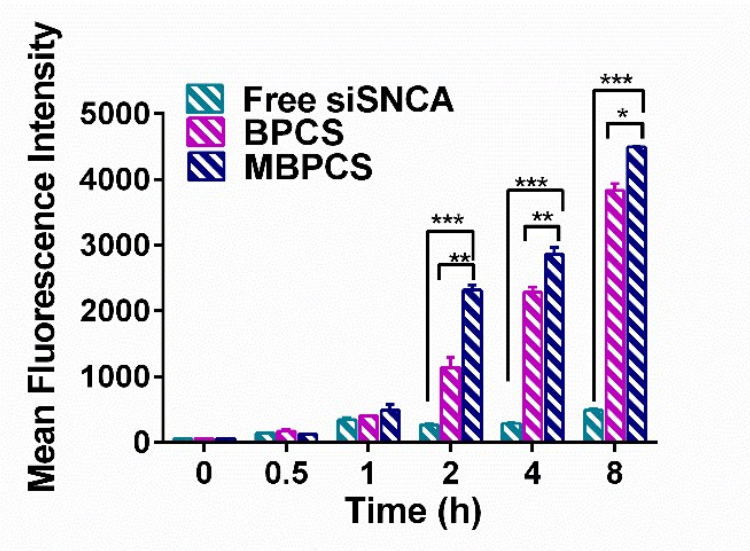


**Figure S28.** The internalization of SH-SY5Y cells treated with free siRNA, BPCS and MBPCS.

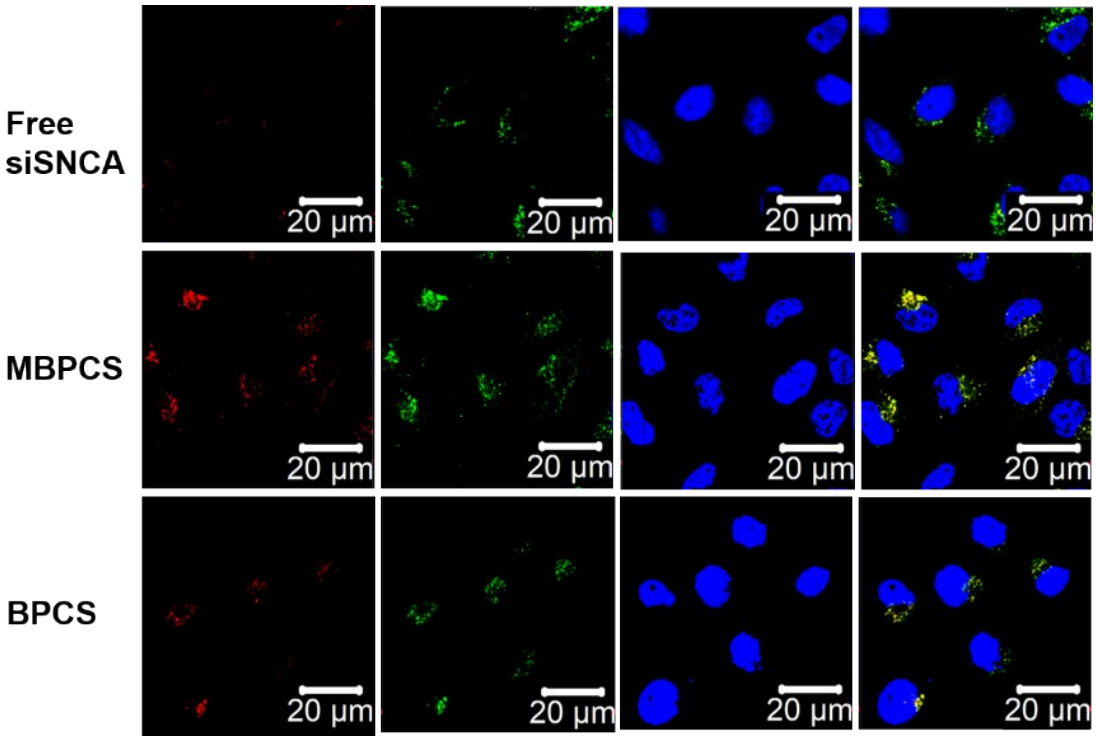


**Figure S29.** Assessment of by CLSM of free siSNCA, MBPCS and BPCS in SH-SY5Y cells after incubation with SH-SY5Y cells for 2 h (Cy5-siRNA: red; DAPI: blue; endosome/lysosome: green).

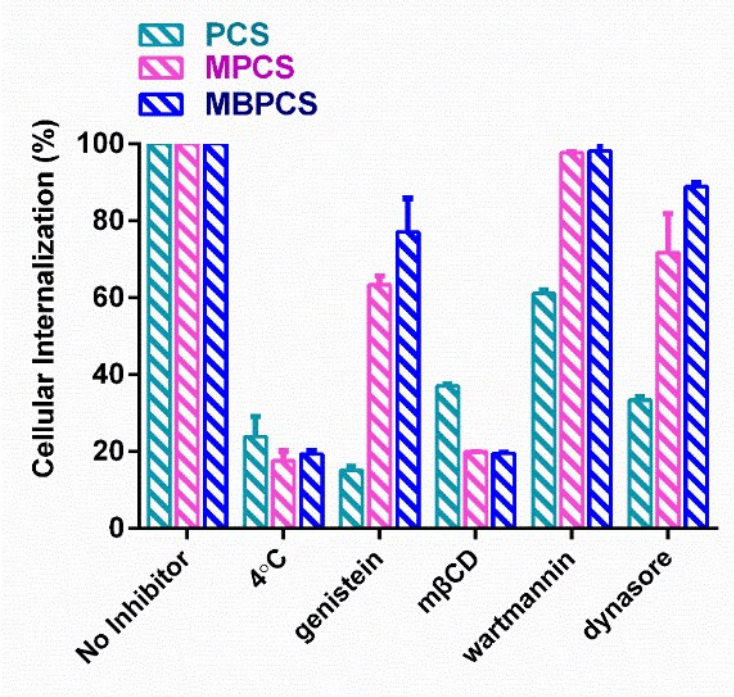


**Figure S30.** Mechanistic probes of the intracellular kinetics of the PCS, MPCS and MBPCS in SH-SY5Y cells by monitoring the cellular uptake level at 4 ºC or in the presence of various endocytic inhibitors. Data are shown as the mean ± S.D. of three independent experiments.

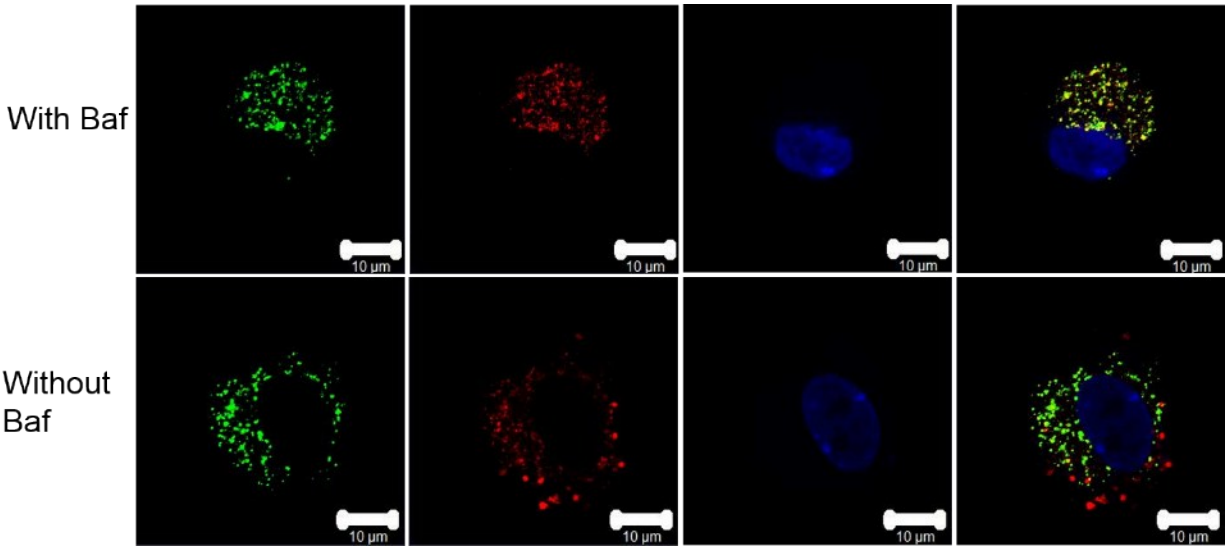


**Figure S31.** Assessment of CLSM of MBPCS in SH-SY5Y cells after incubation for 8 h with SH-SY5Y cells with or without 200 nM bafilomycin A1. (Cy5-siRNA: red; DAPI: blue; endosome/lysosome: green)

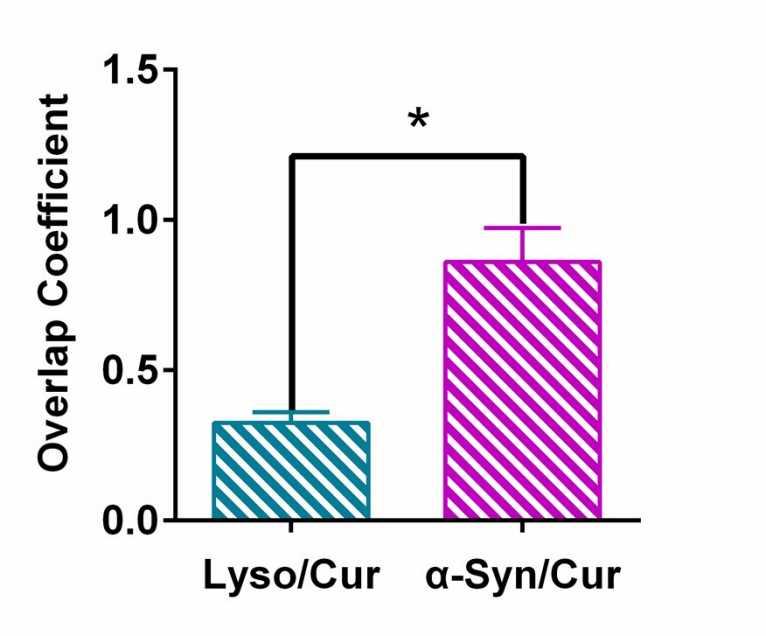


**Figure S32.** The overlap coefficient of the auto-fluorescence of curcumin with lysosome and with α-syn-mCherry.

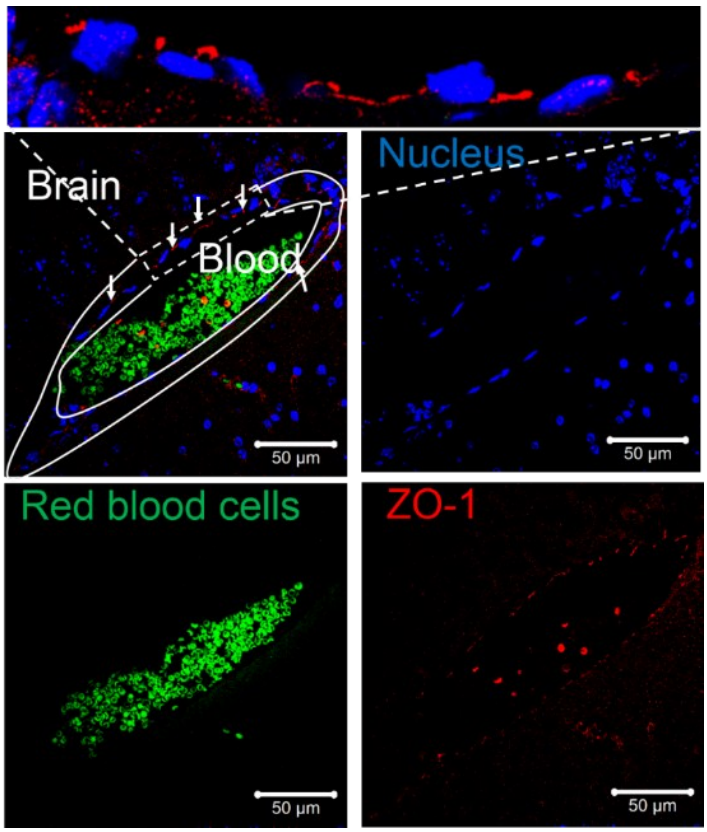


**Figure S33**. BBB formation in C57BL/6 mice brain by immunostaining of inter-endothelial tight junction molecule ZO-1.

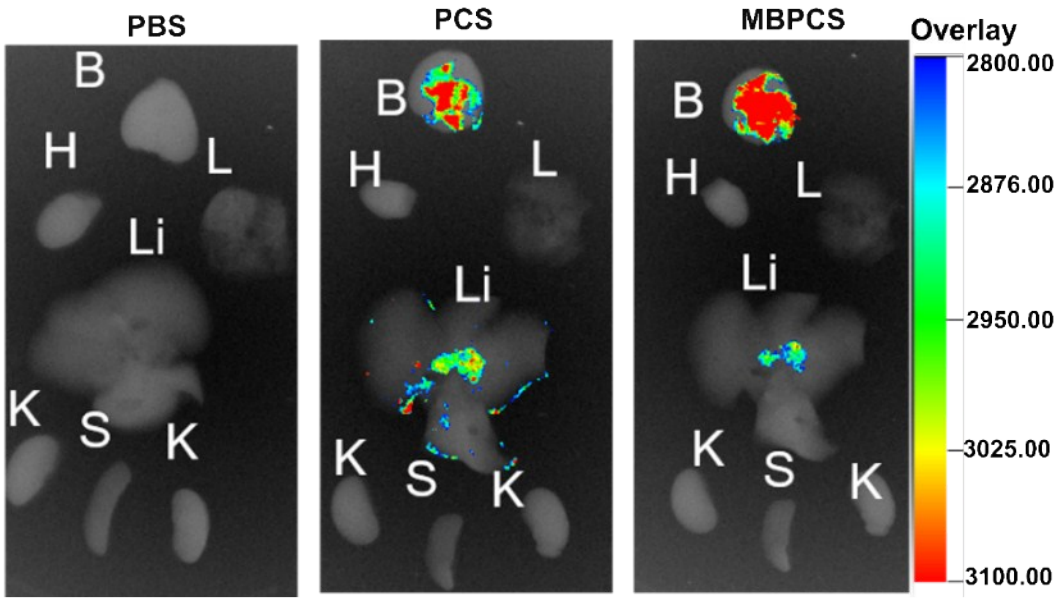


**Figure S34.** Ex-vivo bioluminescence imaging of control mice, PCS and MBPCS treated mice after 24 h via intravenous injection (curcumin was auto-fluorescent by excitation of 425 nm, emission of 530 nm, B (brain); H (heart); L (lung); Li (liver); K (kidney); S (spleen).

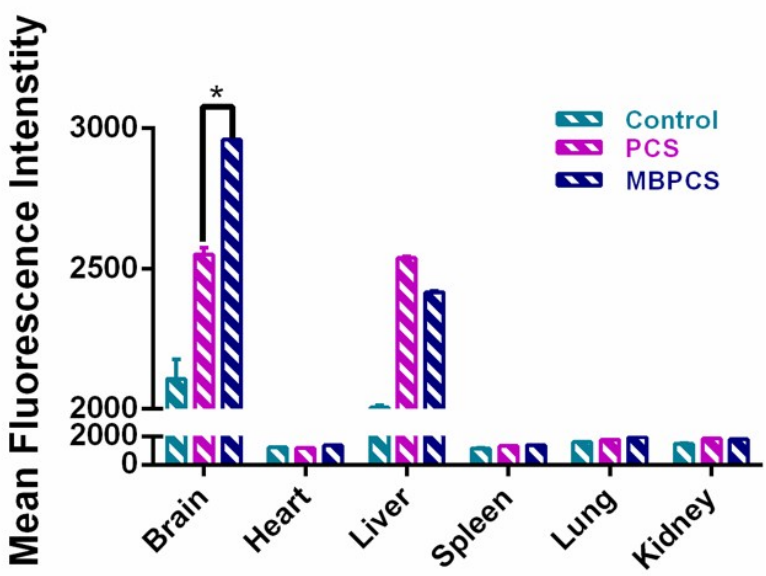


**Figure S35.** Quantitation of ex-vivo bioluminescence imaging of control mice, PCS and MBPCS treated mice after 24 h via intravenous injection. The abbreviations: MFI (mean fluorescence intensity); B (brain); H (heart); L (lung); Li (liver); K (kidney); S (spleen).

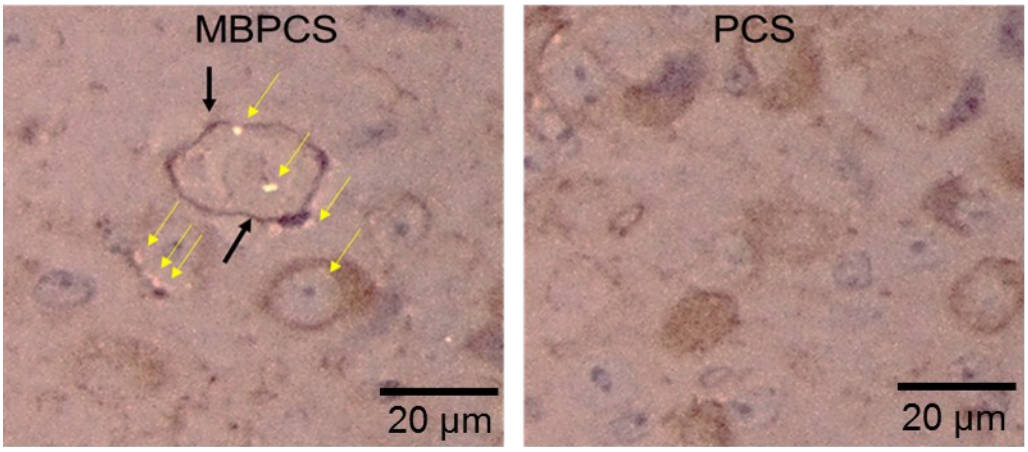


**Figure S36.** Dark field microscopy imaging of MBPCS and PCS treated mice brain slides. Immunohistochemistry of mouse brain substantia nigra was black arrow which indicated the cells were TH positive cells. Yellow arrow pointed to the positive particles which were gold nanoparticles.

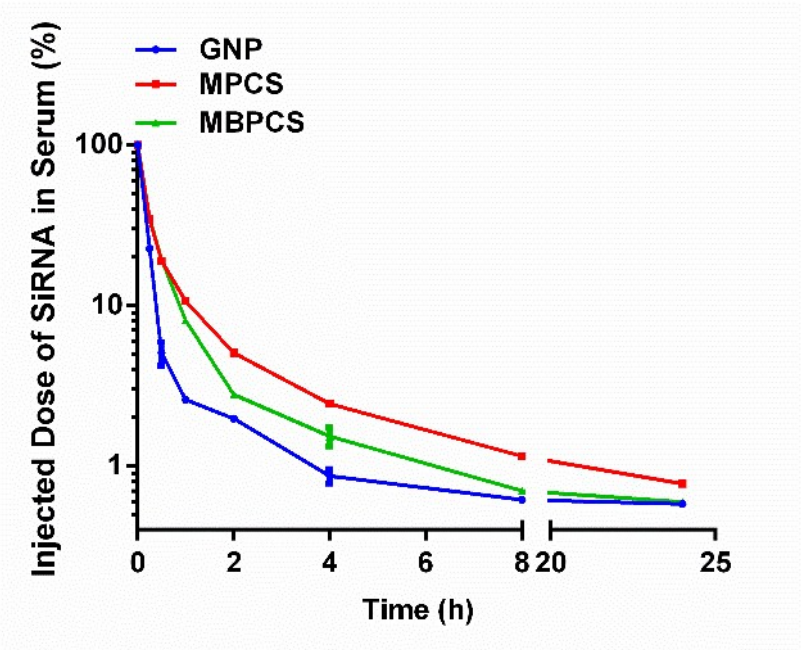


**Figure S37.** Pharmacokinetic profiles in MPTP-induced C57BL/6 mice. Mice were pretreated with GNP, MPCS and MBPCS.

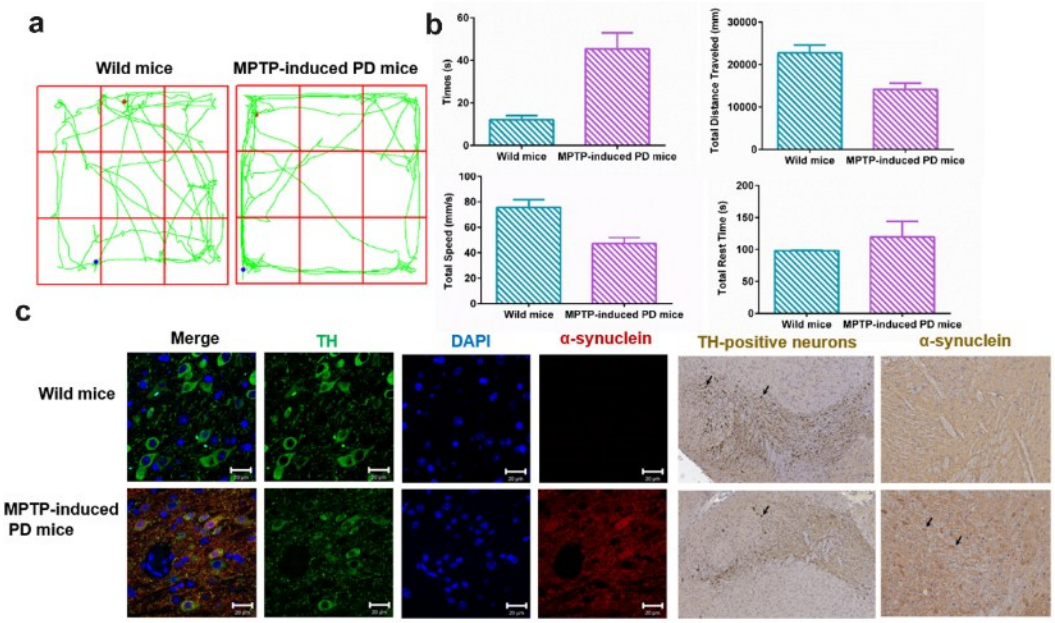


**Figure S38.** PD model mice evaluation. (a) Open-field experiment of MPTP treated mice. (b) Pole test score, total distance traveled, total speed and total rest time of MPTP treated mice. (c) Immunofluorescence and immunohistochemistry staining of treated mice brain slices in SN region: cell nuclear (DAPI, blue), tyrosine hydroxylase (green), α-synuclein (red). The scale bar in (c) is 20 μm.

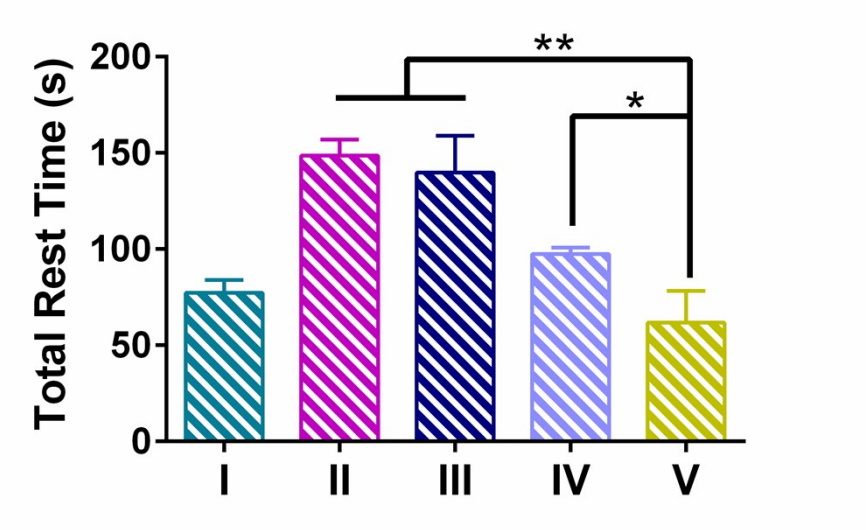


**Figure S39.** Total rest time of treated mice of in open-field experiment (I: wild control; II: PD control; III: free curcumin & siSNCA; IV: PCS; V: MBPCS).

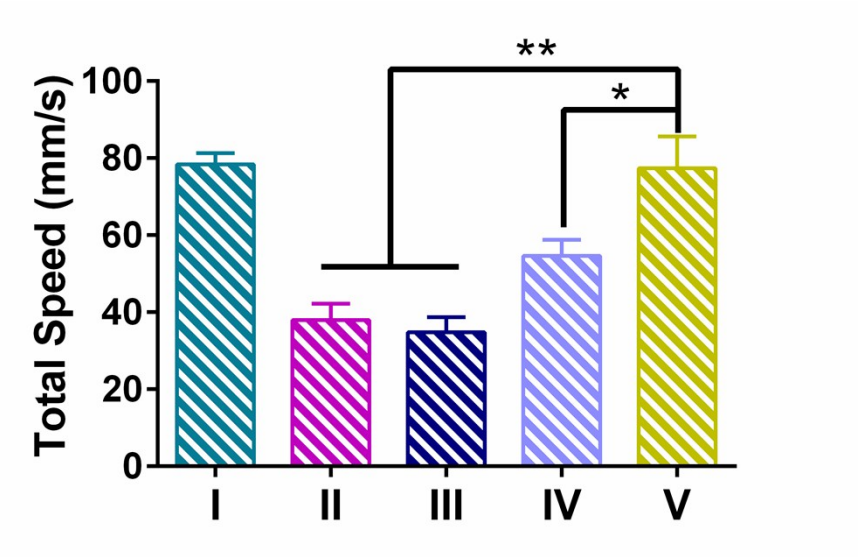


**Figure S40.** Total speed of treated mice of in open-field experiment (I: wild control; II: PD control; III: free curcumin & siSNCA; IV: PCS; V: MBPCS).

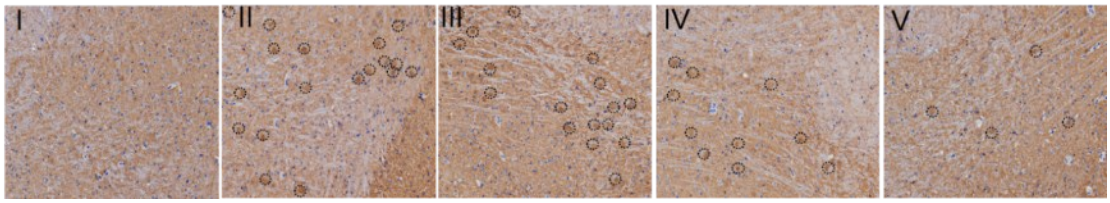


**Figure S41.** The immunofluorescence staining of treated mice brain SN region slides. (the deep granules were α-synuclein, I: wild control; II: PD control; III: free curcumin & siSNCA; IV: PCS; V: MBPCS.)

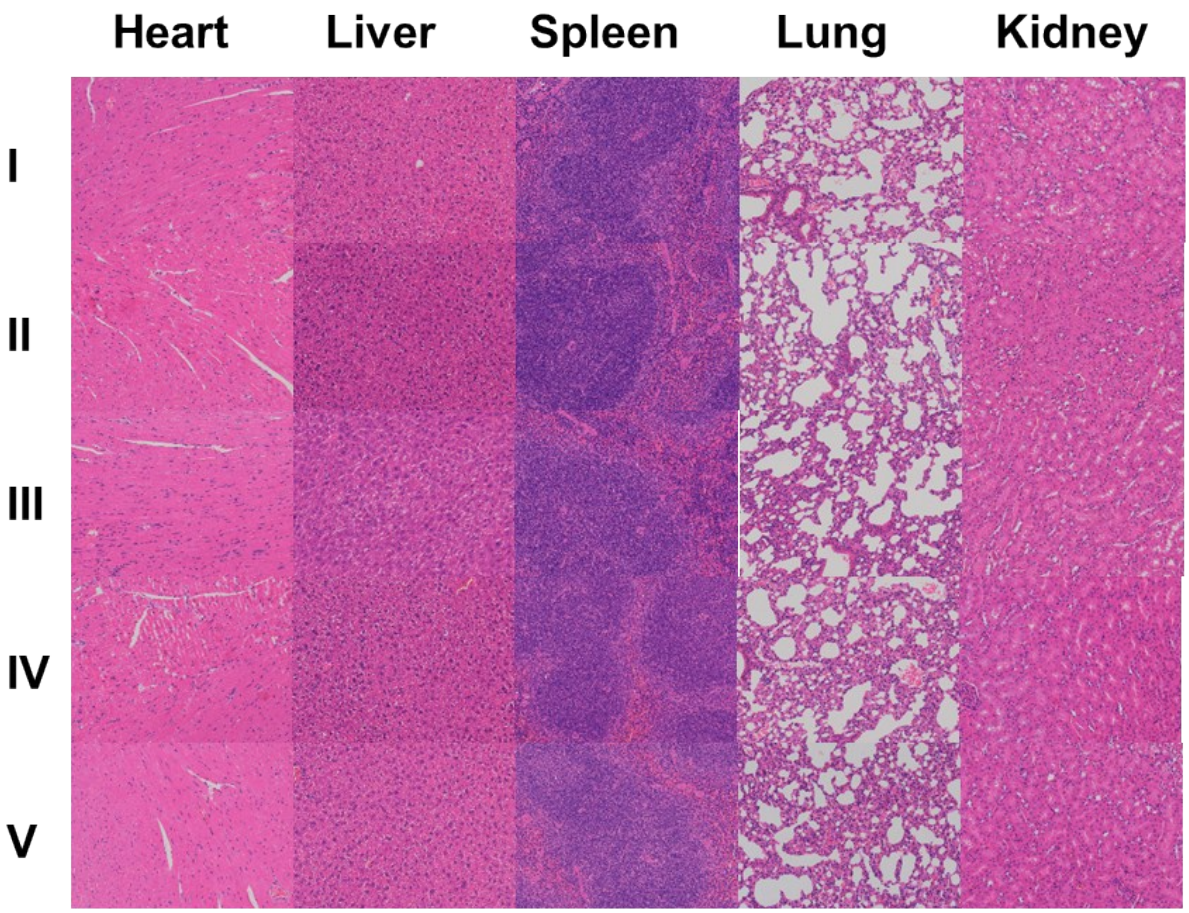


**Figure S42.** Hematoxylin-eosin (H&E) staining of treated mice organs' slices. (I: wild control; II: PD control; III: free curcumin&siSNCA; IV: PCS; V: MBPCS.)

## Notes and references

1 J. M. Cooper, P.B. O. Wiklander, J. Z. Nordin, R. Al-Shawi, M. J. Wood, M. Vithlani, A. H. V. Schapira, J. P. Simons, S. El-Andaloussi, and L. Alvarez-Erviti, *Mov. Disord.* **2015**, 29, 1476.