Supplementary Information (SI) for Journal of Materials Chemistry B.
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Supporting Information

Organ Targeting Drug Delivery Systems (OTDDS) of poly[(*N*-acryloylglycine)-*co*-(*N*-acryloyl-L-phenylalanine methyl ester)] Copolymer Library and Effective treatment of Triple Negative Breast Cancer

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Synthesis of NAG monomers

Solution A: It was prepared in a 100 mL round-bottom flask, containing 20 mmol of glycine and 20 mL of aqueous 2 M KOH, which was maintained in an ice bath with continuous stirring at 600 RPM. **Solution B: It** was prepared in a 50 mL of round-bottom flask, containing 20 mmol of acrylol chloride and 5 mL of 1,4-dioxane in an ice bath with continuous stirring at 900 RPM. Solution B was gradually added to Solution A over the course of one hour, ensuring continuous stirring to facilitate the reaction. Following the addition, the mixture was allowed to stir overnight at RT to ensure complete reaction. After 12h, the mixture was washed with 20 mL of diethyl ether for 3 times to remove unreacted materials and by products. The bottom layer was collected after each wash. The pH of the resulting solution was then adjusted to 2 by the dropwise addition of 5M HCl. Subsequently, the solution was saturated with excess NaCl, and the aqueous phase was extracted within 20 mL of ethyl acetate for 5 times to separate N-acryloyl glycine. The moisture was dried over $MgSO_4$ and the filtrate was then subjected to rotary evaporation to concentrate the solution, yielding white powder named as *N*-acryloyl glycine (NAG).

Synthesis of NAPA monomers

Solution A: It was prepared in a 100 mL round-bottom flask containing 1.6g of L-phenylalanine methyl ester, 1.6 mL of triethylamine, and 60 mL of dry DCM, which was maintained in an ice bath with continuous stirring at 600 RPM. **Solution B:** It was prepared in a 50 mL round-bottom flask containing 0.9 mL of acryloyl chloride in 5 mL of DCM. **Solution B** was gradually added to **Solution A** over the course of one hour, ensuring continuous stirring to facilitate the reaction. This controlled addition was important for exothermic nature of the reaction and enhance the formation of the desired product. After the complete addition, whole mixture was stirred for 24h. Further, DCM was removed using a rotary evaporator at 30 °C, yielding a white residue. Then 100 mL of ethyl acetate was added to the residue, and the mixture was

filtered using filter paper to remove insoluble impurities. The resulting solution underwent a series of wash, which include 40 mL of sodium sulfate ($NaHSO_4$) five times, followed by 40 mL of sodium bicarbonate ($NaHCO_3$) five times, and finally with 40 mL of brine solution three times. These washing steps are essential for the removal of impurities. Further, to ensure the removal of moisture, $MgSO_4$ was added and filtered through a 0.45micron filter. The filtrate was then subjected to rotary evaporation to concentrate the solution, yielding white powder named as *N*-acryloyl-L-phenylalanine methyl ester (NAPA).

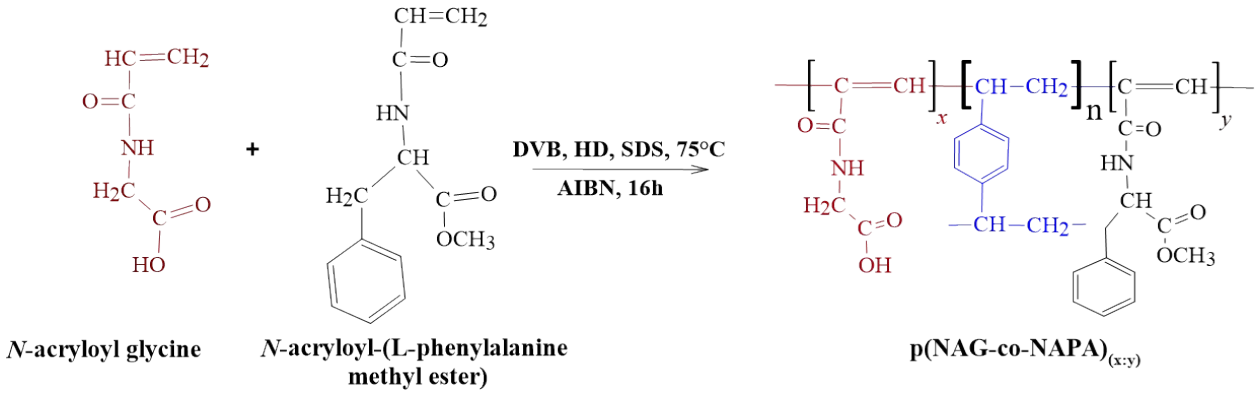

Figure S1. Schematic for the synthesis of p(NAG-*co*-NAPA)$_{(x:y)}$ NPs.

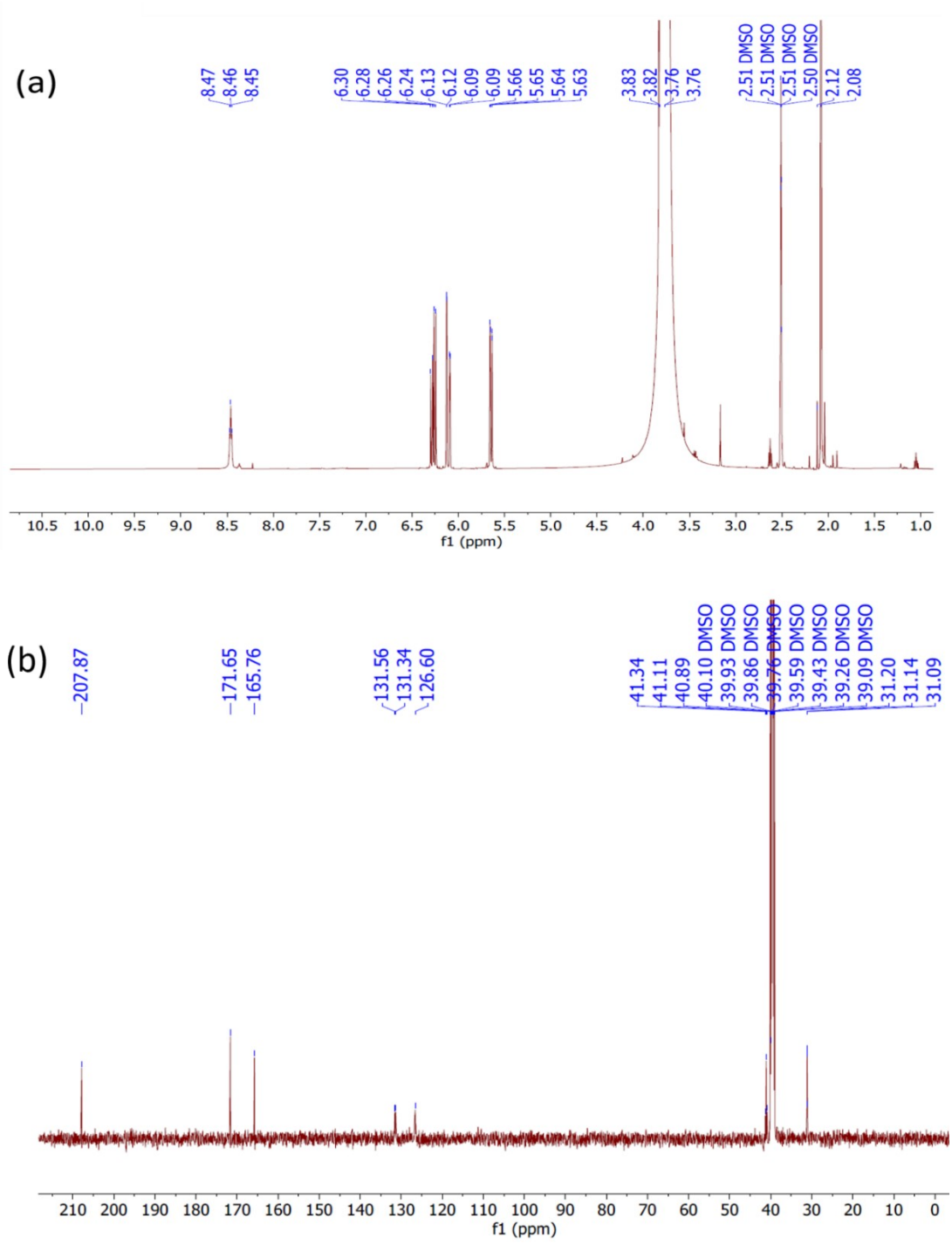

Figure S2. (a) ^{1}H NMR and (b) ^{13}C NMR of NAG. ^{1}H NMR (δ): 8.45 (1H, t (sec. amide)) 6.34, (-C (=O) N) gem 6.10 (-C (=O) N) cis and 5.62 (-C (=O) N) trans, 3.85 (2H, d), ^{13}C-NMR (δ): 165.4 (-NH-CO-), 171.7 (-

CO- (ester)), 126.1 and 131.7 (-C=C-), 41.1(-CH_2 aliphatic) are the corresponding ppm values. Already attached in our previous research article. Only for reference, it has been attached here.

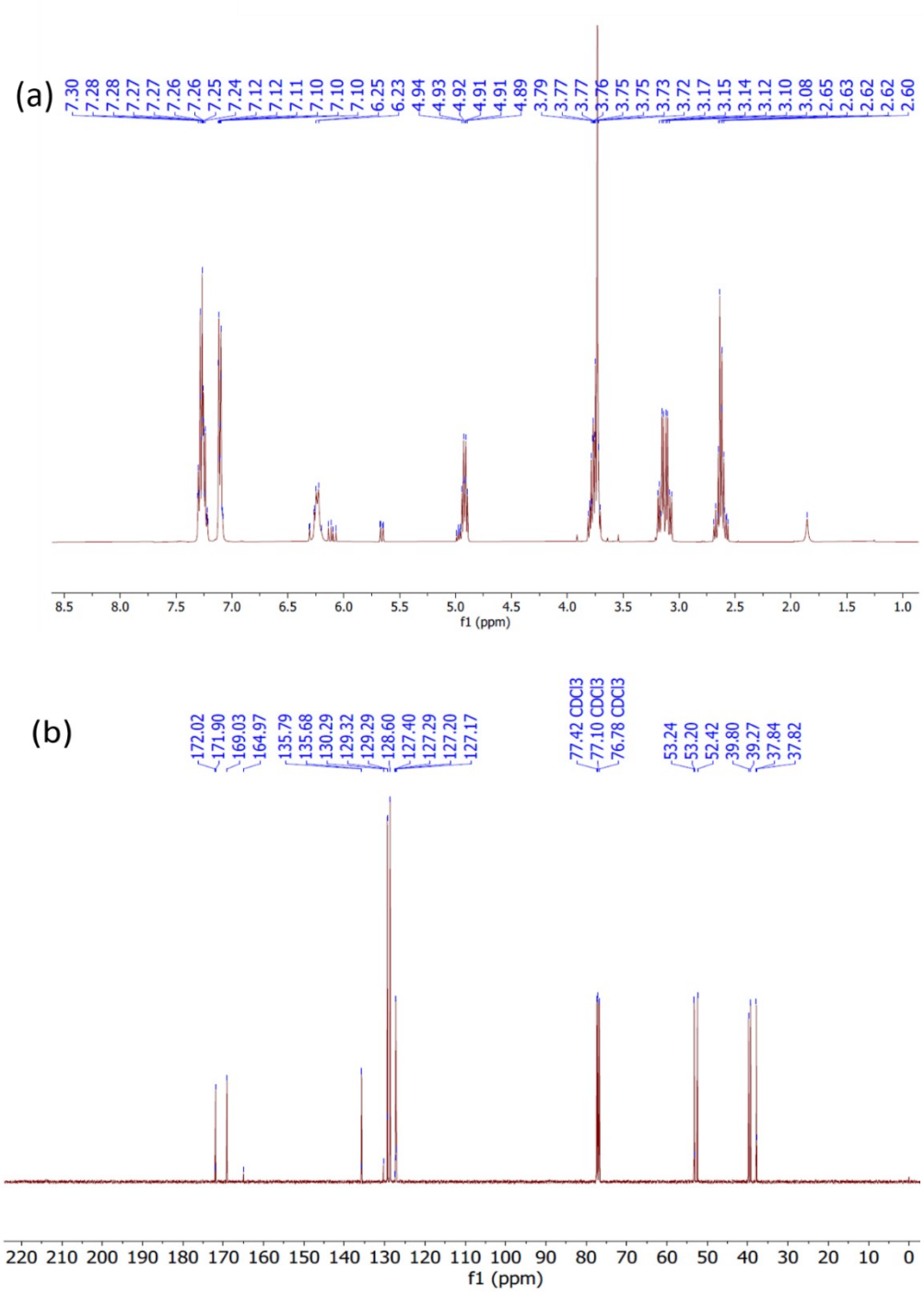

Figure S3. (a) ^{1}H NMR and (b) ^{13}C NMR of NAPA. ^{1}H NMR (δ): 7.3 (5H, m), 7.10, 6.25, and 6.23 (3H, alkene protons), 4.94 (1H, t), 3.79 (3H, s), 3.15 (2H, d) and ^{13}C-NMR (δ): 169.03(-NH-CO-), 172.02 (-CO-), 127 and

130.29 (-C=C) are the corresponding ppm values. Already attached in previous research article. Only for reference, it has been attached here.

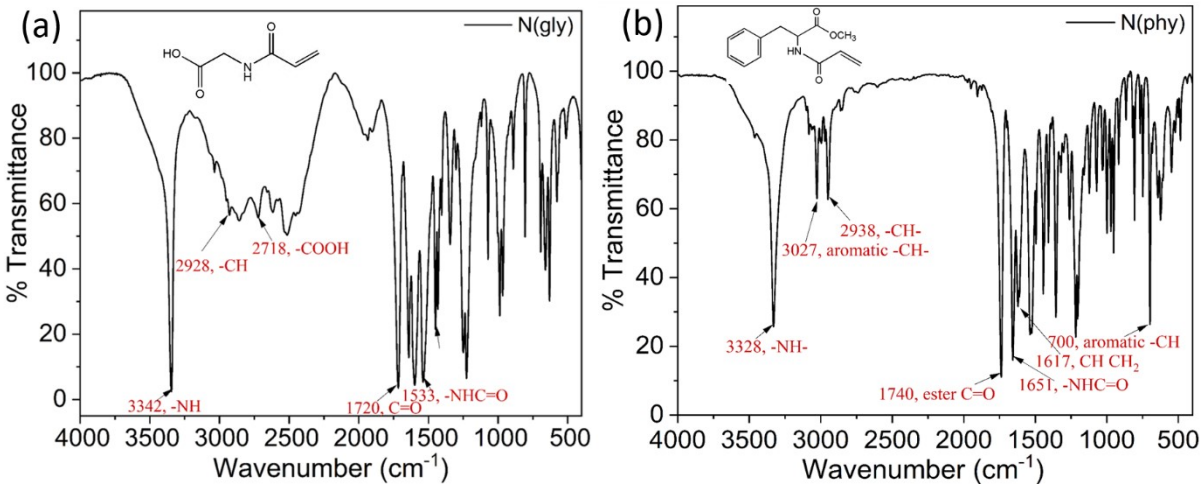

Figure S4: FTIR spectra of (a) NAG and (b) NAPA. Already attached in previous research article. Only for reference, it has been attached here. Respective distinct peaks corresponding to monomers are mentioned in figure (red colour).

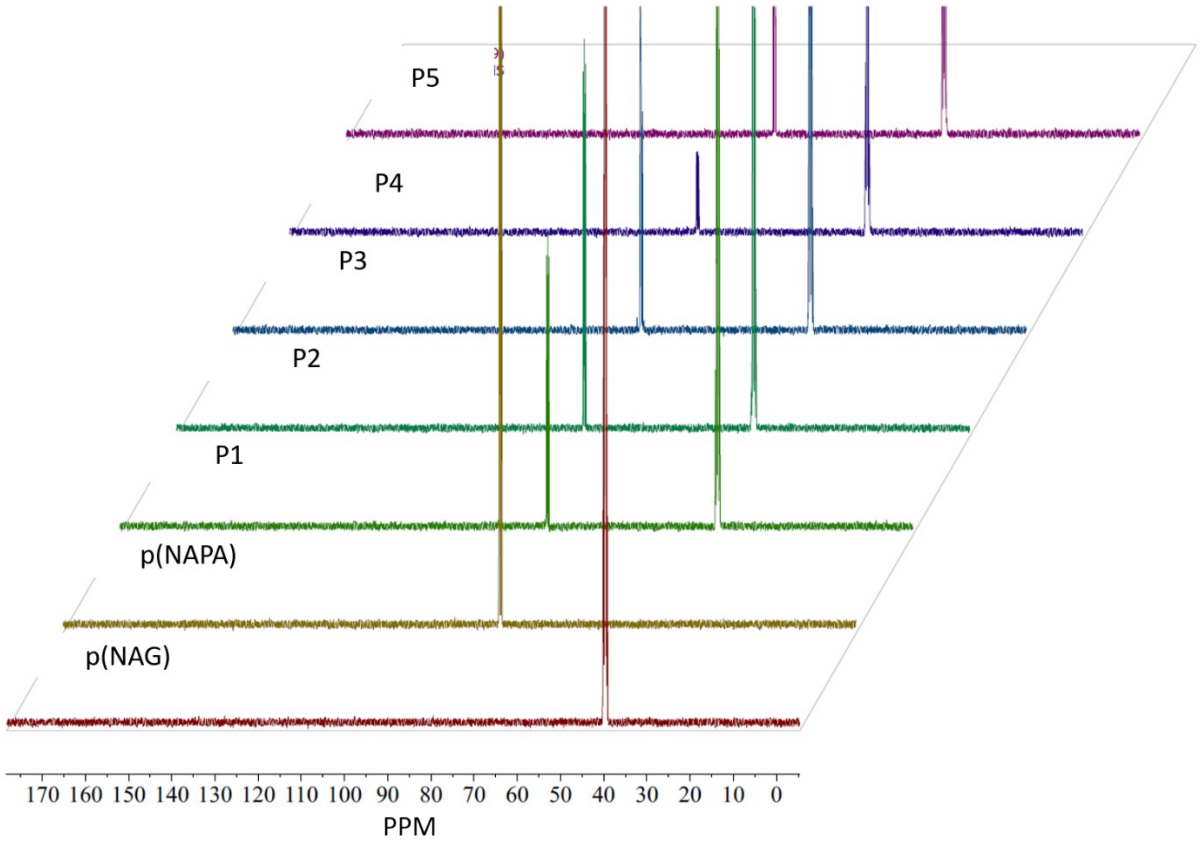

Figure S5. Represents stacked ^{13}C NMR of p(NAG), p(NAPA), P1, P2, P3, P4, and P5. The single peak in the range of δ = 40.27 to 39.18, indicating the presence of a split 2° alkane. The at δ =70 ppm is due to solvent only.

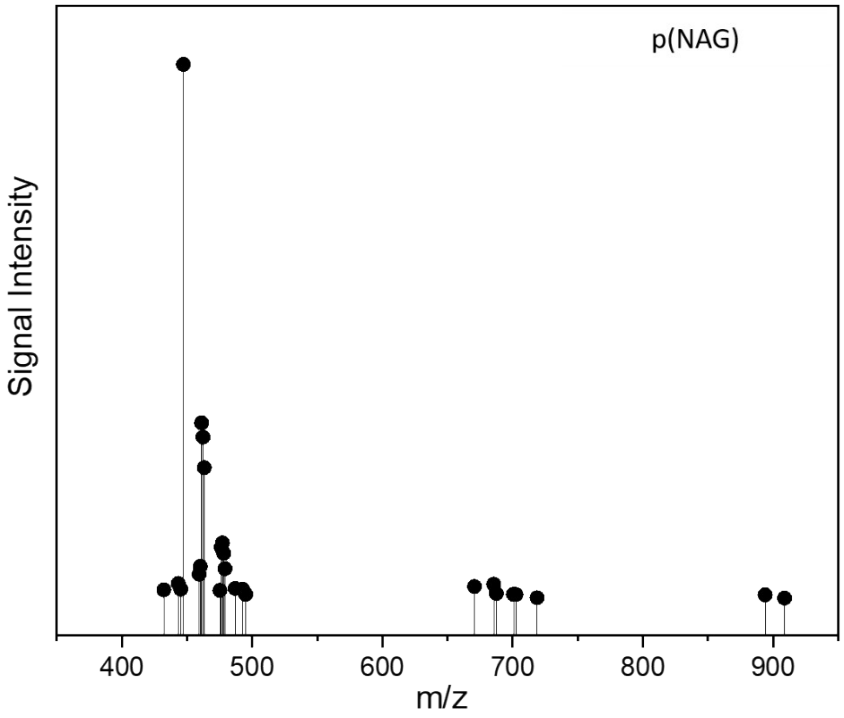

Figure S6. MALDI-ToF spectra of p(NAG) NPs.

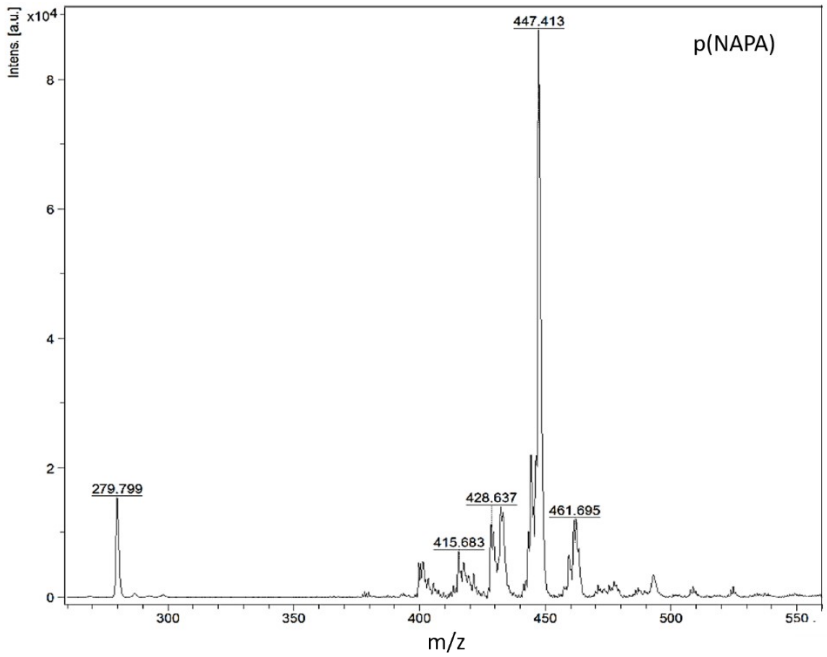

Figure S7. MALDI-ToF spectra of p(NAPA) NPs.

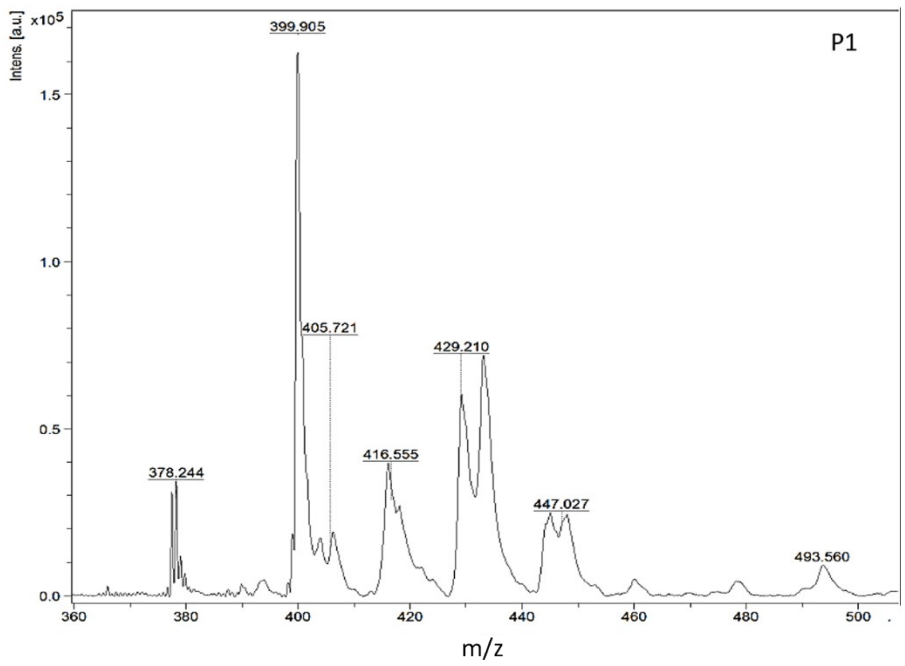

Figure S8. MALDI-ToF spectra of P1 NPs.

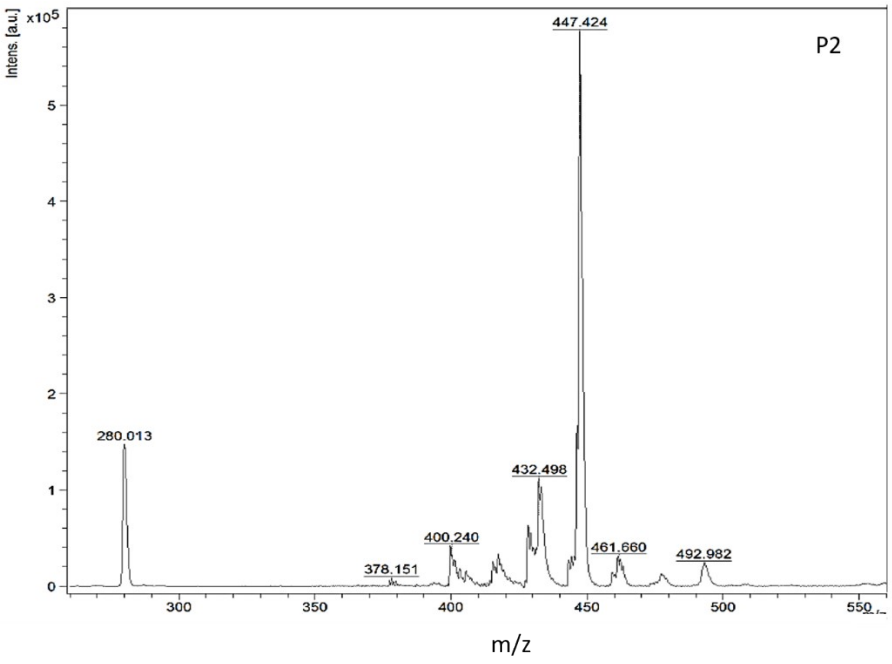

Figure S9. MALDI-ToF spectra of P2 NPs.

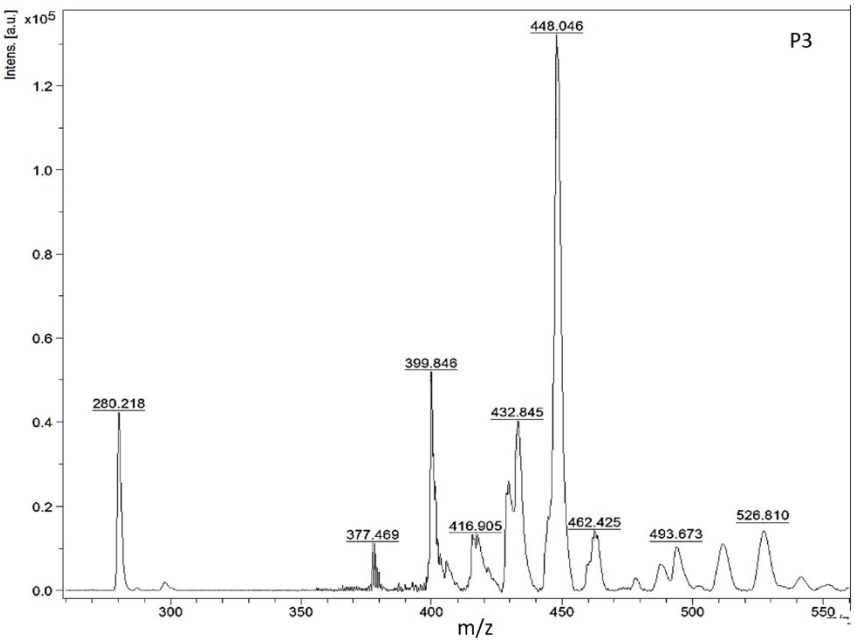

Figure S10. MALDI-ToF spectra of P3 NPs.

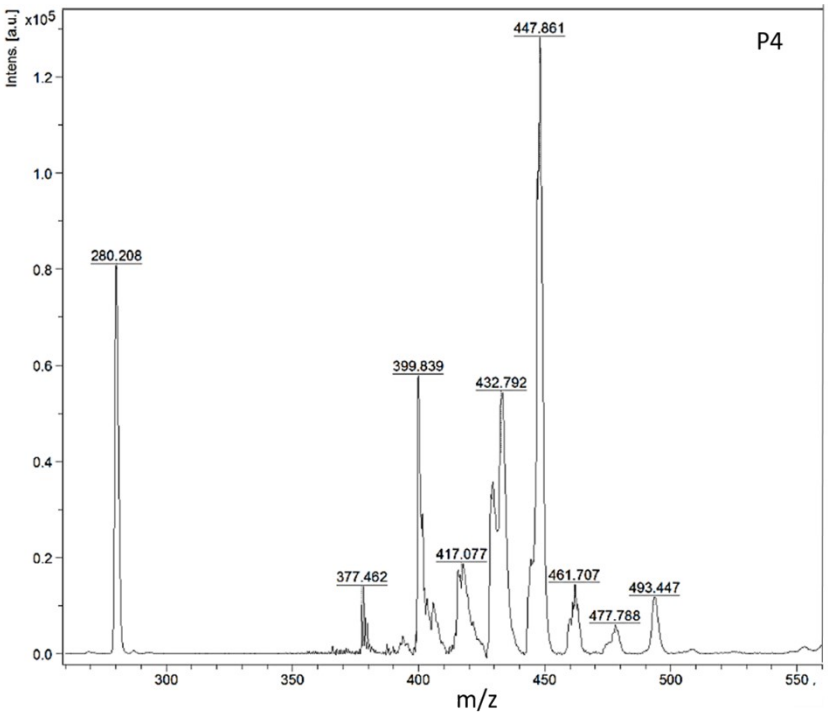

Figure S11. MALDI-ToF spectra of P4 NPs.

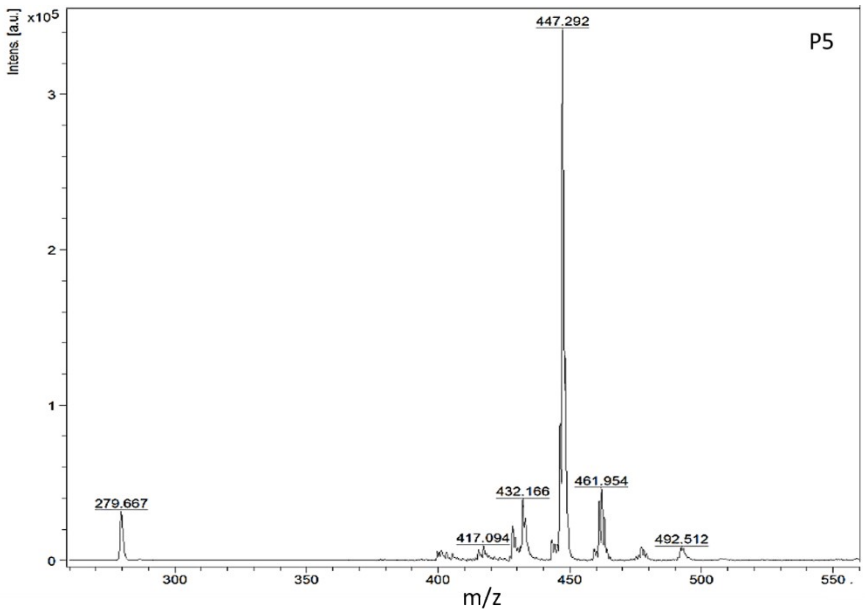

Figure S12. MALDI-ToF spectra of P5 NPs.

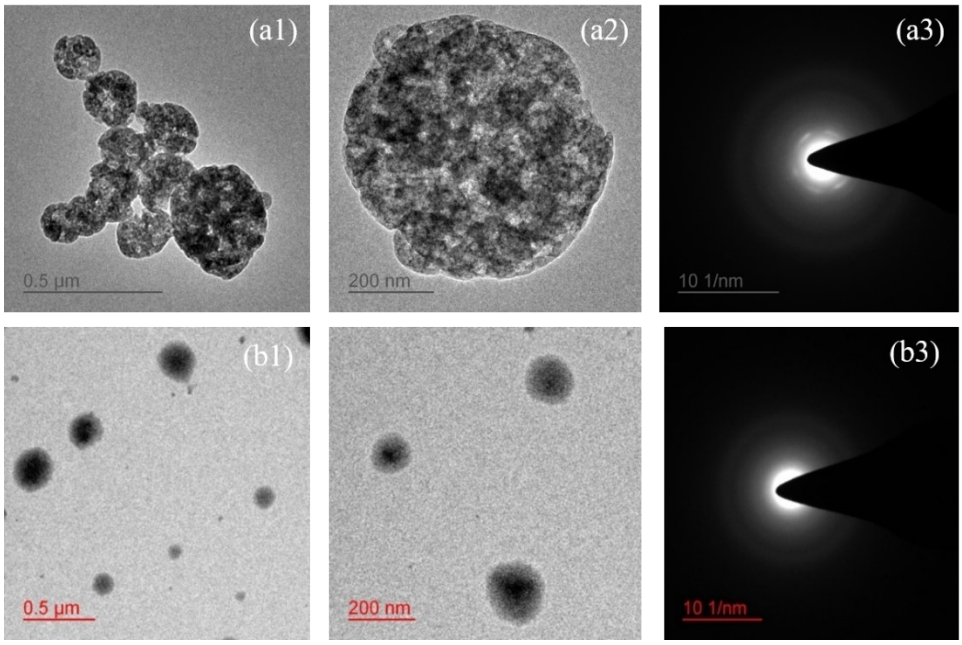

Figure S13. HRTEM images of (a1-a3) p(NAG) and (b1-b3) p(NAPA) NPs.

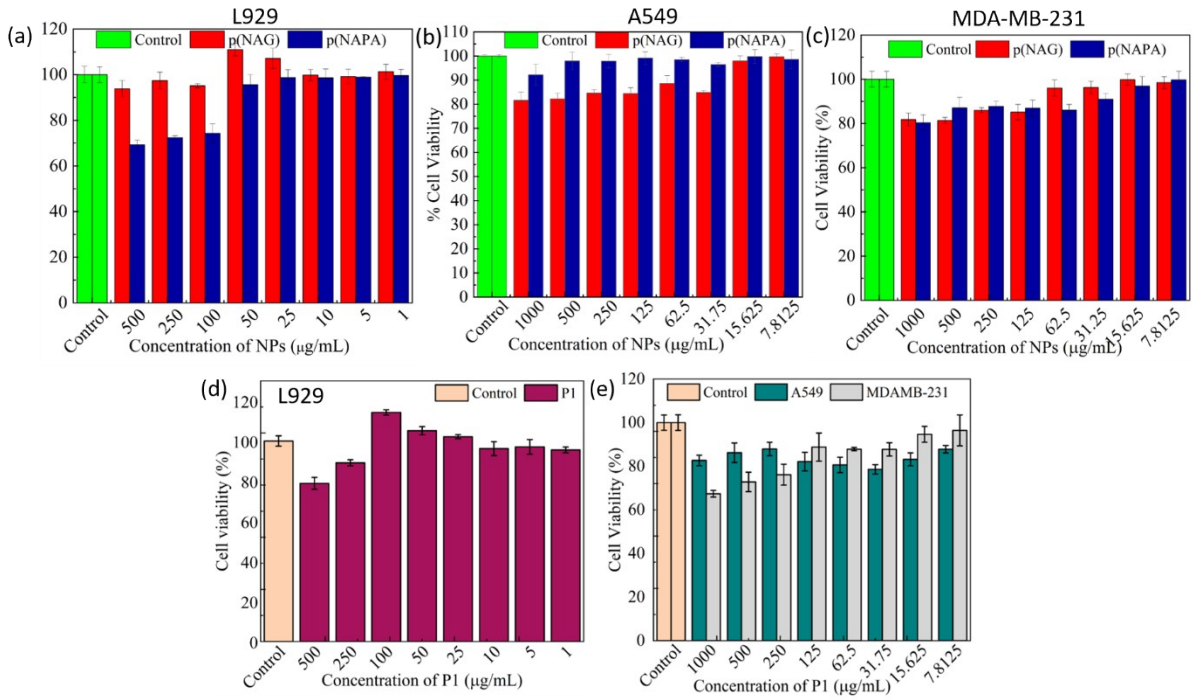

Figure S14. Cytotoxicity study of (a-c) p(NAG) and p(NAPA) NPs against L929, A549 and MDA-MB-231 cells and (d-e) P1 NPs against L929, A549 and MDA-MB-231 cells.

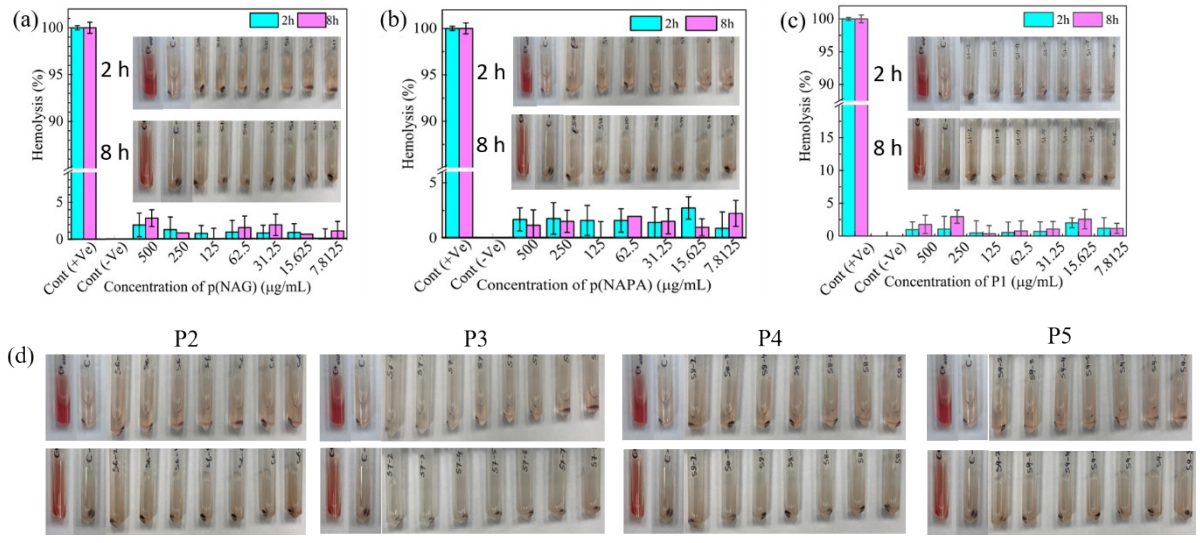

Figure S15. Hemolysis (%) of (a) p(NAG), (b) p(NAPA), (c) P1 NPs and (d) image representation of tubes at 2 and 8 h for P2 to P5 NPs.

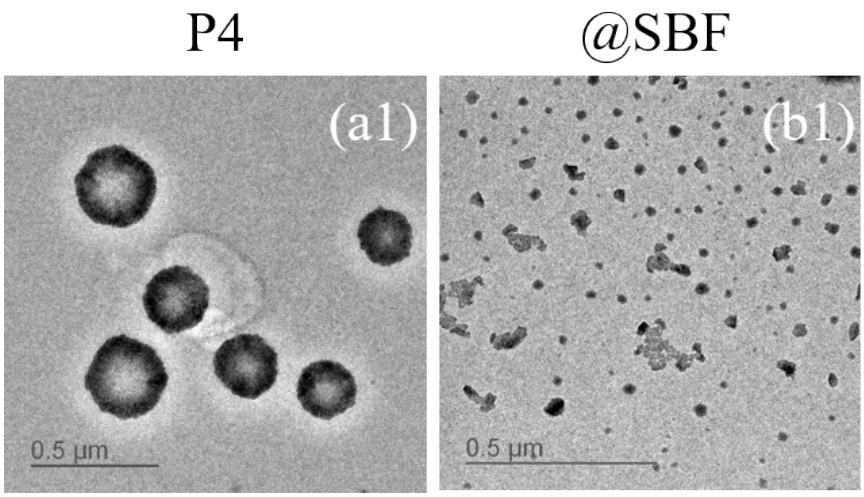

Figure S16. HRTEM micrograph of P4 NP incubated in SBF (pH 7.4). Results shows that after 7 days of incubation the P4 NPs degraded from 180-200 nm to fragments of 10-20 nm in size.

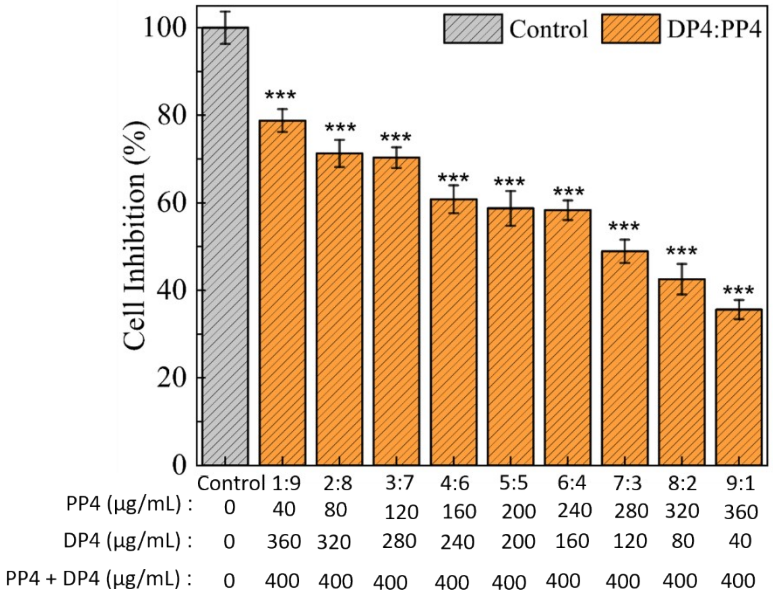

Figure S17. Cell inhibition (%) shown by DP4:PP4 at different ratio. The final concentration is fixed to 400 μg mL^{-1}.

Table S1. List of chains, inhibitors and ions removed from protein structure before docking

Protein Name	**Removal Item**
Caspase-9	Chain A, Zn^{2+}
CDK2	(4-amino-2-{[1-(methylsulfonyl)piperidin-4-yl]amino}pyrimidin-5-yl)(2,3-difluoro-6-methoxyphenyl)methanone
ER α	Chain B, N-[(1R)-3-(4-HYDROXYPHENYL)-1-METHYLPROPYL]-2-(2-PHENYL-1H-INDOL-3-YL)ACETAMIDE
BCL-2	3-nitro-n-{4-[2-(2-phenylethyl)-1,3-benzothiazol-5-yl]benzoyl}-4-{[2-(phenylsulfanyl)ethyl]amino}benzenesulfonamide
CXCR-2	Cl^-
PR	[(8s,11r,13s,14s,17r)-17-acetyl-11-[4-(dimethylamino)phenyl]-13-methyl-3-oxo-1,2,6,7,8,11,12,14,15,16-decahydrocyclopen ta[a]phenanthren-17-yl] acetate
EGFR	FLAVIN-ADENINE DINUCLEOTIDE, NADP NICOTINAMIDE-ADENINE-DINUCLEOTIDE PHOSPHATE, BICINE, caprolactone
β-tubulin	Chain A, TAXOTERE, GUANOSINE-5'-TRIPHOSPHATE, GUANOSINE-5'-DIPHOSPHATE
Bax	NA
p53	NA
C-SRC	Phosphoaminophosphonic acid-adenylate ester, l-peptide linking

HSP90	5-(5-chloro-2,4-dihydroxyphenyl)-n-ethyl-4-[4-(morpholin-4-ylmethyl)phenyl]isoxazole-3-carboxamide
P-glycoprotein	Chain B, (4S,11S,18S)-4,11,18-tri(propan-2-yl)-6,13,20-triselena-3,10,17,22,23,24-hexaazatetracyclo[17.2.1.1~5,8~.1~12,15~]tetracosa-1(21),5(24),7,12(23),14,19(22)-hexaene-2,9,16-trione
AKT1	1-(1-(4-(7-phenyl-1H-imidazo[4,5-g]quinoxalin-6-yl)benzyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one
CXCR4	(6,6-dimethyl-5,6-dihydroimidazo[2,1-b][1,3]thiazol-3-yl)methyl N,N'-dicyclohexylimidothiocarbamate, (2R)-2,3-dihydroxypropyl (9Z)-octadec-9-enoate, Glycerol
VEGF-2	Chain B
HDAC3	Chain A, Chain C, Chain D
mTOR	Chain C, Chain B, RAPAMYCIN IMMUNOSUPPRESSANT DRUG, SULFATE ION
VEGF A	Chain B, TRIETHYLENE GLYCOL, SULFATE ION
CCR5	Chain B, 4,4-difluoro-N-[(1S)-3-{(3-exo)-3-[3-methyl-5-(propan-2-yl)-4H-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl}-1-phenylpropyl]cyclohexanecarboxamide, (2R)-2,3-dihydroxypropyl (9Z)-octadec-9-enoateZn

GSK 3β	Chain B, 4-(2-methoxyphenyl)-3,7,7-trimethyl-1,6,7,8-tetrahydro-5H-pyrazolo[3,4-b]quinolin-5-one, Both L-PEPTIDE LINKING
TGF β1	Chain B
DNMT3B	Chain B, Chain C, Chain D, S-ADENOSYL-L-HOMOCYSTEINE
STAT 3	[(2-{[(5S,8S,10aR)-3-acetyl-8-({(2S)-5-amino-1-[(diphenylmethyl)amino]-1,5-dioxopentan-2-yl}carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl]carbamoyl}-1H-indol-5-yl)(difluoro)methyl]phosphonic acid (non-preferred name)

Table S2. List of % of secondary structures present in different NPs of mini library.

Sample Name	α-helix (%)	β-sheet (%)	Turn	Random Coil (%)
p(NAG)	21.9	0	31.2	46.9
p(NAPA)	0	79.2	0	20.8
P1	0	0	100	0
P2	0	0	71.1	28.9
P3	0	0	77.4	22.6
P4	0	44.6	33.8	23.6
P5	0	0	55.5	44.5

Table S3. Statistical significance of Cytotoxicity study of NPs against L929 cells.

Concentration ($\mu g\ mL^{-1}$)	**L929**						
	p(NAG)	**p(NAPA)**	**P1**	**P2**	**P3**	**P4**	**P5**
500	ns	**	ns	ns	***	ns	**

250	ns	*	ns	ns	**	ns	ns
100	ns	*	ns	ns	**	ns	*
50	ns	ns	ns	ns	***	ns	ns
25	ns	ns	ns	ns	**	ns	ns
10	ns	ns	ns	ns	**	ns	ns
5	ns	ns	ns	ns	**	ns	ns
1	ns	ns	ns	ns	ns	ns	ns
ns: non-significant							

Table S4. Statistical significance of Cytotoxicity study of NPs against A549 cells.

Concentration ($\mu g\ mL^{-1}$)	**A549**						
	p(NAG)	**p(NAPA)**	**P1**	**P2**	**P3**	**P4**	**P5**
1000	ns	ns	ns	ns	**	*	***
500	ns	ns	ns	ns	*	***	**
250	ns	ns	ns	ns	*	ns	**
125	ns	ns	*	ns	ns	ns	ns
62.5	ns	ns	*	ns	ns	ns	ns
31.25	ns	ns	*	ns	ns	ns	ns
15.625	ns	ns	ns	ns	ns	ns	ns
7.8125	ns	ns	ns	ns	ns	ns	ns
ns: non-significant							

Table S5. Statistical significance of Cytotoxicity study of NPs against MDA-MB-231 cells.

Concentration	**MDA-MB-231**

(μg mL^{-1})	p(NAG)	p(NAPA)	P1	P2	P3	P4	P5
1000	***	ns	**	ns	*	ns	ns
500	***	ns	*	ns	*	ns	ns
250	ns	ns	*	ns	ns	ns	ns
125	*	ns	ns	ns	ns	ns	ns
62.5	ns	ns	ns	ns	ns	ns	ns
31.25	ns	ns	ns	ns	ns	ns	ns
15.625	ns	ns	ns	ns	ns	ns	ns
7.8125	ns	ns	ns	ns	ns	ns	ns
ns: non-significant							

Table S6. Statistical significance of Hemolysis study of NPs at 2 h and 8 h.

Concentration (μg mL^{-1})	Hemolysis													
	p(NAG)		p(NAPA)		P1		P2		P3		P4		P5	
	2 h	8 h	2 h	8 h	2 h	8 h	2 h	8 h	2 h	8 h	2 h	8 h	2 h	8 h
500	ns	ns	ns	ns	ns	***	ns	ns	***	***	ns	ns	ns	ns
250	ns	ns	ns	ns	ns	ns	ns	*	***	**	ns	ns	ns	ns
125	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
62.5	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
31.25	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
15.625	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	*	ns	*
7.8125	ns	ns	ns	ns	ns	ns	*	ns	ns	ns	ns	ns	ns	ns
ns: non-significant														

Table S7. List of proteins with their respective PDB ID considered for individual docking with ligands (piperine and DHA) and their binding energy, inhibition constant and amino acid residues.

Protein Name	PDB ID	Ligand	Binding Energy (kcal/mol)	Inhibition Constant (μM)	Amino acid residues
Bax	1f16	DHA	-6.17	30.25	Glu44, Leu125, Ala35, Leu45, Asp48, Gln32, Ala42, Pro43
Bax	1f16	Piperine	-7.92	1.57	Trp151, Leu 148,Arg147,Arg109, Asn106, Phe105, Met99, Gly103, Asn104, Asp102,Phe100
CASPASE-9	1nw9	DHA	-7.77	2	Pro336, Thr337, Leu275, Gly276, Lys280, Gly269, Phe267, Asn268, Pro338, Ile341, Ser339
CASPASE-9	1nw9	Piperine	-6.62	14.14	Pro336, Leu335, Lys280, Phe267, Asn268, Ile341, Val264, As265, Pro338, ser339, Thr337
Tubilin	1tub	DHA	-9.89	56.26	Gln43, Ile24, Glu22, Phe83, Val78, Gly84, Ile86, Ala65, Trp21, Leu44, Pro63, Ser25
Tubilin	1tub	Piperine	-10.58	0.01746	Gln8, Phe83, Ile24, Gly58, Pro63, asn59, Arg48, Tyr61, Ser25, Lys60, Glu47, Val162, Gln43, Trp21, Leu44, Val178, Ala18, gly17
p53	1ycr	DHA	-7.76	2.06	Gln59, Phe55, Leu54, Leu26, Trp23, Lys24, Met62
p53	1ycr	Piperine	-6.93	8.32	Met62, Ser20, Trp23, Lys24, Glu28, Leu26, Leu54, Lys51, Phe55, Gln59
CDK2	2fvd	DHA	-7.5	3.2	Gly16, Lys33, Asp145, Thr14, Tyr15, Gly13
CDK2	2fvd	Piperine	-9.31	0.15	Phe82, Ala31, Ala144, Leu134, Lys89, His84, Leu83

Er Alpha	2iok	DHA	-8.37	0.728	Phe445, Pro324, Glu353, Pro325, Ile326, Trp393, Arg394, Gly390, Ile386, Lys449
Er Alpha	2iok	Piperine	-8.43	0.663	Gly420, Met421, Leu428, Ile424, Arg394, Phe404, Leu391, Leu387, Glu353, Met388, His 524, Gly521
Bcl-2	2o21	DHA	-7.38	3.9	Glu149, Phe101, Phe109, Met112, Glu133, Val130, Phe150, Val131, Leu134, Ala146
Bcl-2	2o21	Piperine	-7.26	4.76	Leu94, Trp192, Phe194, Gly191, Trp141, Asn189, Leu198, Ala194, Leu182, Ile144, Ile186
C-SRC	2src	DHA	-7.34	4.13	Lys458, Leu360, Leu363, Thr456, Pro488, Cys487, Glu486, Leu358
C-SRC	2src	Piperine	-6.89	8.83	Met341, Leu393, Val281, Cys277, Gly276, Arg388, Leu273, Ala293
HSP90	2vcj	DHA	-6.07	35.74	Thr109, Gly108, Leu107, Lys58, Ile96, Gly97, Ala55, Thr184, Met98, Asn51
HSP90	2vcj	Piperine	-7.07	6.53	Thr184, Met98, Asn51, Thr109, Gly108, Gly135, Leu107, Val186, Phe138, Leu48
P-glycoprotien	3g61	DHA	-5.67	69.4	Gln326, Val732, Phe310, Ile214, Leu210, Thr314, Ile318, Tyr322, Trp311
P-glycoprotien	3g61	Piperine	-8.05	1.25	Phe263, Thr259, Val253, Val260, Leu793, Met792, Phe789, Leu254, Ala255, Phe1119, Ala256
AKT1	3o96	DHA	-8.23	0.93	Ile290, Thr211, Thr291, Asp292, Leu210, Ala212, Ser205, Leu213, Val270, Trp80, Leu264
AKT1	3o96	Piperine	-6.09	34.64	Cys296, Thr160, Lys158, Leu295, Val164, Leu156, Phe293,Gly157,

					Glu298, Gly159, Lys297
CXCR4	3oe6	DHA	-6.64	13.49	Ala303, Gly55, Pro299, Val59, Val62, Tyr302, Leu305
CXCR4	3oe6	Piperine	-6.92	8.51	Leu69, Gln66, Met63, leu58, val159, pro299, gly55. ala303, val62, Asp74, Tyr302
VEGFR-2	3v2a	DHA	-6.28	25.04	Gln210, Ala202, Tyr209, Glu201, Val159, Trp179, Leu151, Cys150, Cys200, Ser211
VEGFR-2	3v2a	Piperine	-5.86	50.25	Ile212, Pro149, Leu151, Cys150, Ala202, Val159, Trp179, Tyr209, Gln210, Glu201, Ser211, Tyr214
HDAC3	4a69	DHA	-6.27	25.25	Ala20, Phe144, Gly21, Pro23, Asp93, Asp92, His22, Tyr18, Pro95
HDAC3	4a69	Piperine	-8.41	0.683	Asp259, Leu266, Phe144, Tyr298, Met24, GLY296, Cys145, Gly143, Gly132, Gly295, His135, Leu133, Gln255, Asp175, Asp168, His134, His172, Asp170, Phe200, Asp93
mTOR	4drh	DHA	-6.59	14.83	Tyr113, Val186, Phe77, Gln85, Ile87
mTOR	4drh	Piperine	-7.48	3.28	Phe2108,Leu2031,Trp2101, Ser2035, Leu2097, The2098, Phe2039, Asp2102, Tyr2105, Glu2032
CxCR2	4jl7	DHA	-7.1	6.24	Arg80, Ile79, Tyr24, Phe26, Gly25, Gly23, Lys19, Asn22
CxCR2	4jl7	Piperine	-7.03	7.08	Glu43, Asn22, Gly25, Phe26, Try24, Gly23, Ile79, Arg80, His27
VEGF-A	4kzn	DHA	-5.63	74.2	Glu42, Met94, Tyr39, Ser95, Glu93, Arg82, Phe47
VEGF-A	4kzn	Piperine	-6.77	10.87	Pro40, Glu42, Tyr39, Asn75, Leu97,

					Glu38, Asp41
CCR5	4mbs	DHA	-6.17	29.88	Tyr37, Glu283, Tyr108, Trp86
CCR5	4mbs	Piperine	-7.45	3.45	Trp248, Tyr108, Glu283, Phe109, Trp86, Tyr37, Tyr251, Phe112
PR	4oar	DHA	-7.96	1.46	Met756, Met759, Arg766, Leu763, Phe778, Leu721, Gln725, Leu718, Gly722, Leu887, Val760, Met801
PR	4oar	Piperine	-8.18	1.01	Arg766, Leu763, Met759, Val760, Met756, Leu887, Met801, Leu797, Tyr890, Thr894, Cys891, Phe778, Leu721, Gln725
EGFR	4rg3	DHA	-8.11	1.14	Asp39, Ala142, Gly15, Val143, Phe38, Lys40, Ile14, Asn388, Ser147, Trp50, Gly46
EGFR	4rg3	Piperine	-9.24	0.169	Thr110, val112, Glu111, Gly46, Thr47, Gly144, Phe18, Ile441, Gly19, Ala142, Asp39, Gly15, Lys40, Phe38, Ile14
GSK3 Beta	5hlp	DHA	-7.05	6.84	Pro136, Val135, Tyr134, Ala83, Leu132, Asp133, Cys199, Leu188, Thr138
GSK3 Beta	5hlp	Piperine	-5.39	111.69	Gln99,Lys94, Asn95, Asp90, Phe93, Gln89, Val126, Tyr177, Leu98, Arg102
TGF-Beta1	5vqp	DHA	-5.71	65.53	Leu51, Val48, Thr55, Tyr52, Lys77, Glu78, Val79
TGF-Beta1	5vqp	Piperine	-8.04	1.28	His222, Arg215, Ile221, Tyr92, Val85, Tyr103, Ile91, Phe105, Asn89, Thr87, Glu86, His88
DNMT3B	6kdl	DHA	-7.83	1.83	Arg832, Cys651, Glu697, Ser833, Trp834, Asp582, Gly583, Phe581, Glu605, Pro650, Gly648, Ser649

DNMT3B	6kdl	Piperine	-9.26	0.162	Arg832, Ser604, Glu605, Val606, Gly648, Val628, Phe581, Asp627, Trp834, Leu671, Ser833, Asp582
Stat3	6njs	DHA	-6.82	9.98	Asp334, Lys573, Asp570, Ile569, Lys574, Arg335, Met331, His332, Pro333
Stat3	6njs	Piperine	-6.15	30.96	Arg609, Pro639, Thr620, Glu638, Ser636, Tyr657, Val637, Glu612, Ser613, Ser611

Table S8. Docking results of 8 selected proteins with combination of ligands (piperine followed by DHA)

Sr. No.	PDB ID	Combination type (Piperine_DHA)				Paclitaxel		
		Binding Energy (kcal/mol)	Inhibition constant (µM)	Amino acid residues		Binding Energy (kcal/mol)	Inhibition constant (µM)	Amino acid residues
				Piperine	DHA			
1	1tub	-7.87	1.69	Gln8, Phe83, Ile24, Gly58, Asn59, Pro63, Arg48, Tyr61, Ser25, Lys60, Glu47, Val62, Gln43, Trp21, Leu44, Val78, Ala18, Gly17	Leu371, Ser232, His229, Phe272, Leu230, Ala233, Leu217, Leu275, Thr276, Pro274	-6.24	26.47	Thr314, Pro261, Val260, Phe262, Pro263, Arg264, Glu431, Tyr435, Trp346, Ile347
2	4jl7	-6.58	15	Asn22, His27, Gly25, DHA, Ile79, Phe26, Arg80, Gly23, Tyr24, Glu43	His27, PIP, Phe26, Arg80, Leu28, Val176, His72	-4.81	300.48	Phe26, Gly25, Arg80, Ile79, Val76, His72, Gis29, Gly30, His27, Arg40, Leu28, Gly23, Tyr24
3	1nw9	-7.09	6.32	Pro336, Leu335, Lys280, Phe267, Asn268, Ile341, Val264, Asn265, Pro338, Ser339, Thr337	Lys414, Arg146, Thr415, Phe413, Try153, Phe412, Leu155, Ser156	-6.83	9.89	Thr347, Gly395, phe348, Ile396, Pro349, Trp354, phe351, Gly350, Arg355, Lys398, arg178, Leu177, Gly176, His237, Cys287, Gly288
4	2o21	-7.47	3.37	Leu94, trp192, Phe195, Gly191, Trp141, Asn189, Leu198, Ala194,	Ala146, Glu149, Leu134, Phe150,	-5.3	129.56	Arg143, tyr105, Gly142, tyr199, Ala97, Gln96, Thr93, Pro201,

				Leu182, Ile144, Ile186	Val130, Val131, Glu133, Met112, Phe109, Phe101			Asp100, Val145, Phe101, Arg104
5	4oar	-7.15	5.69	Gln725, Phe778, Leu721, Met759, DHA, Thr894, Leu797, Leu887, Cys891, Tyr890, Met801, Val760, Met756, Arg766, Leu763	PIP, Trp755, Gly722, leu726, Met759, Glu723, Asn719, Leu718	-2.63	11780	Gln752, Ile751, Trp755, Gln916, Asn719, Ala915, Phe895, Leu726, Val730
6	2iok	-8.22	0.94	Glu353, Met421, Gly420, Gly521, His524, Arg394, Leu391, Leu387, Met388, Phe404, Ile424, Leu428	Glu353, Leu327, Pro325, Ile326, try393, Arg394, Phe445, Gly390, lys449, Pro324, Ile386	-4.29	716.79	Leu536, Glu380, Ala350, Trp383, Leu354, Thr347, Asp351, Val355, Leu539, Pro535, Tyr526, Lys529, Met528, Leu525
7	4rg3	-7.44	3.5	Thr110, Val112, Glu111, Gly46, Thr47, Gly144, Phe18, Ile441, Gly19, Ala142, Asp39, gly15, Lys40, Phe38, Ile14	Thr60, tyr65, Phe248, Thr47, ser58, Asp59, Leu57, Arg329, trp48	-1.84	44580	His166, Trp50, Lys40, Arg52, Asp42, Tyr49, Glu172, Pro171, Trp170, Ala169, Thr164, phe151
8	2fvd	-7.89	1.64	Ala31, Ala144, Leu134, Lys89, His84, Leu83, Phe82	Lys33, Gly16, Asp145, Gly13, Tyr15, Thr14	-4.76	326.45	Ile10, Glu12, Gly11, Gln131, Asn132, Glu162, Lys88, Asp86, Lys89, Asp92

Table S9. Docking results of 8 selected proteins with combination of ligands (DHA followed by piperine)

Sr. No.	**PDB ID**	**Combination type (DHA_piperine)**				**Paclitaxel**		
		Binding Energy (kcal/mol)	**Inhibition constant (µM)**	**Amino acid residues**		**Binding Energy (kcal/mol)**	**Inhibition constant (µM)**	**Amino acid residues**
				DHA	Piperine			
1	1tub	14.53	--	Pro63, Leu44, Ser25, Ile24, Gln43, Glu22,	Asn206, Leu209, Ile16, Val231, Gln8, Phe20, Gln136, Leu137, His6,	-6.24	26.47	Thr314, Pro261, Val260, Phe262, Pro263, Arg264,

				Trp21, Val78, Gly84, Phe83, Ile86, Ala65	Trp21, Ile7, Met235, Phe169, Thr138, Ile204, Val171, Ser170			Glu431, Tyr435, Trp346, Ile347
2	4jl7	-7.35	4.12	Ile79, Arg80, PIP, Tyr24, Gly25, Asn22, Phe26, Gly23, Lys19	Val76, DHA, His27, Gly25, Glu43, Asn22, Phe26, Leu28	-4.81	300.48	Phe26, Gly25, Arg80, Ile79, Val76, His72, Gis29, Gly30, His27, Arg40, Leu28, Gly23, Tyr24
3	1nw9	-6.86	9.39	Gly269, Lys280, Asn268, Ile341, Pro338, Phe267, Ser339, Thr337, Pro336, Gly276, Leu275	Cys287, Phe351, Pro357, Thr179, Arg178, Thr181, Ser183, Arg180, Asp186, Ser361	-6.83	9.89	Thr347, Gly395, phe348, Ile396, Pro349, Trp354, phe351, Gly350, Arg355, Lys398, arg178, Leu177, Gly176, His237, Cys287, Gly288
4	2o21	-7.12	6.04	Phe101, Leu134, Glu149, Ala146, Phe150, Val131, Val130, Met112, Glu133, Phe109	Tyr26, Glu27, Asp29, Ser164, Pro165, Trp28, Asp168	-5.3	129.56	Arg143, tyr105, Gly142, tyr199, Ala97, Gln96, Thr93, Pro201, Asp100, Val145, Phe101, Arg104
5	4oar	-7.91	1.59	Met756, Met801, Leu887, Val760, Leu718, Leu763, Gly722, PIP, Gln725, Leu721, Arg766, Phe778, Met759	Phe794, Met801, Leu797, Leu718, Leu726, Gly722, Asn719, DHA, Trp755, Phe778, Met759, Glu723	-2.63	11780	Gln752, Ile751, Trp755, Gln916, Asn719, Ala915, Phe895, Leu726, Val730
6	2iok	-8.09	1.18	Glu353, Pro325, Ile326, Gly390, Trp393, Phe445, lys449, Ile386, Pro324, Arg394	Glu353, Leu391, leu387, Leu346, Met421, Met343, Val418, Met528, His524, Glu419, Gly420, Ile424, Leu349, Phe404, Ala350, Arg394	-4.29	716.79	Leu536, Glu380, Ala350, Trp383, Leu354, Thr347, Asp351, Val355, Leu539, Pro535, Tyr526, Lys529, Met528, Leu525

7	4rg3	-9.24	0.167	Lys40, Ile14, Gly15, Ala142, Phe38, Asp39, Val143, Gly46, Ser147, Trp50, Asn388	Leu437, Thr435, Phe434, Phe507, Leu145, Trp492, Leu146, Phe382, Gly381, Thr189, Gly187, Ser188, Arg329, Phe279	-1.84	44580	His166, Trp50, Lys40, Arg52, Asp42, Tyr49, Glu172, Pro171, Trp170, Ala169, Thr164, phe151
8	2fvd	-9.19	0.183	Thr14, Asp145, Tyr15, Gly16, Lys33, Gly13,	Val64, Ala31, Leu83, Phe82, Leu134, Lys89, Gln85, His84, Val18, Glu81, Phe80	-4.76	326.45	Ile10, Glu12, Gly11, Gln131, Asn132, Glu162, Lys88, Asp86, Lys89, Asp92