Supporting Information.

The critical size of gold nanoparticles for overcoming P-gp mediated multidrug resistance

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Table S1. The hydrodynamic size and Zeta potential of different NanoDDSs.

Drug	Hydrodynamic Size/nm	PDI	Zeta Potential/mV
$AuNPs_{4.1nm}$	35.1 ± 1.6	0.27± 0.11	-20.6±2.1
$AuNPs_{5.4nm}$	42.3 ± 1.2	0.27 ± 0.07	-22.6 ± 1.1
ANS–$AuNPs_{4.1nm}$	86.8 ± 6.9	0.28 ± 0.03	-12.5 ± 2.2
ANS–TAT–$AuNPs_{4.1nm}$	268.3 ± 6.4	0.24 ± 0.03	5.8 ± 0.2
ANS–$AuNPs_{5.4nm}$	118.2 ± 2.2	0.40 ± 0.03	-4.8±1.4
ANS–TAT–$AuNPs_{5.4nm}$	83.8 ± 1.1	0.36 ± 0.03	10.1±1.6
6-MP–$AuNPs_{4.1nm}$	176.8 ± 5.6	0.43±0.04	-13.4 ± 1.5
6-MP–TAT–$AuNPs_{4.1nm}$	213.5 ± 4.3	0.19 ± 0.01	3.2 ± 1.0
6-MP–$AuNPs_{5.4nm}$	148.3 ± 5.5	0.27 ± 0.05	-16.4 ±1.4
6-MP–TAT–$AuNPs_{5.4nm}$	162.3 ± 2.8	0.20 ± 0.05	10.6 ± 1.5

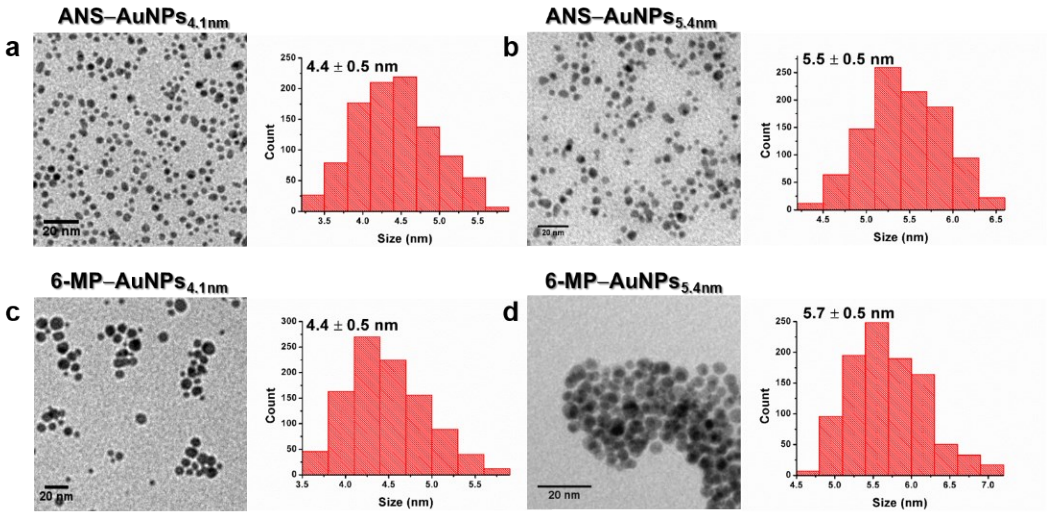

Fig. S1 The images of transmission electron microscopy and distribution of the particle size of corresponding NanoDDSs. (a) ANS–AuNPs$_{4.1nm}$, (b) ANS–AuNPs$_{5.4nm}$, (c) 6-MP–AuNPs$_{4.1nm}$, (d) 6-MP–AuNPs$_{5.4nm}$.

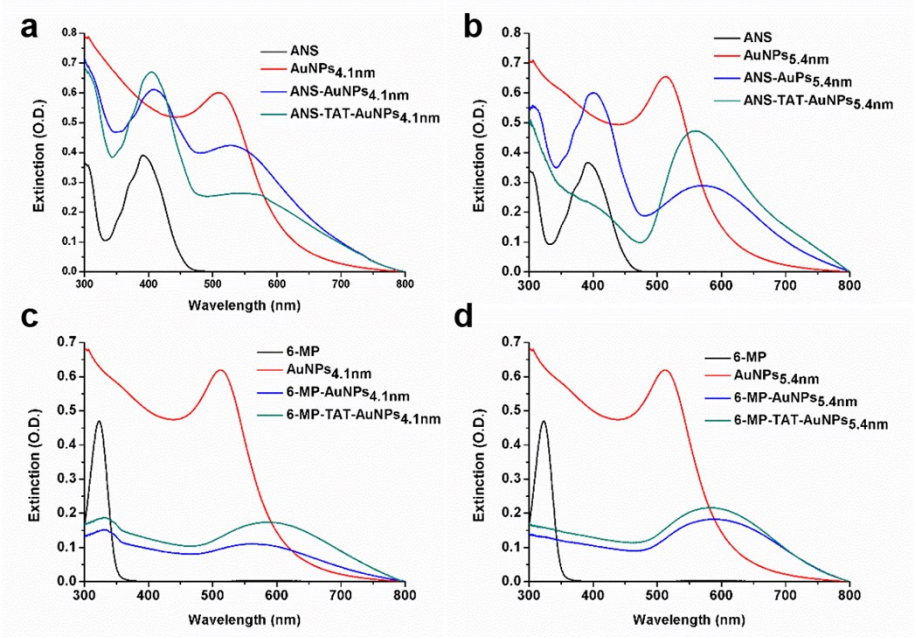

Fig. S2 UV-visible spectrum of different NanoDDSs. (a) ANS–AuNPs$_{4.1nm}$, (b) ANS–AuNPs$_{5.4nm}$, (c) 6-MP–AuNPs$_{4.1nm}$, (d) 6-MP–AuNPs$_{5.4nm}$.

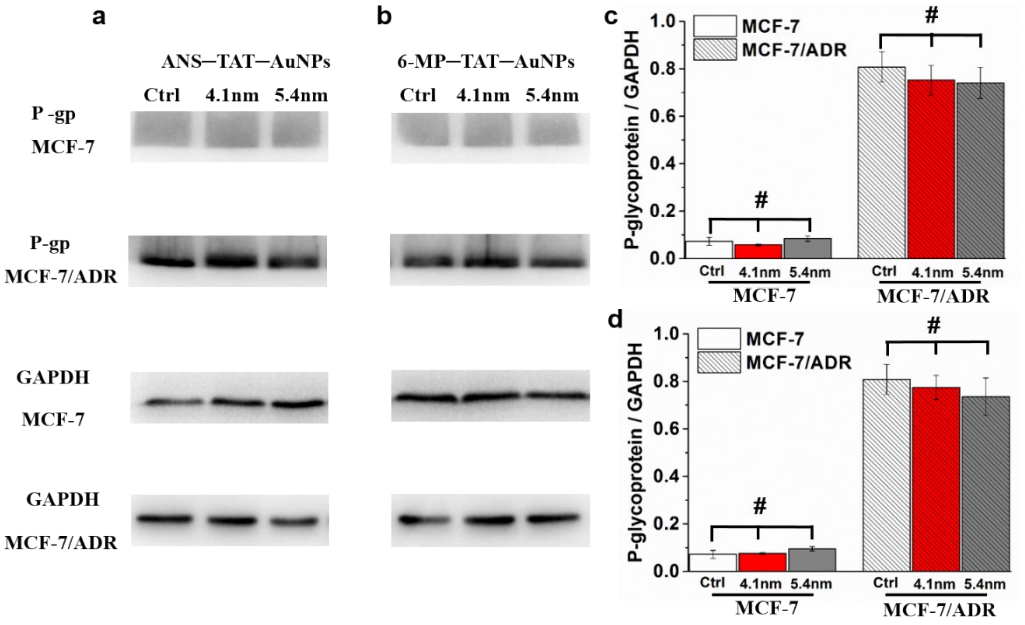

Fig. S3 Statistical analysis of the expression effect of P-gp in MCF-7 and MCF-7/ADR cells expose under different sized (c) ANS–TAT–AuNPs and (d) 6-MP–TAT–AuNPs. Error bars indicate SD (n = 3).

Table S2. UPLC-MS detected metabolites that varied in MCF-7/ADR cell with significant difference (corrected $p < 0.05$).

Metabolite	m/z	Mass Error (ppm)	$AuNPs_{4.1nm}$ vs $AuNPs_{5.4nm}$	p-value (BH corrected)	Class
Galactonic acid[a]	217.0325	-2.27	↓	4.73E-02	Hydroxy acids and derivatives
MG(16:0/0:0/0:0) [a]	367.2269	3.76	↓	6.05E-04	Glycerolipids
MG(22:5(7Z,10Z,13Z,16Z,19Z)/0:0/0:0) [a]	425.2662	-2.78	↓	2.86E-03	Glycerolipids
PA(18:4(6Z,9Z,12Z,15Z)/14:0) [a]	661.3861	1.66	↓	1.64E-02	Glycerophospholipids
PA(P-16:0e/18:2(9Z,12Z)) [a]	677.4533	0.88	↓	2.31E-05	Glycerophospholipids
PC(14:1(9Z)/24:0) [a]	852.5897	0.84	↓	4.16E-03	Glycerophospholipids
PC(P-18:1(11Z)/20:1(11Z)) [a]	818.6060	1.84	↓	5.34E-03	Glycerophospholipids
PE(20:3(5Z,8Z,11Z)/22:0) [a]	862.5758	2.90	↓	1.97E-02	Glycerophospholipids
PE-NMe(14:0/18:4(6Z,9Z,12Z,15Z)) [a]	718.4416	-1.94	↓	2.49E-02	Glycerophospholipids
TG(14:0/16:1(9Z)/22:6 (4Z,7Z,10Z,13Z,16Z,19Z)) [a]	885.6374	-0.74	↓	5.72E-03	Glycerolipids
Cysteinyl-Lysine[b]	297.1909	-2.38	↓	7.63E-04	Carboxylic acids and derivatives
DG(18:4n3/0:0/18:4n3) [b]	653.4133	-3.20	↓	2.37E-02	Fatty Acyls
Galactosyl hydroxylysine[b]	357.1873	1.78	↑	3.29E-06	Fatty Acyls
Hexyl glucoside[b]	297.1909	0.63	↓	7.49E-06	Fatty Acyls
PA(18:3(9Z,12Z,15Z)/20:0) [b]	790.5364	0.92	↑	4.79E-03	Glycerophospholipids
PC(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/16:1(9Z)) [b]	836.5807	0.83	↓	4.75E-02	Glycerophospholipids
PC(P-18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)) [b]	862.5682	-1.87	↓	2.42E-02	Glycerophospholipids
PC(16:1(9Z)/18:4(6Z,9Z,12Z,15Z)) [b]	784.5470	-2.24	↓	2.87E-02	Glycerophospholipids
PC(16:1(9Z)/P-18:1(9Z)) [b]	759.6010	-0.11	↓	1.23E-02	Glycerophospholipids
PC(18:4(6Z,9Z,12Z,15Z)/14:0) [b]	385.7394	1.04	↑	1.73E-03	Glycerophospholipids
PG(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/ 20:3(8Z,11Z,14Z)) [b]	862.5635	4.98	↓	1.30E-02	Glycerophospholipids
PS(16:1(9Z)/15:0) [b]	752.5073	0.12	↓	9.80E-04	Glycerophospholipids

PS(16:1(9Z)/18:1(9Z)) [b]	402.7417	-0.21	↑	1.19E-04	Glycerophospholipids
TG(8:0/12:0/i-12:0) [b]	627.4548	-3.91	↓	5.13E-04	Glycerolipids
2-(acetylamino)-1,5-anhydro-2-deoxy-3-O-b-D-galactopyranosyl-D-arabino-Hex-1-enitol[b]	379.1431	-1.93	↓	3.18E-02	Organooxygen compounds

[a] Metabolites were detected in negative ion mode.

[b] Metabolites were detected in positive ion mode.

[c] Arrows indicate increase (↑) or decrease (↓) in the cells treated with 6-MP–TAT–$AuNPs_{4.1nm}$ compared with that in 6-MP–TAT–$AuNPs_{5.4nm}$.

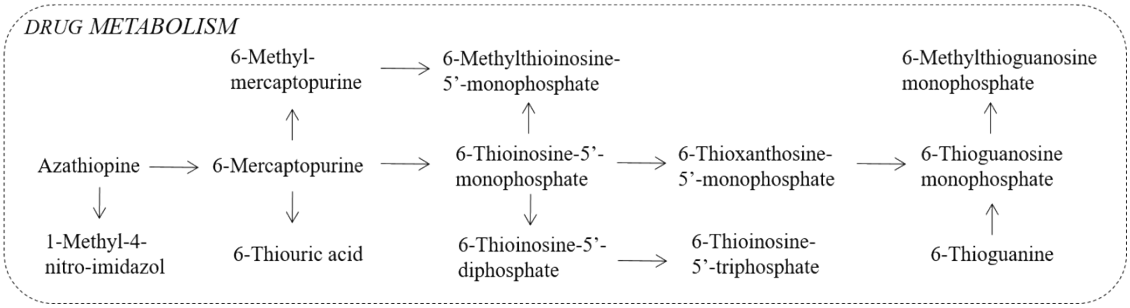

Fig. S4 Metabolic pathway diagram showing altered metabolites of 6-MP.