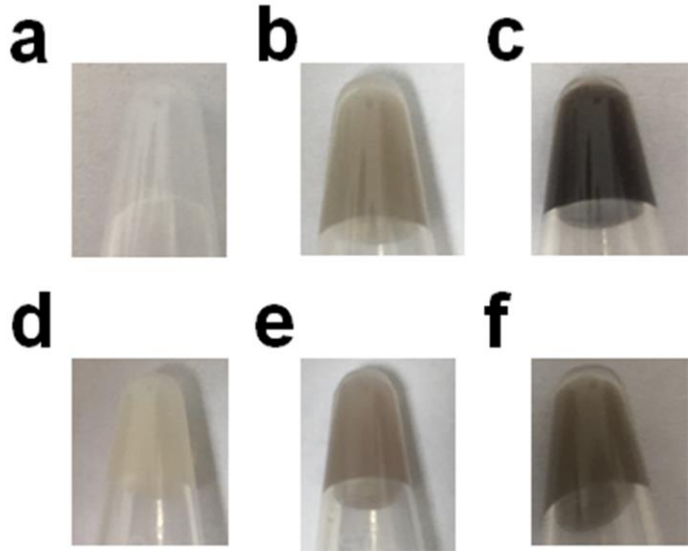
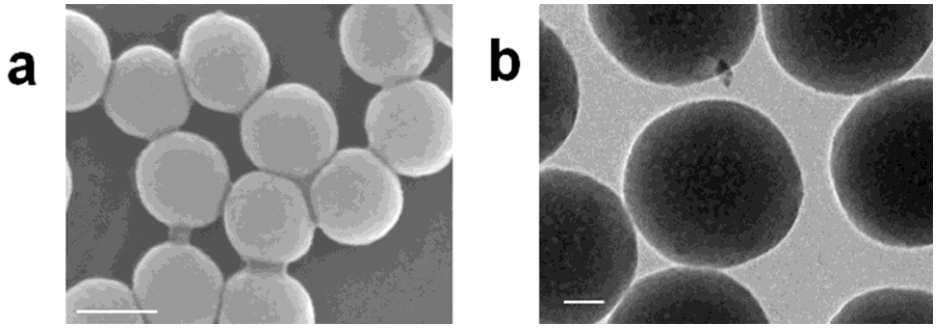
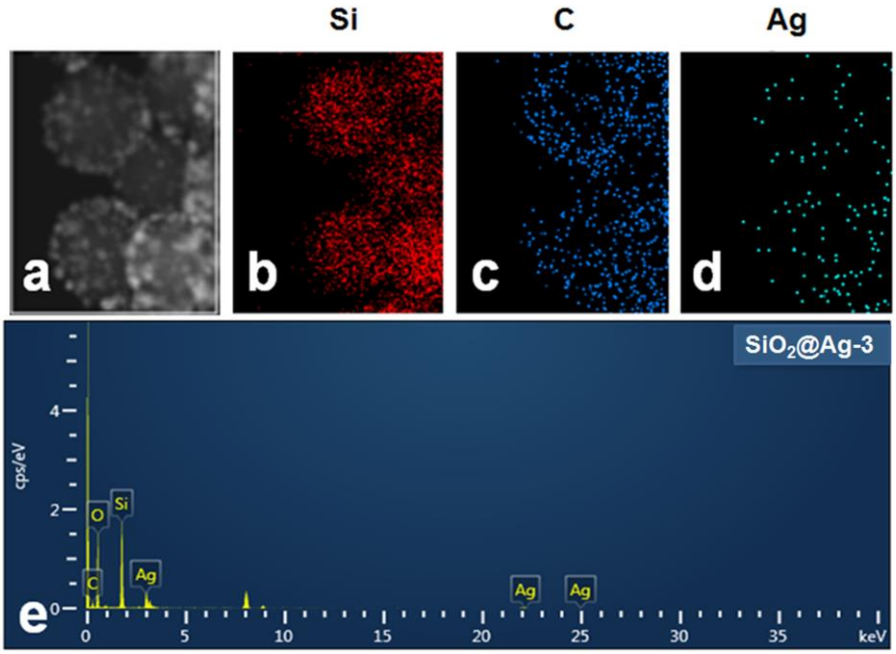
File Name: Supplementary Information
Description: Supplementary Figures and Supplementary Tables



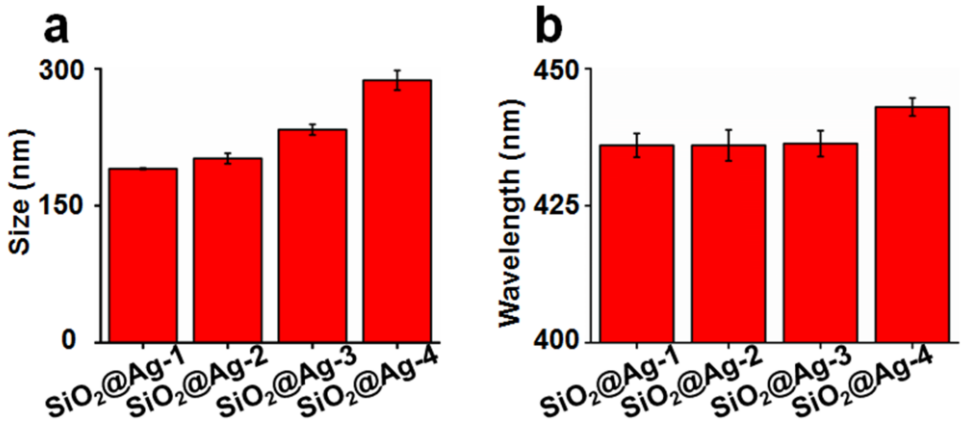
Supplementary Fig. 1. Synthesis conditions for SiO_2@Ag. Digital images recorded of SiO_2@Ag reaction mixtures at a) 30 °C, b) 50 °C, and c) 70 °C for 7 h and at 70 °C for d) 2 h, e) 4 h, and f) 5 h.



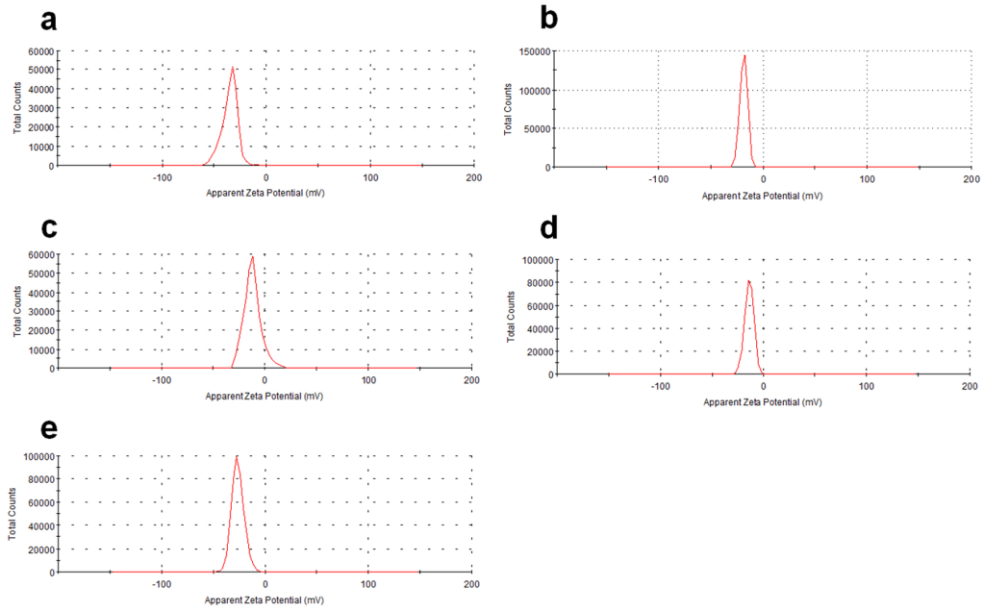
Supplementary Fig. 2. Electron microscopy images of pure silica. a) SEM and b) TEM images of bare SiO_2 particles. Scale bars: a) 150 nm and b) 50 nm.



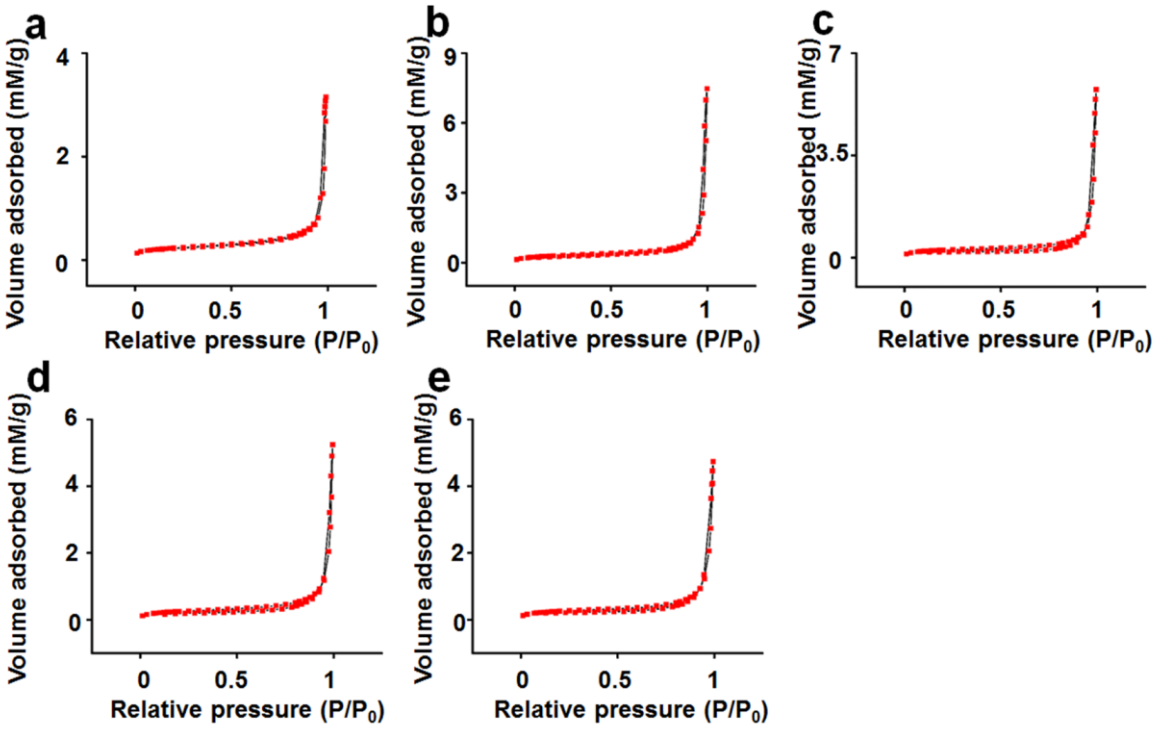
Supplementary Fig. 3. Elemental mapping results. a) scanning transmission electron microscopy (STEM) image and b) silicon, c) carbon, d) silver mappings, and e) typical EDX spectra for nanoshells-metabolites hybrids.



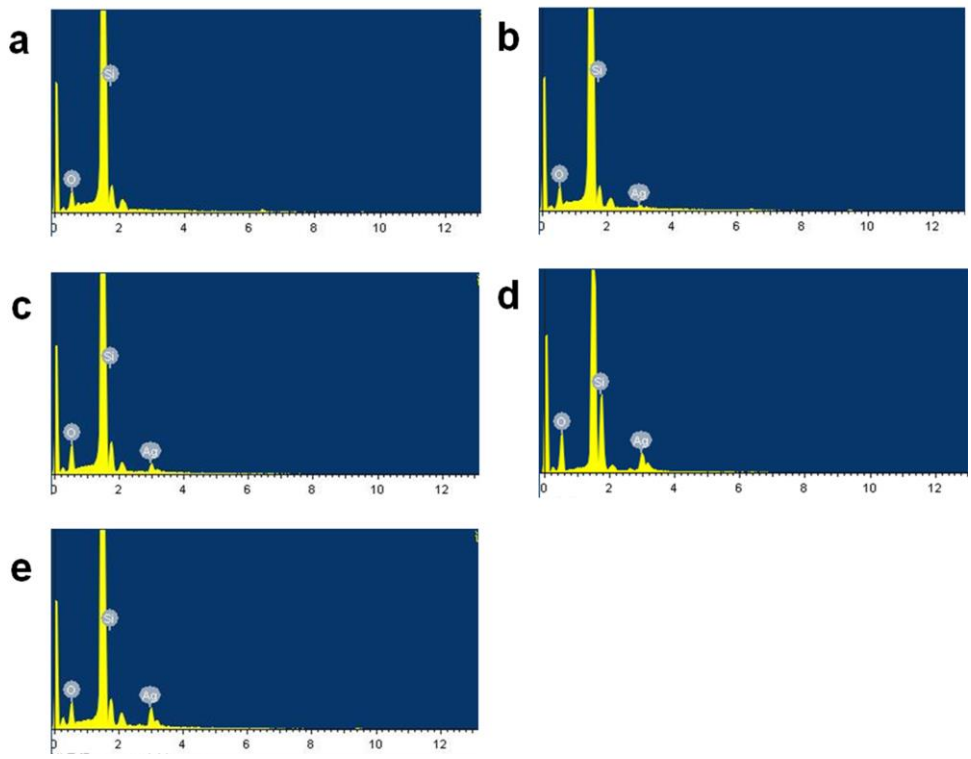
Supplementary Fig. 4. Synthesis reproducibility. a) Average sizes by DLS and b) wavelengths of UV-Vis absorption peaks for three batches of SiO_2@Ag-1/2/3/4 particles. 3 independent experiments were performed to calculate the standard deviation (s.d.) as error bars. Data were shown as the mean ± s.d. (n=3).



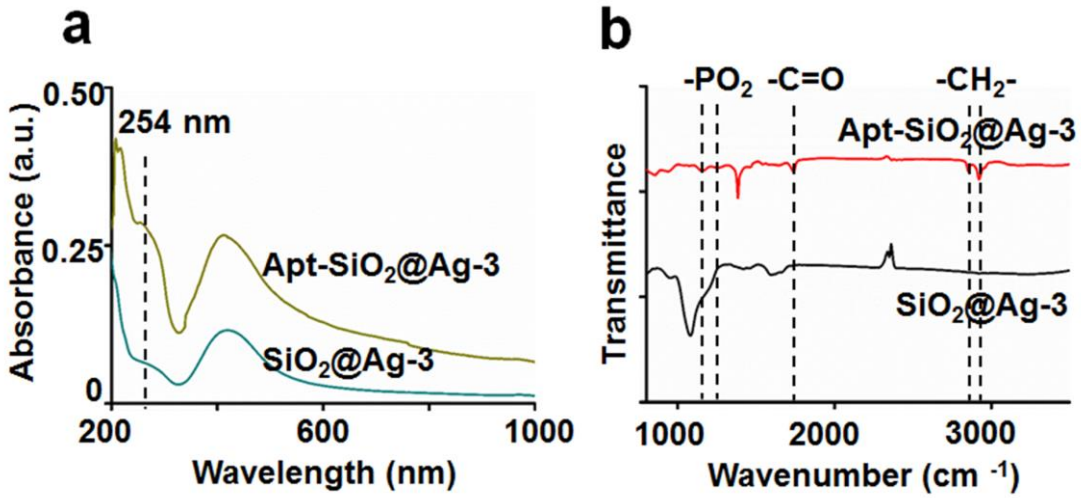
Supplementary Fig. 5. Typical zeta potential distributions of materials. a) SiO_2, b) SiO_2@Ag-1, c) SiO_2@Ag-2, d) SiO_2@Ag-3, and e) SiO_2@Ag-4.



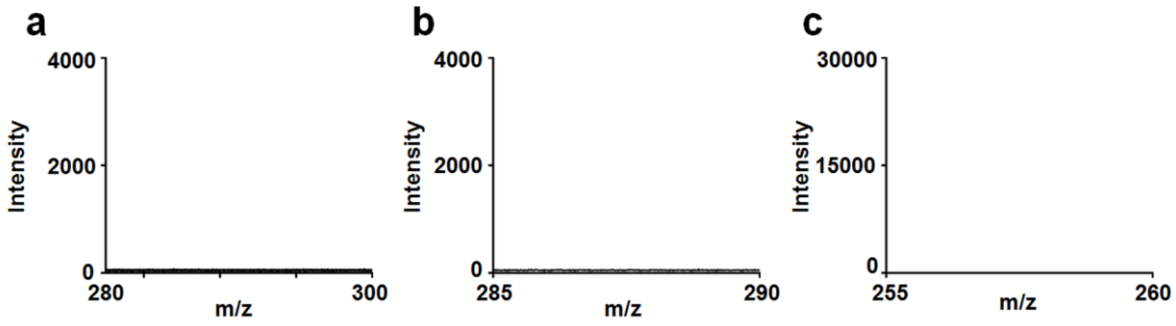
Supplementary Fig. 6. Typical nitrogen adsorption isotherms of materials. a) SiO_2, b) SiO_2@Ag-1, c) SiO_2@Ag-2, d) SiO_2@Ag-3, and e) SiO_2@Ag-4.



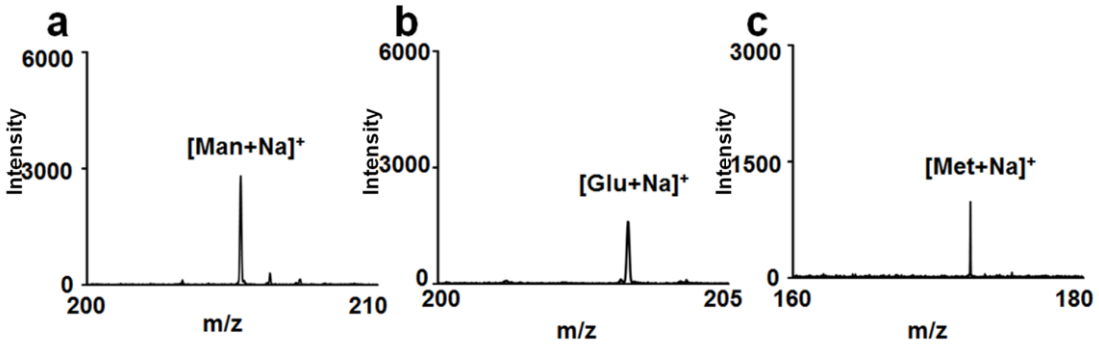
Supplementary Fig. 7. Typical EDX spectra of materials. a) SiO_2, b) SiO_2@Ag-1, c) SiO_2@Ag-2, d) SiO_2@Ag-3, and e) SiO_2@Ag-4.



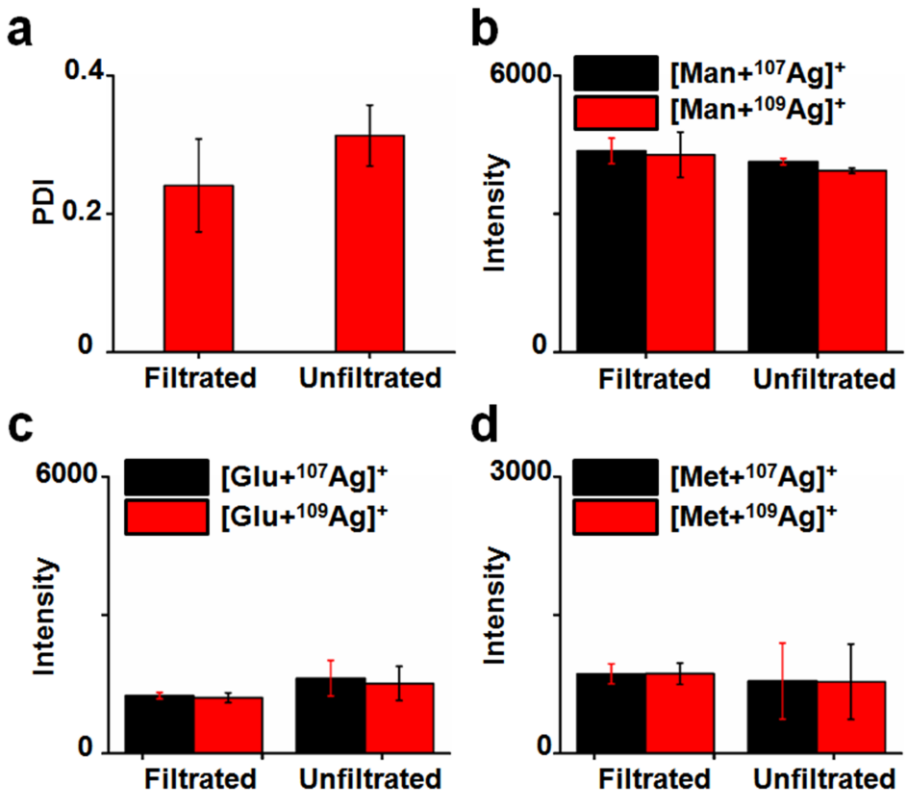
Supplementary Fig. 8. Surface modification of silver nanoshells. a) UV-Vis absorption spectra and b) FTIR spectra of SiO_2@Ag-3 and aptamers modified SiO_2@Ag-3 (denoted as Apt-SiO_2@Ag-3).



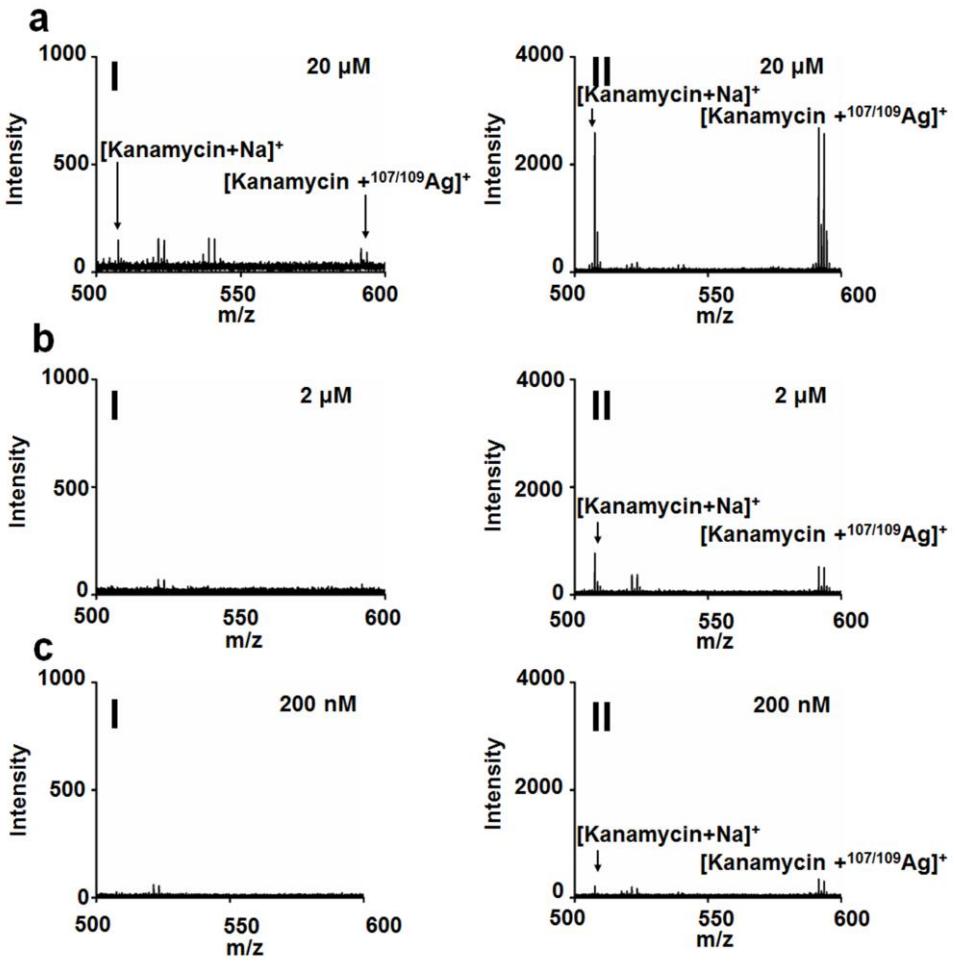
Supplementary Fig. 9. D**etection of small molecules using bare silica.** Mass spectra of 10 ng μL^{-1} a) mannitol, b) glucose, and c) methionine in the positive ion mode using bare SiO_2 particles as matrix.



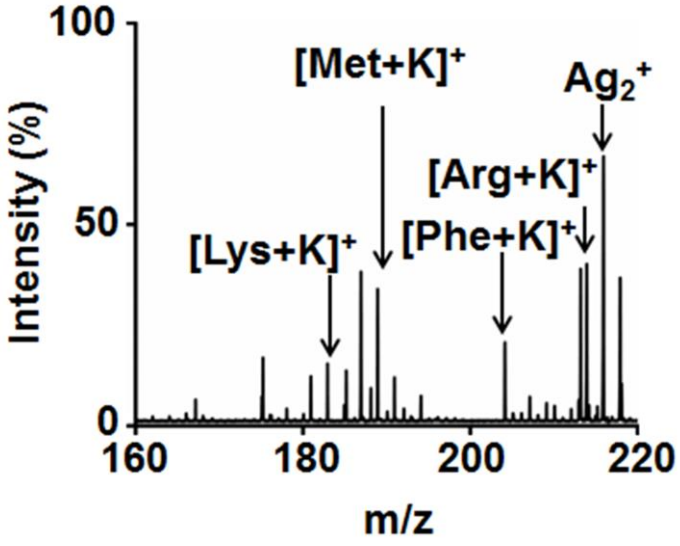
Supplementary Fig. 10. Detection of small molecules using silver nanoshells. Mass spectra of 10 ng μL^{-1} a) mannitol, b) glucose, and c) methionine in the positive ion mode with sodium adducted molecular peaks using SiO_2@Ag-3 as matrix.



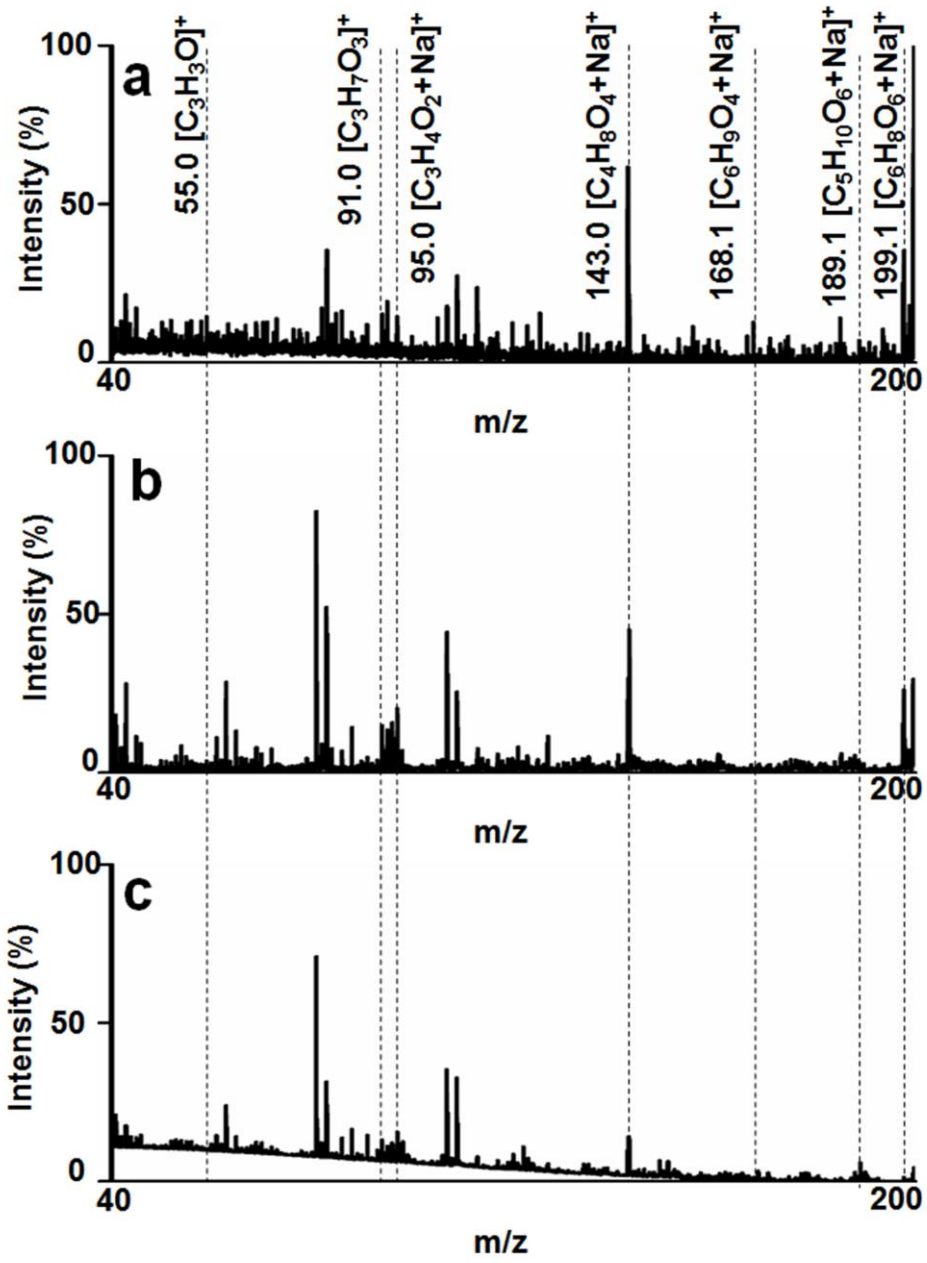
Supplementary Fig. 11. Filtration of particles for use. a) PDI values of SiO_2@Ag-4 before and after filtration by polymer membranes (pore size of 450 nm). Mean intensities of signals for 10 ng μL^{-1} b) mannitol, c) glucose, and d) methionine in the positive ion mode using SiO_2@Ag-4 before and after filtration by polymer membranes (pore size of 450 nm). 3 independent experiments were performed to calculate the standard deviation (s.d.) as error bars. Data were shown as the mean ± s.d. (n=3). The concentrations of all matrices were set as 0.5 mg mL^{-1}.



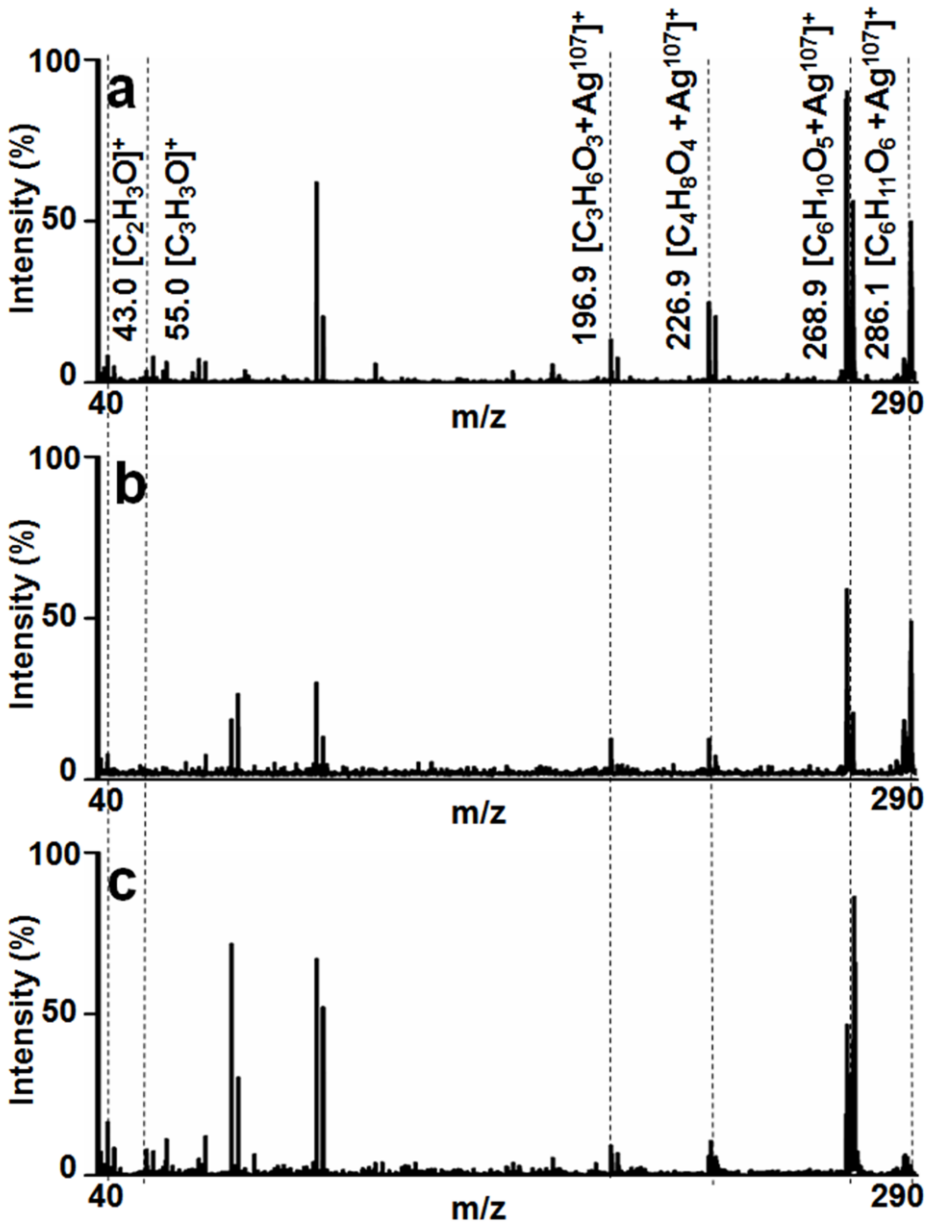
Supplementary Fig. 12. Enrichment and detection of kanamycin. Mass spectra of kanamycin at a) 20 μM, b) 2 μM, and c) 200 nM, I) before and II) after enrichment by Apt-SiO_2@Ag-3.



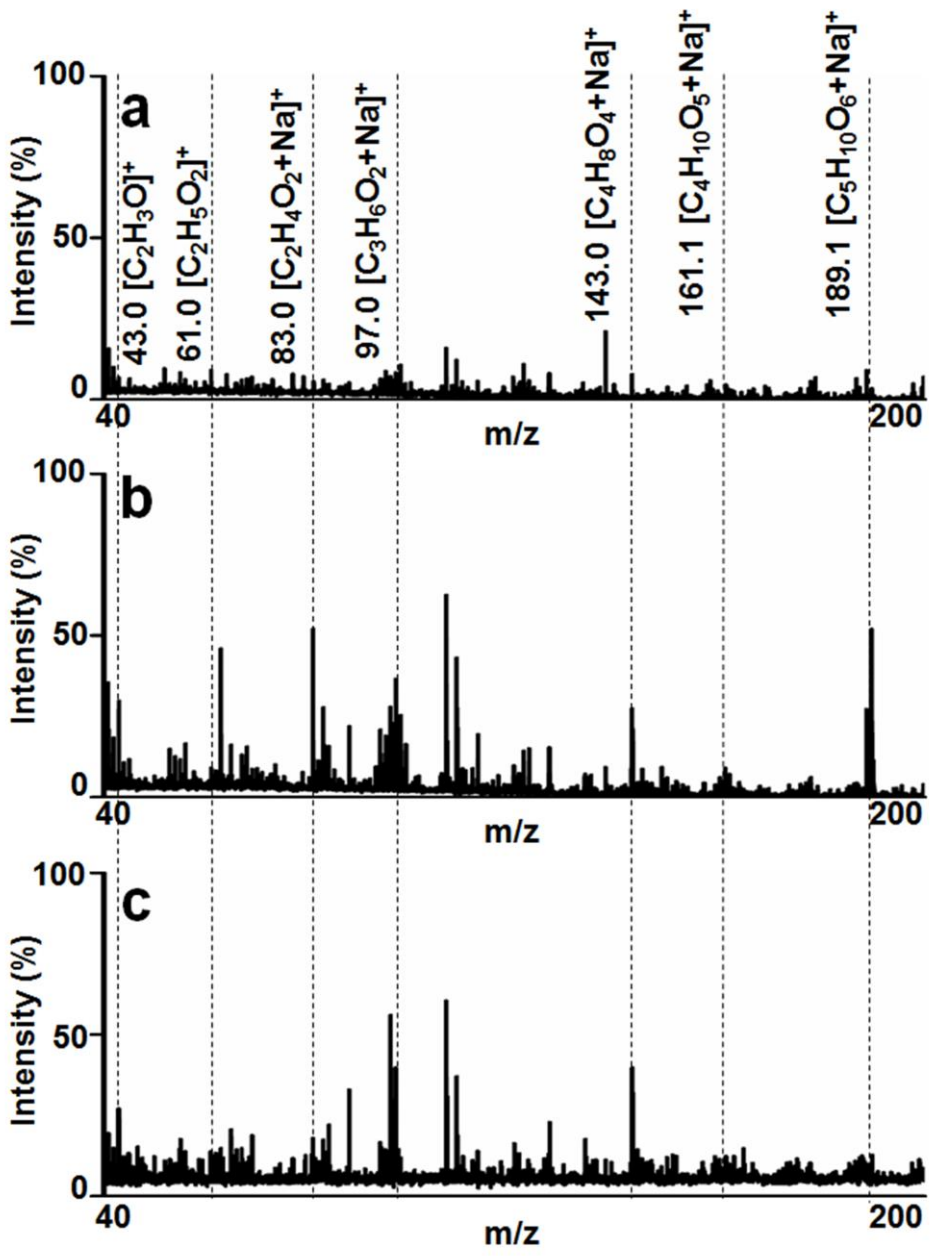
Supplementary Fig. 13. Salt tolerance of silver nanoshells. Mass spectra of 2 nM lysine, methionine, arginine, and phenylalanine in 0.5 M KCl using SiO_2@Ag-3.



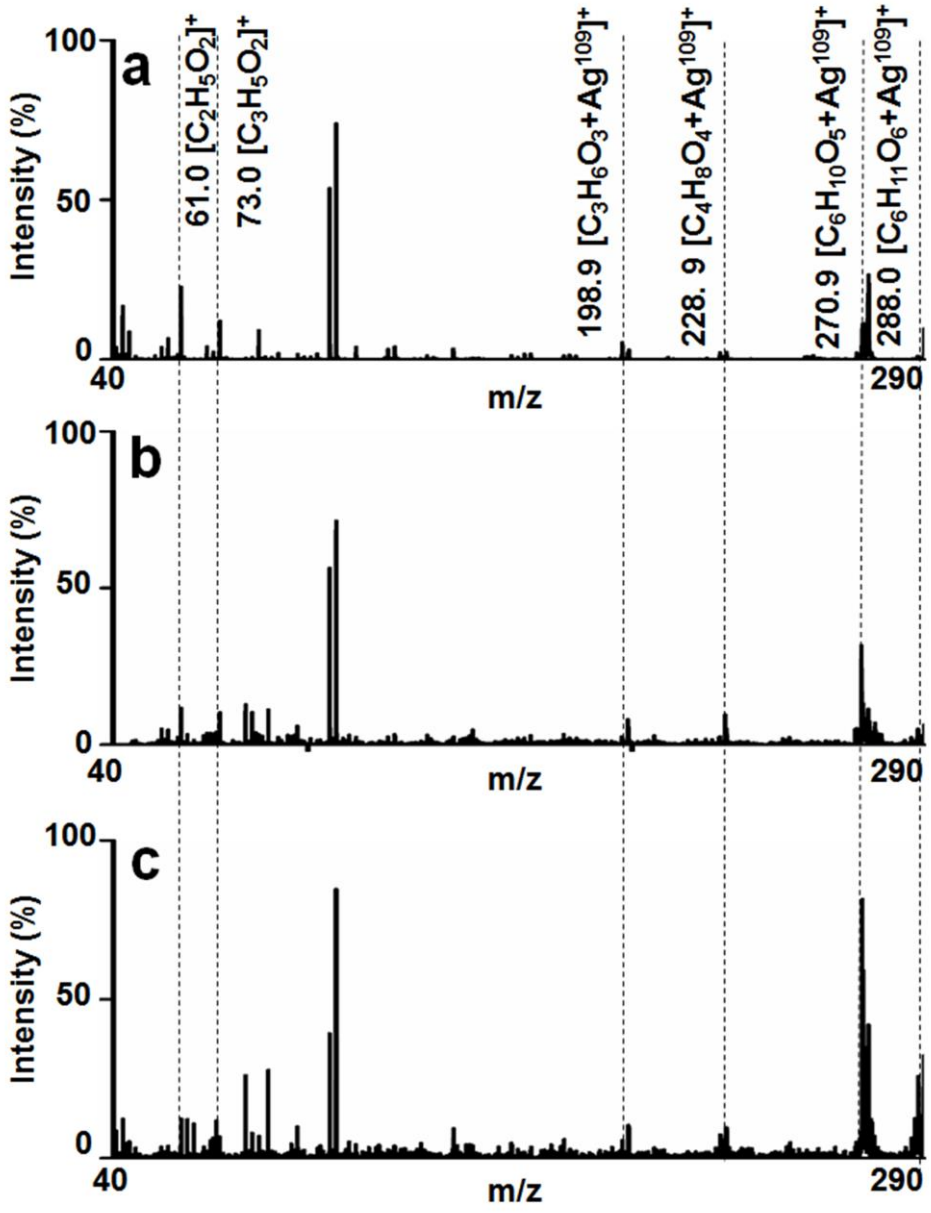
Supplementary Fig. 14. Tandem mass spectra of sodium adducted glucose. MS/MS of glucose at m/z of 203.2 for $[M+Na]^+$ in a) standard sample, b) CSF, and c) serum.



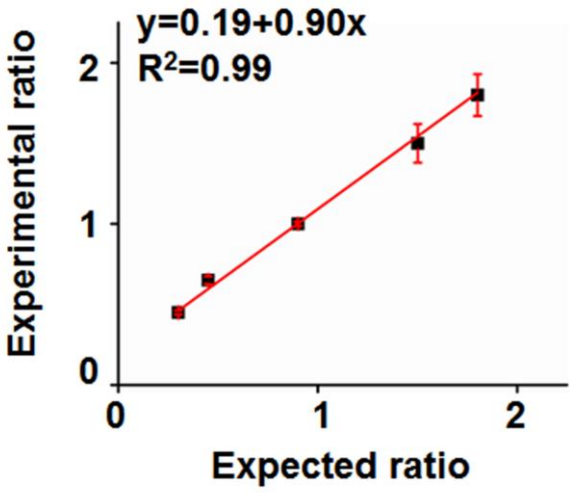
Supplementary Fig. 15. Tandem mass spectra of silver adducted glucose. MS/MS of glucose at m/z of 287.2 for $[M+^{107}Ag]^+$ in a) standard sample, b) CSF, and c) serum.



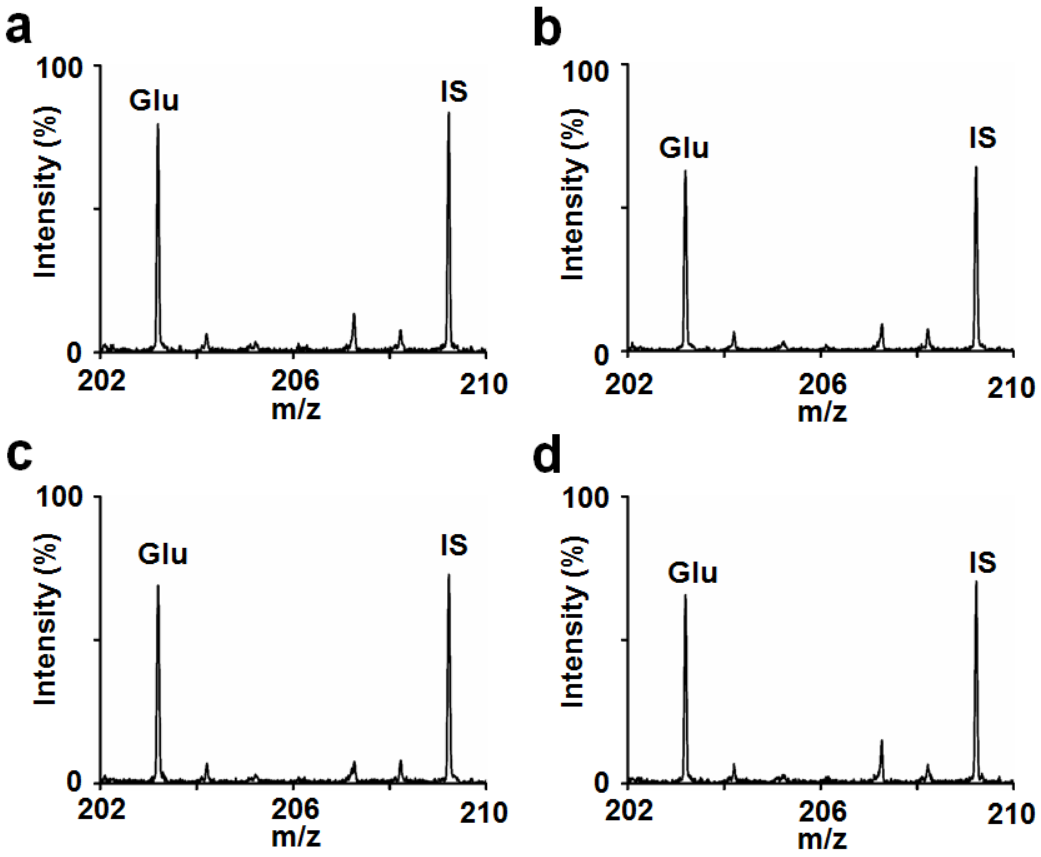
Supplementary Fig. 16. Tandem mass spectra of sodium adducted mannitol. MS/MS spectra of mannitol at m/z of 205.2 for $[M+Na]^+$ in a) standard sample, b) CSF, and c) serum.



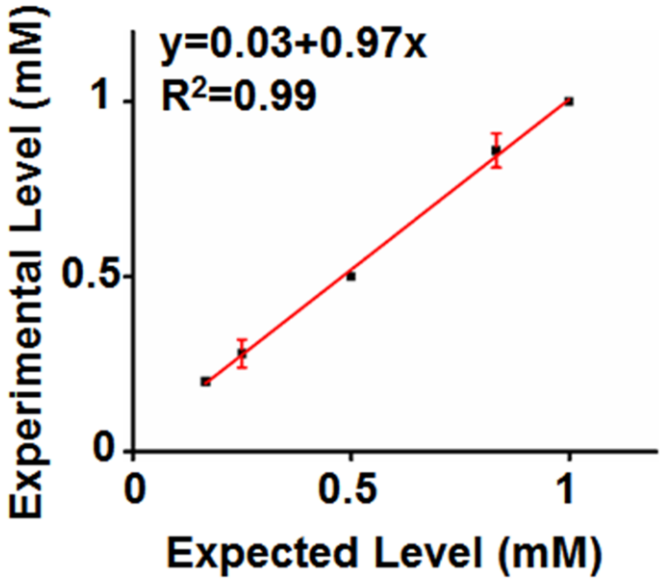
Supplementary Fig. 17. Tandem mass spectra of silver adducted mannitol. MS/MS of mannitol at m/z of 291.2 for $[M+^{109}Ag]^+$ in a) standard sample, b) CSF, and c) serum.



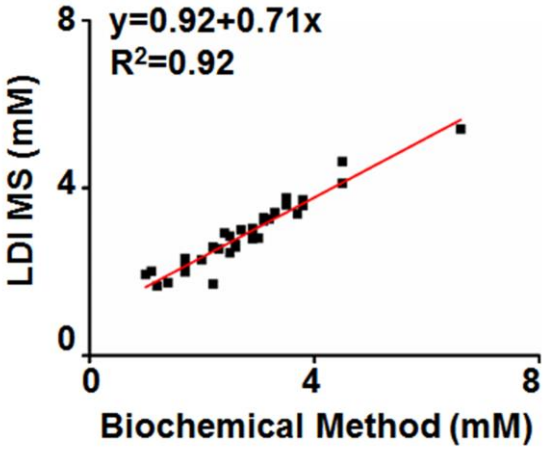
Supplementary Fig. 18. The calibration curve obtained by plotting experimental ratio of analyte/isotope (A/I) as a function of expected ratio of A/I for glucose. The isotope (IS) contained one ^{13}C. 5 independent experiments were performed for each sample to calculate the standard deviation (s.d.) as error bars. Data were shown as the mean ±s.d. (n=5).



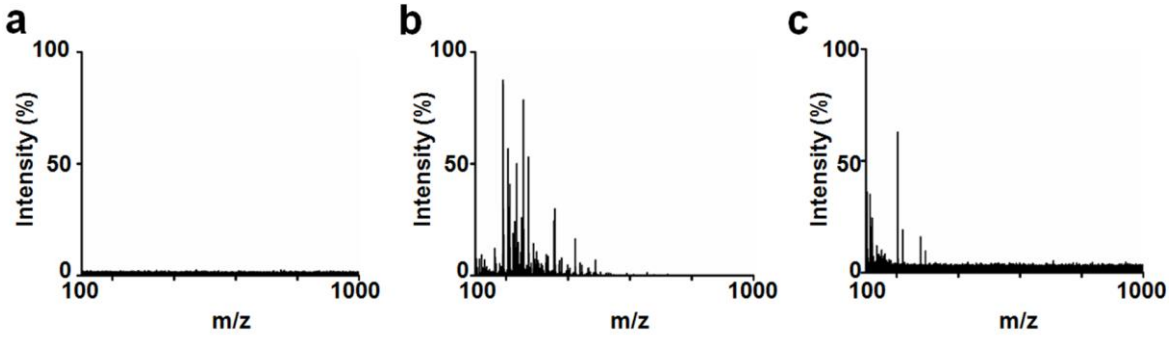
Supplementary Fig. 19. Quantitation of glucose using isotope. Typical mass spectra of glucose and its isotope for quantification by the other 4 independent experiments (in addition to Figure 3d) in parallel (A/I, 1/1).



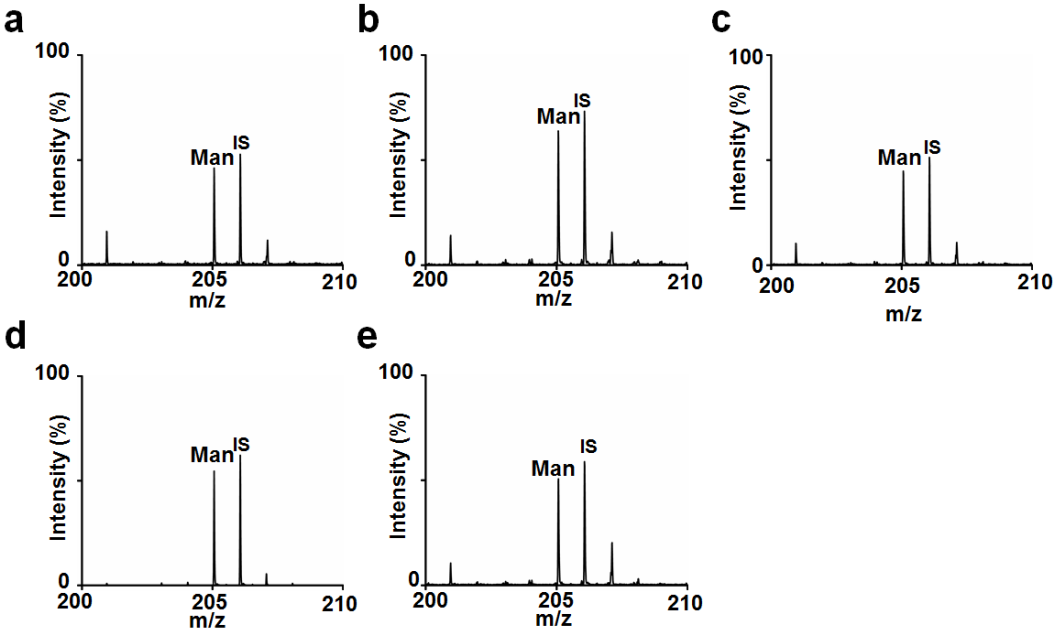
Supplementary Fig. 20. The calibration curve by the biochemical method. 5 independent experiments were performed for each sample to calculate the standard deviation (s.d.) as error bars. Data were shown as the mean ±s.d. (n=5).



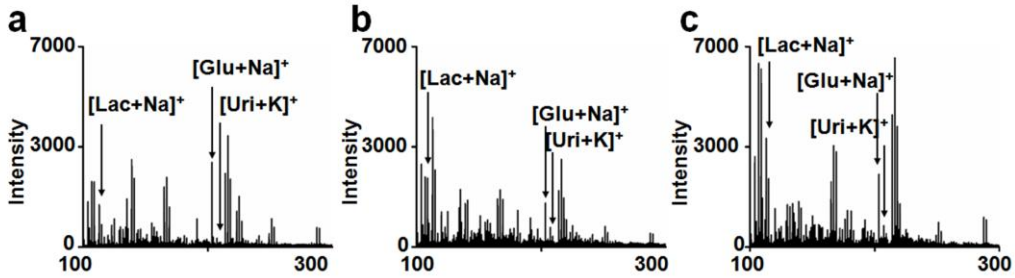
Supplementary Fig. 21. Linear correlation. Quantification results from the biochemical method and LDI MS, affording R^2 of 0.92.



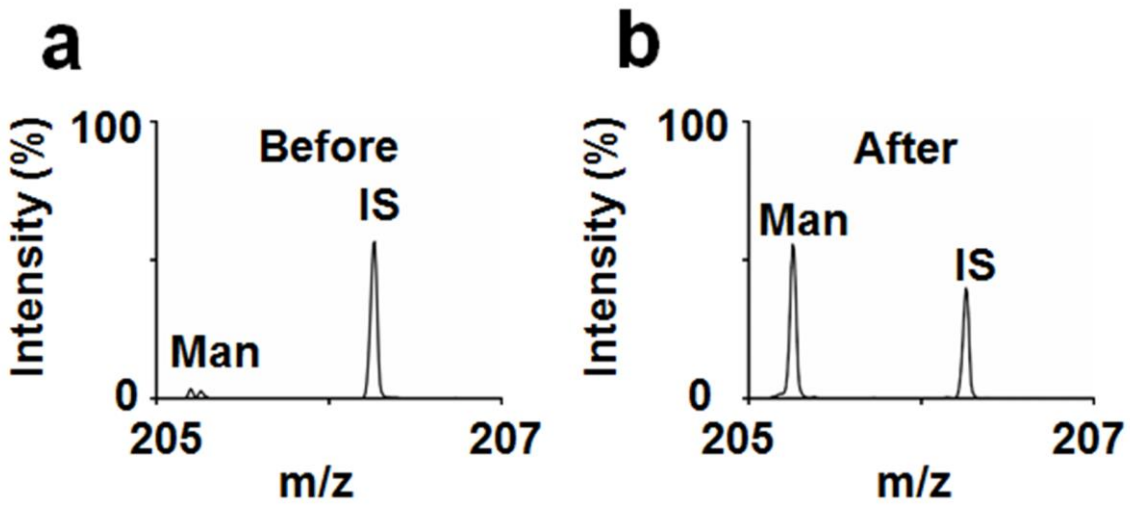
Supplementary Fig. 22. Serum detection using other matrices. Mass spectra of 500 nL of native serum using a) no matrix; b) CHCA; c) gold nanoparticles in the positive ion mode.



Supplementary Fig. 23. Quantitation of mannitol using isotope. Mass spectra of mannitol and its isotope for quantification by 5 independent experiments in parallel. The isotope (IS) contained one ^{13}C.



Supplementary Fig. 24. Stability of silver nanoshells for serum detection. Mass spectra of native serum using a) newly prepared SiO_2@Ag-3, b) SiO_2@Ag-3 stored for 2 months, and c) SiO_2@Ag-3 stored for 5 months. For clarity, only some of the signals were labeled.



Supplementary Fig. 25. Typical mass spectra of mannitol and its isotope in serum from a patient undergoing mannitol treatment. The figures showed mannitol levels a) before injection and b) 30 min after injection.

Supplementary Table 1 Structural parameters of the particles

Samples	Average Size (nm)[a]	PDI[a]	Zeta Potential (mV)	Surface Area ($m^2 g^{-1}$) [b]
SiO_2	181.8±12.53	0.203±0.112	-40.7±0.681	18.58±0.095
SiO_2@Ag-1	185.8±0.611	0.105±0.064	-37.4±1.760	24.20±0.069
SiO_2@Ag-2	194.6±2.007	0.190±0.008	-25.9±1.650	21.17±0.168
SiO_2@Ag-3	210.8±9.717	0.202±0.020	-22.2±1.130	20.72±0.115
SiO_2@Ag-4	289.7±74.19	0.313±0.044	-26.7±0.520	21.15±0.110

[a] The measurements of particle size and PDI were according to the DLS experiments.

[b] The surface areas were obtained in nitrogen adsorption analysis.

Supplementary Table 2 Signal intensities of silver adducted signals for SiO_2@Ag-1/2/3/4

Small molecules		SiO_2@Ag-1	SiO_2@Ag-2	SiO_2@Ag-3	SiO_2@Ag-4
Mannitol	m/z $[M+^{107}Ag]^+$	2077.0±337.36	2618.0±682.12	5393.7±279.39	4131.3±67.61
	m/z $[M+^{109}Ag]^+$	1952.7±296.84	2535.3±685.89	5146.7±294.88	3933.7±58.02
Glucose	m/z $[M+^{107}Ag]^+$	587.3±58.91	2407.0±208.23	5240.7±777.72	1629.3±385.92
	m/z $[M+^{109}Ag]^+$	535.0±49.93	2219.7±174.17	4899.3±762.50	1516.0±370.01
Methionine	m/z $[M+^{107}Ag]^+$	190.7±19.14	1011.3±227.99	2035.3±300.48	783.7±411.72
	m/z $[M+^{109}Ag]^+$	182.7±13.07	991.7±221.93	1994.7±288.59	776.3±408.46

Supplementary Table 3 m/z values of characteristic molecular peaks of typical metabolites by SiO_2@Ag assisted LDI MS

Small molecules	m/z $[M+Na]^+$	m/z $[M+K]^+$	m/z $[M+^{107}Ag]^+$	m/z $[M+^{109}Ag]^+$
Methionine	172.21	188.20	256.20	258.20
Glucose	203.26	219.22	287.23	289.23
Mannitol	205.28	221.27	289.26	291.26

Supplementary Table 4 m/z values of characteristic molecular peaks of typical metabolites from CSF by SiO_2@Ag assisted LDI MS

Small molecules	m/z $[M+Na]^+$	m/z $[M+K]^+$	m/z $[M+^{107}Ag]^+$	m/z $[M+^{109}Ag]^+$
Glucose	203.26	219.22	287.23	289.23
Mannitol	205.28	221.27	289.23	291.23
Uric acid	197.07	207.21	275.36	277.33
Tryptophan	227.04	243.30	311.01	313.01

Supplementary Table 5. Glucose levels from 38 CSF samples obtained by biochemical analyzer and particle assisted LDI MS

Sample number	Glucose detected by biochemical analyzer (mM)	Glucose detected by particle assisted LDI MS (mM)
1	2.5	2.5
2	2.4	2.9
3	3	2.8
4	3.3	3.4
5	3.8	3.7
6	3.1	3.2
7	1.7	2.2
8	3.7	3.4
9	3.8	3.6
10	1.7	2.3
11	3.2	3.3
12	6.6	5.4
13	4.5	4.6
14	1.1	2.0
15	1	1.9
16	1.2	1.7
17	1.4	1.7
18	2.6	2.7
19	2.9	3.0
20	2.9	2.8
21	1.7	2.0
22	2.9	2.8
23	2.9	2.8
24	3.1	3.2
25	3.5	3.8
26	2.2	2.6
27	2.6	2.6
28	2.5	2.8
29	2.2	1.7
30	2.9	2.9
31	3.5	3.6
32	2.9	2.9
33	2	2.3
34	4.5	4.1
35	2.9	3.0
36	2.3	2.5
37	3.1	3.3
38	2.7	3.0

Supplementary Table 6 m/z values of characteristic molecular peaks of typical metabolites from serum by SiO_2@Ag assisted LDI MS

Small molecules	m/z $[M+Na]^+$	m/z $[M+K]^+$	m/z $[M+^{107}Ag]^+$	m/z $[M+^{109}Ag]^+$
Glucose	203.26	219.22	287.23	289.23
Mannitol	205.28	221.27	289.23	291.23
Lactic acid	113.03	129.10	197.07	199.07

Supplementary Table 7. Mannitol level in CSF and serum samples from 3 patients before and 30 min after intravenous injection obtained by silver nanoshells assisted LDI MS

Patient number	Mannitol in CSF (mM)		Mannitol in serum (mM)	
	Before	After	Before	After
1	0.086±0.014	0.109±0.015	0.078±0.018	4.239±0.067
2	0.011±0.0001	0.026±0.002	0.100±0.018	5.198±0.260
3	0.019±0.002	0.025±0.004	0.087±0.043	4.022±0.151