Electronic Supplementary Material (ESI) for ChemComm.
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Supporting Information

Flexible and multifunctional metal-organic framework as matrix for analysis of small molecules using laser desorption/ionization mass spectrometry

Wen Ma,[a] Shuting Xu,[a] Wanpeng Ai,[a] Cheng Lin,[b] Yu Bai[a]* and Huwei Liu[a]

aBeijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Institute of Analytical Chemistry, Peking University, Beijing 100871, China. Tel: +86 10 6275 8198; E-mail: yu.bai@pku.edu.cn
bCenter for Biomedical Mass Spectrometry, Boston University School of Medicine, Boston, MA 02118

Experimental Section

Materials

Ovalbumin, α-cyclodextrin, β-cyclodextrin, maltopentaose, maltohexaose, maltoheptaose, bradykinin, glutamic acid, PEG1000 were purchased from Sigma-Aldrich (St. Louis, MO, USA). Glucose, sucrose, PEG2000, PEG4000 and PEG6000 was from Beijng Yili Fine Chemicals Co., Ltd. Drug standards (clozapine, perphenazine, sulpiride, chloropromazine hydrochloride, loxapine succinate) were from National Institute for Food and Drug Control (Beijing, China). Chloroauric acid ($HAuCl_4 \cdot 4H_2O$) was from Beijing Chemical Works. N-acetylglucosamin and 4-mercaptobenzoic acid (4-MBA) were purchased from HEOWNS Technologies Co., Ltd. 11-mercaptoundecanoic acid (11-MUA), 3-mercaptopropanoic acid (3-MPA), L-arginine, L-tryptophan, substance P, 2,5-dihydroxybenzoic acid (DHB) used for MS matrix were obtained from J&K Scientific Ltd. Four lipids standards (triacylglycerol, glucosylceramide, lactosylceramide and galactosylceramide) were purchased from Avanti Polar Lipids (Alabaster, AL). Xylose, L-cysteine and chromic nitrate hydrate were obtained from Sinopharm Chemical Reagent Co., Ltd. Formic acid was from DIKMA Technologies Inc. Sodium borohydride ($NaBH_4$) was purchased from Guangdong Guanghua Chemical Factory Co., Ltd. 2-Aminoterephthalic acid and phenylalanine were from Alfa Aesar China Chemical Co., Ltd. Peptide-N-glycosidase (PNGase F) was from New England Biolabs (Ipswich, MA,

USA). All chemicals were of analytical grade, except ACN, which was of HPLC grade.

Preparation of various functional MOFs

Functional MOFs were synthesized through a simple and generic PSM method,[S1,S2] in which MIL-101(NH_2)@Au was first prepared, followed by the incorporation of various groups. Briefly, 1500 mg chromic nitrate hydrate and 690 mg 2-aminoterephthalic acid were dispersed in 21mL deionized water in a Teflon-lined stainless steel autoclave, the reaction was conducted at 130 ℃ for 24 h to get green MIL-101(NH_2). Subsequently, 200 mg MIL-101(NH_2) was then dispersed in 20 mL of 0.025 M $HAuCl_4 \cdot 4H_2O$ solution containing water and ethanol solvent (1:1, v/v) and stirred continuously in an ice bath for 1 h, then $NaBH_4$ solution (10 mL, 0.05 M) was added. The reaction was conducted for another 0.5 h to get black product MIL-101(NH_2)@Au. Functional MOFs were obtained through the reaction between MIL-101(NH_2)@Au and various functional groups including 11-MUA, 3-MPA, 4-MBA and Cys, and mixtures were reacted at room temperature for at least 12 h. It's noteworthy that amino-derived MOFs with good chemical stability could be used as PSM substrates and Au-S coordination facilitates unlimited functional groups grafting, thus our strategy provides a generic method for fast screening of various functional MOFs as matrices in the detection of small molecules.

Characterization

Fourier-transformed infrared spectroscope (FT-IR) characterization was measured with KBr pellet by Bruker Tensor 27 FT-IR. Transmittance spectrum was acquired with resolution of 4 cm^{-1} and average spectrum of 32-time measurements was recorded. For transmission electron microscopy (TEM) characterization, the material was collected on carbon-coated copper grids. TEM images were recorded on a JEOL JEM-2100 at 200kV. Zeta potential measurement was conducted with a Brookhaven ZetaPlus instrument at room temperature. N_2 adsorption-desorption experiment was conducted in ASAP 2020M apparatus. MIL-101(NH_2), MIL-101(NH_2)@Au, MIL-101(NH_2)@Au-Cys were degassed at 110℃ in case of decomposition. The BET surface area was calculated over the range of relative pressures between 0.05 and 0.20. Surface areas of MIL-101(NH_2), MIL-101(NH_2)@Au, MIL-101(NH_2)@Au-Cys were 2533.6 $m^2\ g^{-1}$, 889.8 $m^2\ g^{-1}$ and 240.4 $m^2\ g^{-1}$, respectively. MALDI-ToF-MS spectra were obtained by a Bruker Daltonics ultraflex ToF mass spectrometer in reflection mode. The laser

frequency was set on 20 Hz and intensity was set to be 30%. Each mass spectrum was generated by an average of 400 laser shots. For SALDI-MS analysis, 1 μL analyte (saccharides, lipids, small peptides, polymers, drugs and amino acids) was mixed with 1 μL matrix solution on the steel plate for MS analysis.

Preparation of OVA protein digestion

2 mg of chicken egg ovalbumin (OVA) was dissolved in 500 μL deionized water, and then the solution was boiled for 5 minutes, after that 500 μL 50 mM ammonium bicarbonate buffer and PNGase F (500U) were added, the mixture which has been denatured was then incubated at 37℃ overnight.

Enrichment of N-glycans

30 μg MIL-101(NH_2)@Au-Cys nanocomposite materials were added into 5 μg OVA digestion in the loading buffer containing ACN/H_2O/FA (85/10/5). The mixture was incubated for 20 min and washed with loading buffer for 3 times. Then N-glycans were eluted with pure water and analyzed by MALDI-ToF MS. For selectivity exploration, different amounts of BSA protein (w/w (OVA digest/BSA protein)=1/10, 1/50, 1/100) were mixed with OVA digest, and mixture was enriched by MIL-101(NH_2)@Au-Cys. Subsequent sample preparation and MS detection were the same as previous protocol.

Recovery and Reproducibility

In order to further investigate the reproducibility of MIL-101(NH_2)@Au-Cys for N-glycans enrichment, 8-parallel enrichment experiments were simultaneously performed with 5 μg OVA digest, all the experiment conditions were strictly kept the same. For recovery experiment, the material was used to enrich 500 ng maltoheptaose and recovery was calculated from relative S/N of eluted maltoheptaose (5 μL in total and 1 μL was spotted on the MALDI plate) and 500 ng maltoheptaose.

Figure and Table

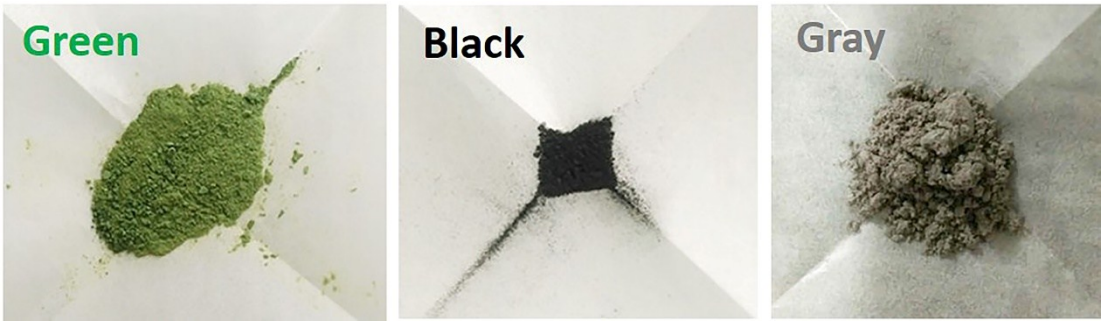

Figure S1 Pictures of MIL-101(NH_2), MIL-101(NH_2)@Au and MIL-101(NH_2)@Au-Cys, respectively

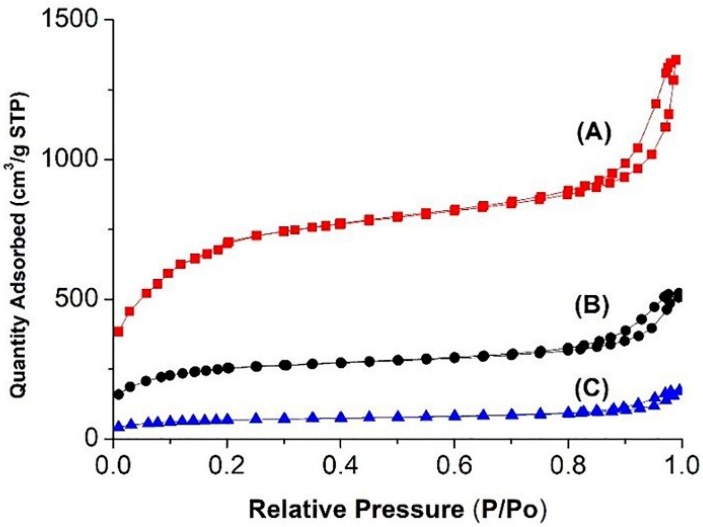

Figure S2 N_2 adsorption–desorption isotherms of (A) MIL-101(NH_2), (B) MIL-101(NH_2)@Au and (C) MIL-101(NH_2)@Au-Cys

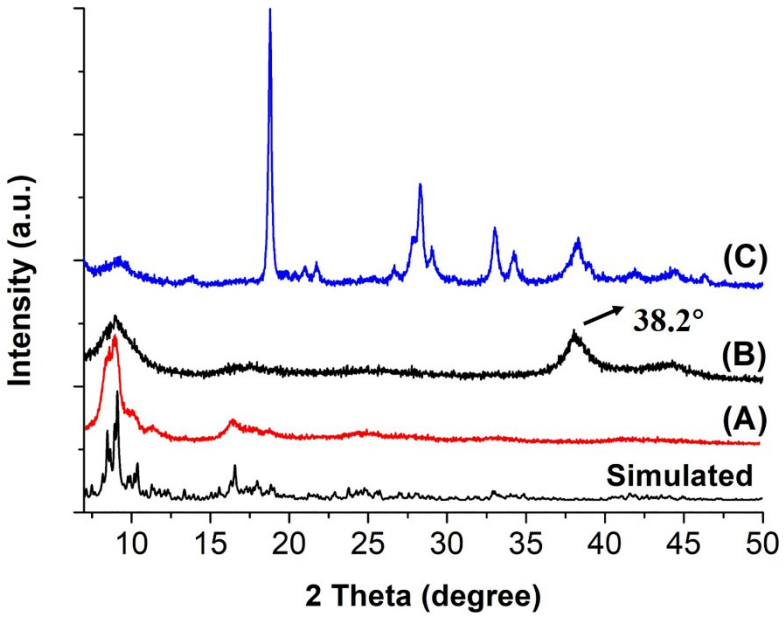

Figure S3 PXRD patterns of (A) MIL-101(NH_2), (B) MIL-101(NH_2)@Au, (C) MIL-101(NH_2)@Au-Cys and simulated one

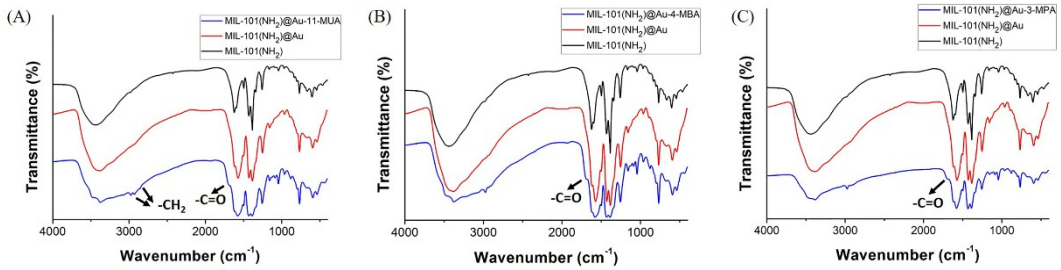

Figure S4 FT-IR spectra of (A) MIL-101(NH_2)@Au-11-MUA, (B) MIL-101(NH_2)@Au-4-MBA and (C) MIL-101(NH_2)@Au-3-MPA

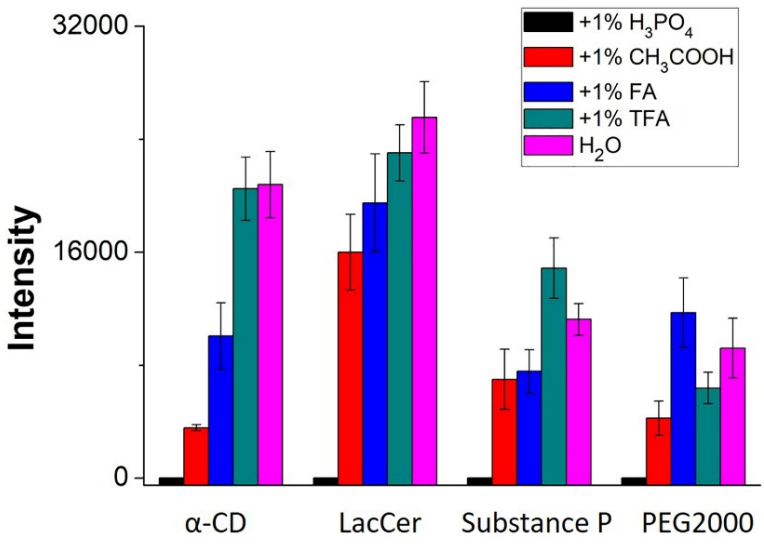

Figure S5 Signal intensity of four representative analytes by using MIL-101(NH_2)@Au-Cys as SALDI matrix with different acid additives

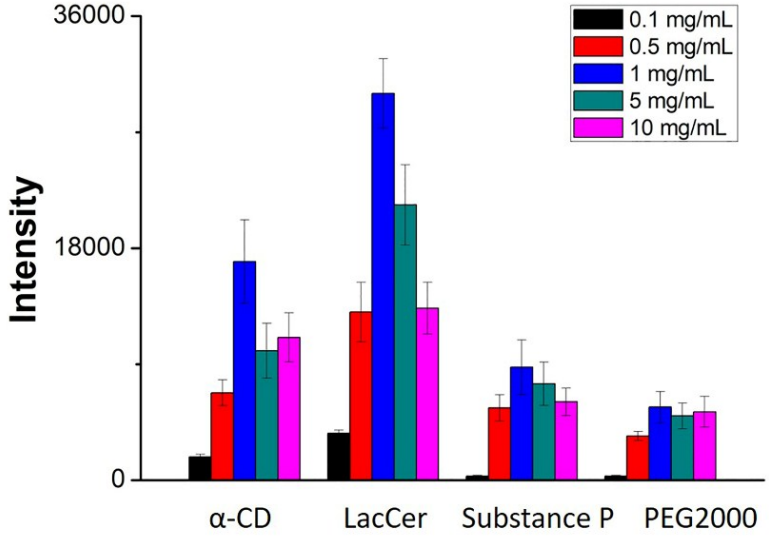

Figure S6 Signal intensity of four representative analytes (50 ppm) by using MIL-101(NH_2)@Au-Cys as SALDI matrix with different concentrations

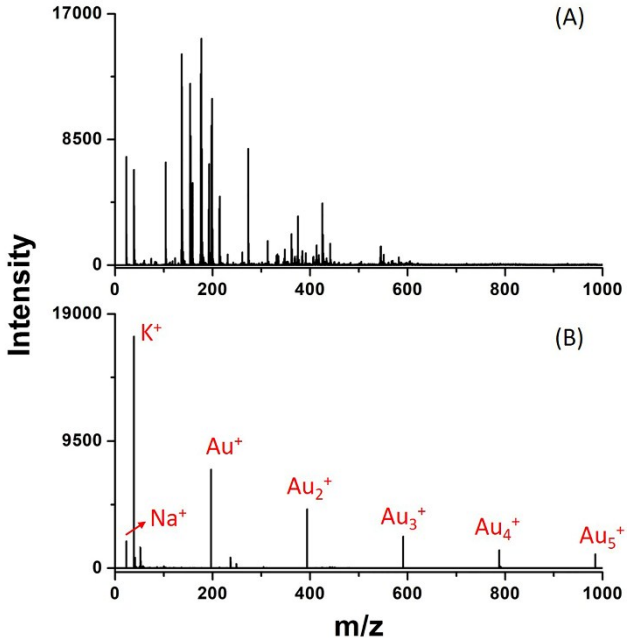

Figure S7 Mass spectra of (A) commonly used organic matrix DHB and (B) MIL-101(NH_2)@Au-Cys in the m/z range from 20 to 1000 Da, laser intensity 30%

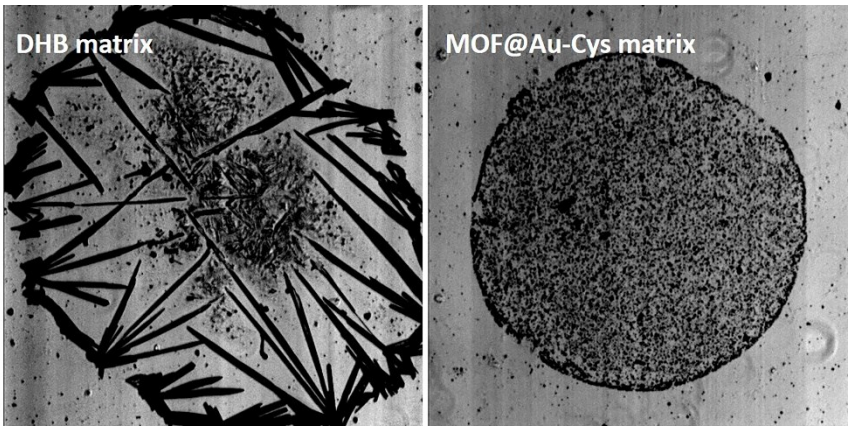

Figure S8 Images of (A) commonly used organic matrix DHB and (B) MIL-101(NH_2)@Au-Cys crystals after deposited on a glass

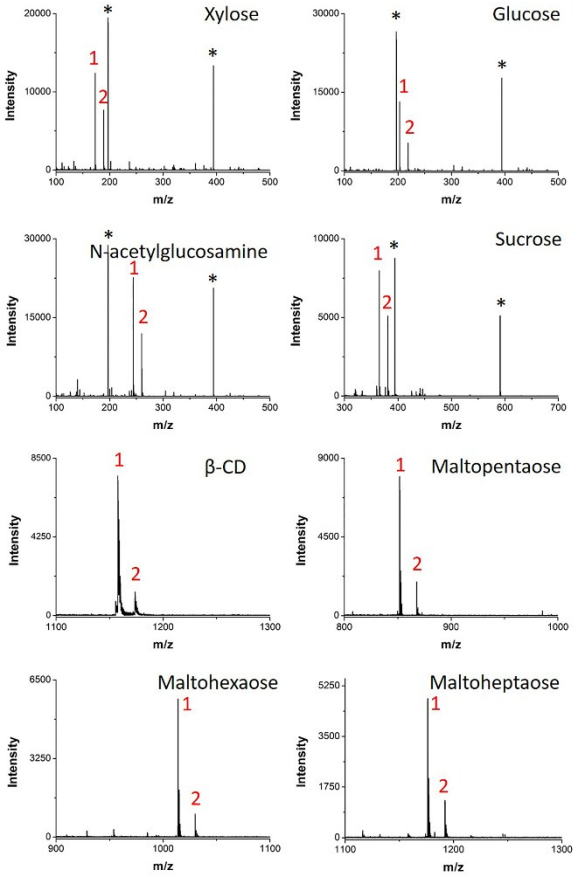

Figure S9 Mass spectra of saccharides using MIL-101(NH_2)@Au-Cys as matrix, number 1 refers to $[M+Na]^+$, 2 refers to $[M+K]^+$, * refers to Au_n^+ clusters.

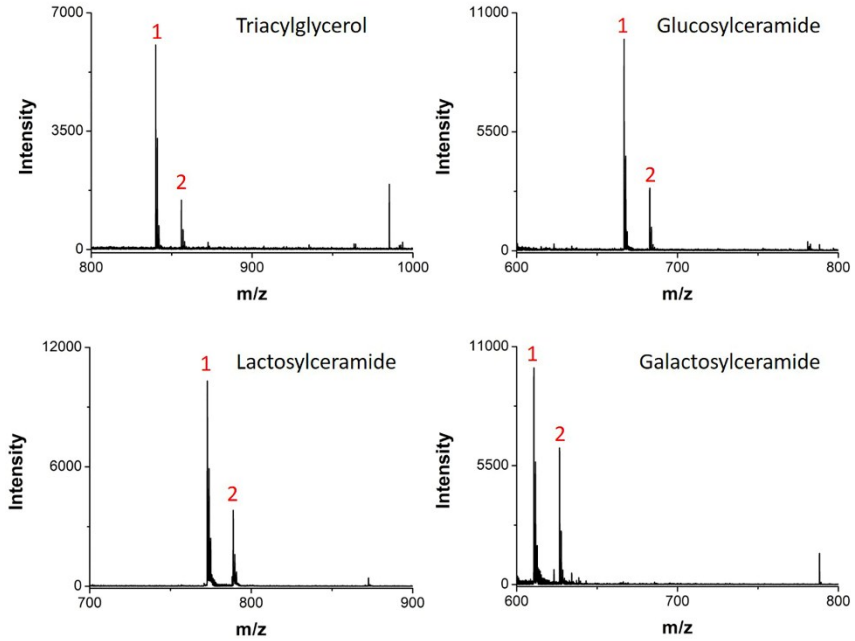

Figure S10 Mass spectra of lipids using MIL-101(NH_2)@Au-Cys as matrix, number 1 refers to $[M+Na]^+$, 2 refers to $[M+K]^+$

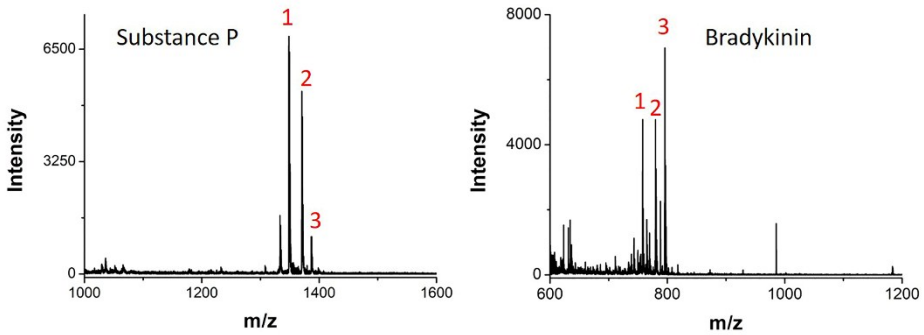

Figure S11 Mass spectra of small peptides using MIL-101(NH_2)@Au-Cys as matrix, number 1 refers to $[M+H]^+$, 2 refers to $[M+Na]^+$, 3 refers to $[M+K]^+$.

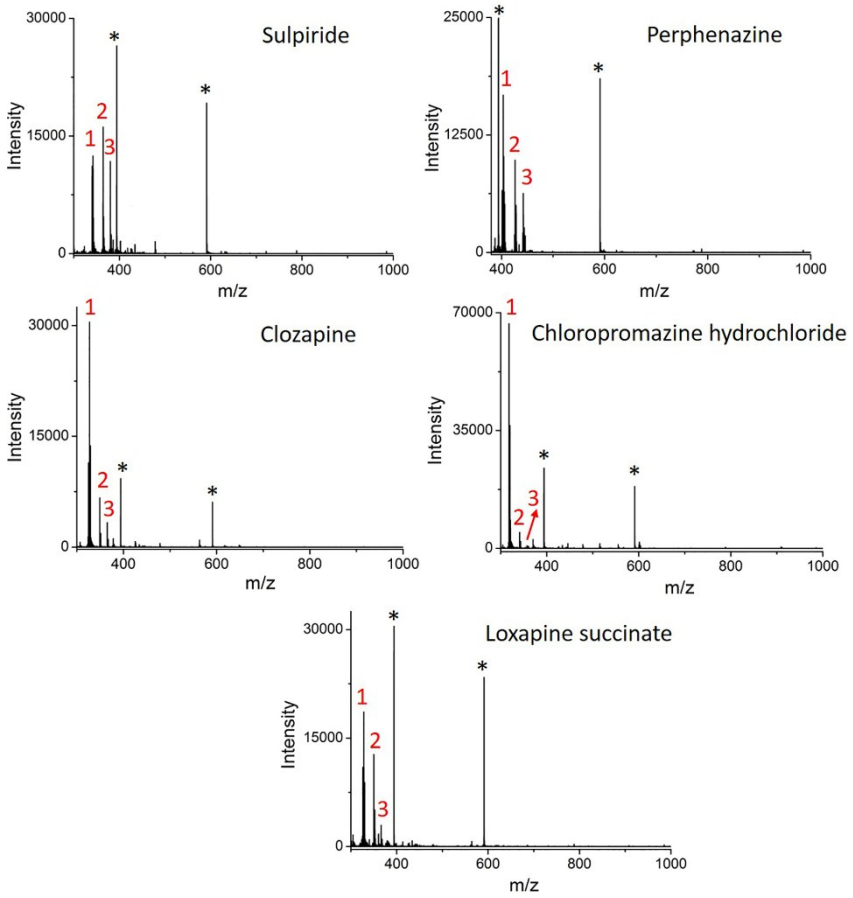

Figure S12 Mass spectra of drugs using MIL-101(NH_2)@Au-Cys as matrix, number 1 refers to $[M+H]^+$, 2 refers to $[M+Na]^+$, 3 refers to $[M+K]^+$, * refers to Au_n^+ clusters.

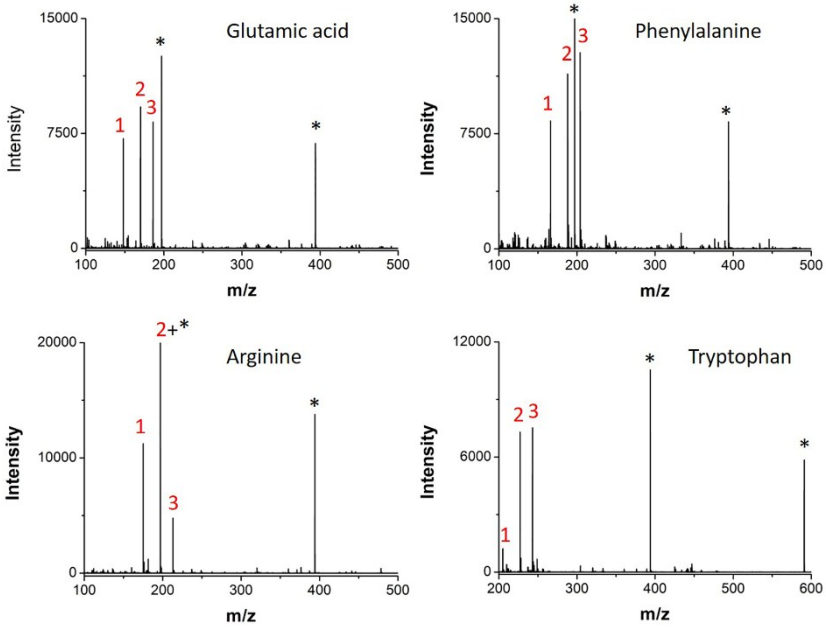

Figure S13 Mass spectra of amino acids using MIL-101(NH_2)@Au-Cys as matrix, number 1 refers to $[M+H]^+$, 2 refers to $[M+Na]^+$, 3 refers to $[M+K]^+$, * refers to Au_n^+ clusters.

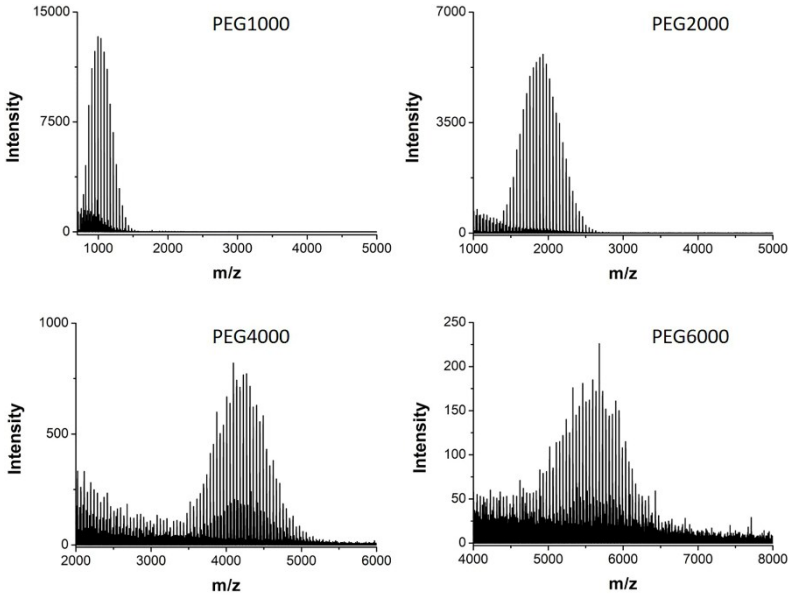

Figure S14 Mass spectra of PEG polymers using MIL-101(NH_2)@Au-Cys as matrix

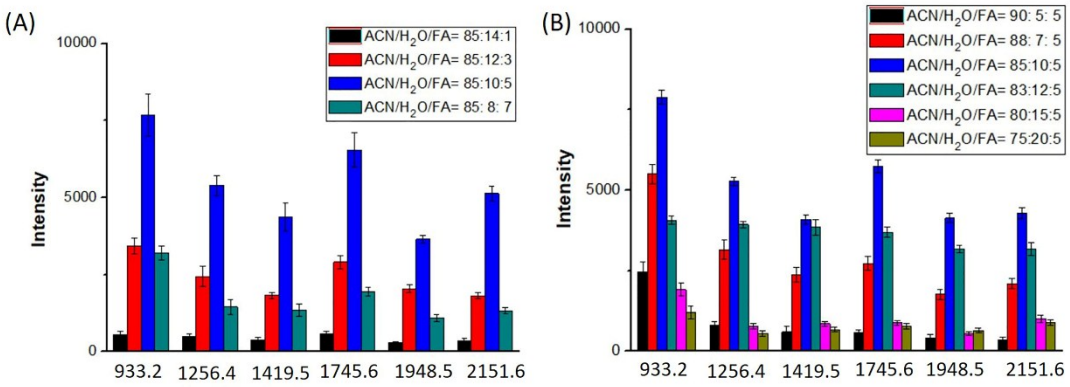

Figure S15 The effect of different acetonitrile and formic acid concentration in loading buffer on intensity of six selected N-glycans captured by MIL-101(NH_2)@Au-Cys from OVA digest.

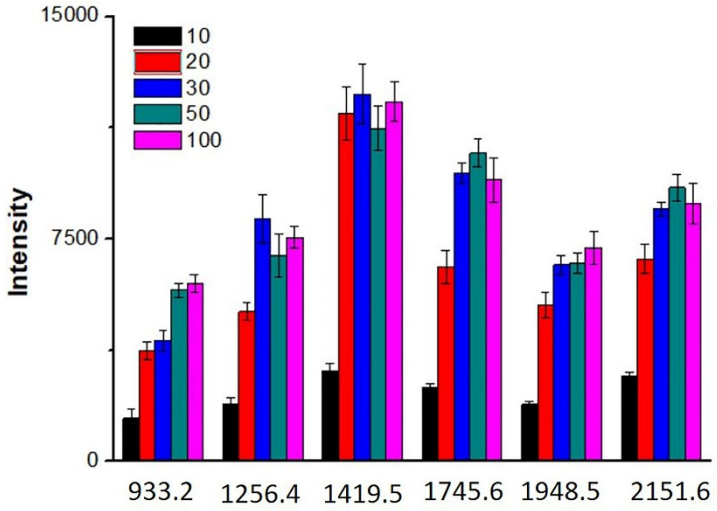

Figure S16 MS intensity of six N-glycans from 5 μg of OVA digest after enrichment by different amounts (10, 20, 30, 50, 100 μg) of MIL-101(NH_2)@Au-Cys nanocomposite.

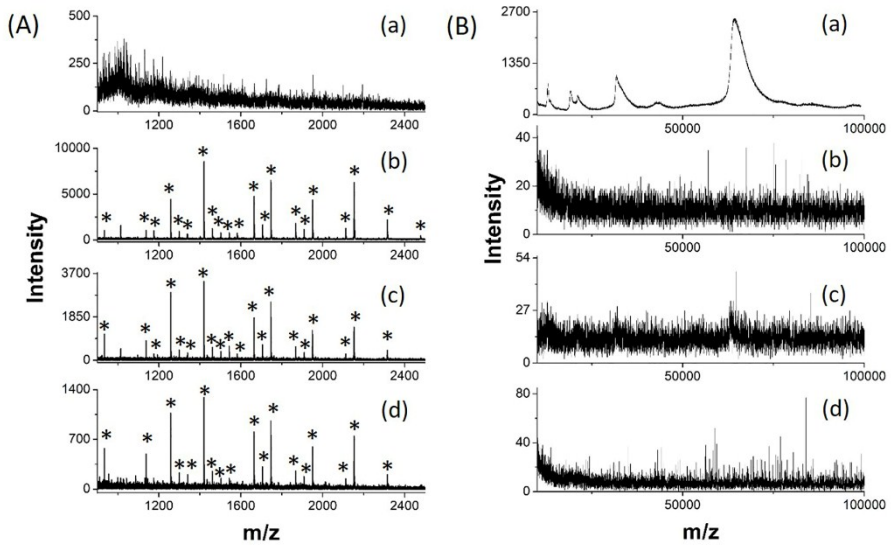

Figure S17 MALDI-ToF MS spectra of eluted mixture in the m/z range (A) 900-2500 Da, and (B) 1 kDa to 100 kDa, N-glycans derived from mixture of OVA digest and BSA protein before enrichment (a) in the molar ratio of 1:10, after enrichment by MIL-101(NH_2)@Au-Cys in the ratio of (b) 1:10, (c) 1:50 and (e) 1:100, predominant glycans were marked with *.

Table S1 Zeta potential of MIL-101(NH_2)@Au-Cys under different pH value

pH	1.6 (ACN:H_2O:FA=85:10:5)	7．1 H_2O	8.2 50 mM NH_4HCO_3
Zeta potential (mV)	146.7±5.6	-155.1±4.9	-123.4±8.4

Table S2 Detailed detected m/z of analytes using MIL-101(NH_2)@Au-Cys matrix

Analytes		$[M+H]^+$	$[M+Na]^+$	$[M+K]^+$
Saccharides	α-CD	/	995.2	1011.2
	β-CD	/	1157.2	1173.2
	Maltopentaose	/	851.0	867.1
	Maltohexaose	/	1013.2	1029.3
	Maltoheptaose	/	1175.4	1191.5
	Xylose	/	173.1	189.1
	Glucose	/	203.1	219.1
	N-Acetylglucosamine	/	244.1	260.1
	Sucrose	/	332.1	348.1
Lipids	Triacylglycerol (18:1/14:0/17:1)	/	839.6	855.6
	Glucosylceramide (12:0)	/	666.1	682.2
	Lactosylceramide (8:0)	/	772.3	788.3
	Galactosylceramide (8:0)	/	610.0	626.0
Small peptides	Substance P	1348.6	1370.6	1386.6
	Bradykinin	757.4	779.4	795.4

Drugs	Sulpiride	342.4	364.4	380.4
	Perphenazine	404.2	426.2	442.2
	Clozapine	327.1	349.1	365.1
	Chloropromazine hydrochloride	319.1	341.1	357.1
	Loxapine succinate	328.1	350.1	366.1
Amino acids	Glutamic acid	148.1	170.1	186.0
	Phenylalanine	166.2	188.2	204.1
	Arginine	175.1	197.0	213.1
	Tryptophan	205.2	227.1	243.1

Table S3 The detected thirty of N-glycans from OVA digest by enriching with MIL-101(NH_2)@Au-Cys materials (Man=Mannose, GlcNAc=N-acetylglucosamine, Fuc=Fucose, Gal=Galactose, Sia=Sialic acid)

Peak number	Observed *m/z*	Glycan composition
1	933.2	[Man]3[GlcNAc]2
2	1095.3	[Man]4[GlcNAc]2
3	1136.3	[Man]3[GlcNAc]3
4	1256.4	[Man]5[GlcNAc]2
5	1298.4	[Man]3[GlcNAc]3[Gal]
6	1339.4	[Man]3[GlcNAc]4
7	1419.5	[Man]6[GlcNAc]2
8	1460.2	[Man]5[GlcNAc]3
9	1485.5	[Man]3[GlcNAc]4[Fuc]
10	1501.4	[Man]3[GlcNAc]4[Gal]
11	1541.5	[Man]3[GlcNAc]5
12	1581.4	[Man]7[GlcNAc]2
13	1606.5	[Man]4[GlcNAc]3[Fuc] [Gal]
14	1663.5	[Man]3[GlcNAc]4 [Gal]2
15	1688.7	[Man]3[GlcNAc]5[Fuc]
16	1704.5	[Man]3[GlcNAc]5[Gal]
17	1745.6	[Man]3[GlcNAc]6
18	1825.5	[Man]6[GlcNAc]4
19	1866.5	[Man]3[GlcNAc]5[Gal]2
20	1890.6	[Man]8[GlcNAc]2[Fuc]
21	1907.5	[Man]4[GlcNAc]6
22	1948.5	[Man]4[GlcNAc]7
23	1976.3	[Man]3[GlcNAc]4[Gal]2Sia
24	2028.8	[Man]3[GlcNAc]5[Gal]3
25	2069.5	[Man]3[GlcNAc]6[Gal]2
26	2110.6	[Man]3[GlcNAc]7[Gal]

27	2151.6	[Man]3[GlcNAc]8
28	2272.9	[Man]2[GlcNAc]7[Gal]2
29	2313.6	[Man]3[GlcNAc]8[Gal]
30	2475.7	[Man]3[GlcNAc]8[Gal]2

Table S4 The S/N ratios of 500 ng maltoheptaose and the elution (5 μL in total and 1 μL was spotted on the MALDI plate) after enrichment with MIL-101(NH_2)@Au-Cys materials and calculated recovery of the maltoheptaose.

No.	S/N	Recovery
1	141.7	87.4%
2	142.6	87.9%
3	158.1	97.5%
4	133.3	82.2%
5	137.2	84.6%
6	130.4	80.4%
500 ng maltoheptaose (S/N=810.8)		

Table S5 Reproducibility of MIL-101(NH_2)@Au-Cys used for N-glycans enrichment from OVA digest.

m/z	Glycan composition	S/N (mean±SD, n=8)	Reproducibility (RSD%, n=8)
933.2	[Man]3[GlcNAc]2	212.2±16.9	8.0
1256.4	[Man]5[GlcNAc]2	455.6±20.1	4.4
1419.5	[Man]6[GlcNAc]2	609.7±33.3	5.5
1745.6	[Man]3[GlcNAc]6	537.3±47.2	8.8
1948.5	[Man]4[GlcNAc]7	386.5±23.4	6.1
2151.6	[Man]3[GlcNAc]8	402.8±35.1	8.7

Table S6 Comparison of MIL-101(NH_2)@Au-Cys binding capacity and other materials towards N-glycans.

No.	Material	Binding capacity (mg/g)	Reference
1	CM-PTs	8	S1
2	ZIF-8@ZIF-67	20 (500 μg material enrich 10 μg glycan)	S2
3	C-Mag G@mSiO_2	20 (500 μg material enrich 10 μg glycan)	S3
4	C-graphene@mSiO_2	12.5 (800 μg material enrich 10 μg glycan)	S4
5	MIL-101(NH_2)@Au-Cys	167	This work

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