Electronic Supplementary Information

Dual-triggered nanoaggregates of cucurbit[7]uril and gold nanoparticles for multi-spectroscopic quantification of creatinine in urinalysis

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1. Current state-of-the-art of CRN detection by SERS

Table S1. SERS detection of CRN in urine or water reported in literature.

Type of substrate	Substrate	Matrix	Range	Limit of detection	Ref.
Solution	Au NPs	Syn. Urine	1.25 – 5 mg/dl	1.25 mg/dl	8
	Au NPs	Syn. Urine	38.4 – 153.6 mg/dl	38.4 mg/dl	4
		Human urine	2.56 – 115.2 mg/dl *	2.56 mg/dl	
	Ag NPs	Water	10 mg/dl – 280 mg/dl	10 mg/dl	23
Solid	Jaffe complex on Ag film	Water	25 -150 µM	25 µM	14
	Ag-coated parylene	Syn. Urine	0.5 – 10.2 µg/ml **	0.5 µg/ml	24
		Human urine	6.1 – 173 mg/dl	6.1 mg/dl	
	Nanoporous Au disk	Water	100 nM – 100 µM	13.2 nM (cal. from SNR)	25
		Syn. Urine	10 – 200 µM	10 µM	
		Mouse urine	2.08 mg/dl – 30.30 mg/dl	0.68 mg/dl (cal.from SNR)	
	Boron nitride / Au nanocomposite	Syn. Urine	10 – 200 µM	10 µM	26
	Superhydrophobic Ag film	Water	5 – 1000 µM	5 µM	27
	Au NP-coated blu-ray DVD	Water	0.2 – 1 µg/ml	32 ng/ml (cal. from equation)	28
		Syn. Urine	0.1 – 10 mg/ml **	0.1 mg/ml	
This study	Au NP:CB7 nanoaggregates	Water	0.06 µg/ml – 1.5 µg/ml	4.69 ng/ml (41.5 nM) (cal. from SNR)	
		Syn. Urine	0.06 µg/ml – 1.5 µg/ml	12.5 ng/ml (111 nM) (cal. from SNR)	

*Linear region: 2.56 - 6.4 mg/dl. **No linear plot shown.

2. Coordinates of [CB7-CRN-H]$^+$ inclusion complex

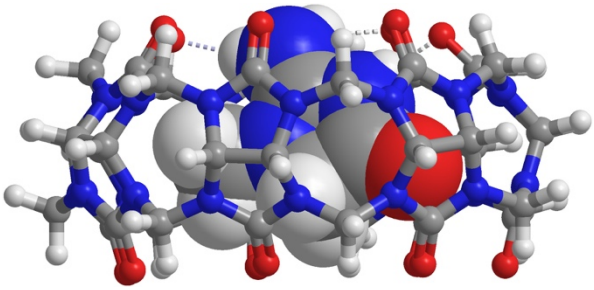

Table S2. Coordinates of the [CB7-CRN-H]$^+$ inclusion complex in water, geometry-optimised at the CPCM /wB97X-D/6-31G* level of theory. Energy = −4607.8120 hartree.

Atom (Centre Nr.)	Coordinates (Å)		
	X	Y	Z
N(1)	0.026	4.901	1.316
C(2)	0.581	5.635	0.209
C(3)	2.099	5.31	0.287
N(4)	2.168	4.295	1.316
C(5)	0.954	4.102	1.944
N(6)	0.207	5.145	-1.101
C(7)	1.301	4.769	-1.853
N(8)	2.412	4.859	-1.044
O(9)	0.748	3.381	2.905
O(10)	1.288	4.452	-3.029
N(11)	4.141	2.897	1.263
C(12)	5.015	3.186	0.141
C(13)	5.748	1.835	-0.063
N(14)	5.477	1.119	1.153
C(15)	4.51	1.734	1.915
N(16)	4.356	3.4	-1.118
C(17)	4.38	2.28	-1.919
N(18)	5.106	1.314	-1.254
O(19)	4.085	1.356	2.992
O(20)	3.885	2.177	-3.027
N(21)	-5.588	1.366	1.076
C(22)	-6.007	0.908	-0.223
C(23)	-6.092	-0.636	-0.046
N(24)	-5.409	-0.846	1.218
C(25)	-5.21	0.334	1.905
N(26)	-5.015	1.051	-1.278
C(27)	-4.675	-0.155	-1.835
N(28)	-5.393	-1.136	-1.202
O(29)	-4.798	0.438	3.046
O(30)	-3.868	-0.33	-2.742

N(31)	0.15	-4.502	1.318
C(32)	0.452	-5.42	0.238
C(33)	1.972	-5.207	0.03
N(34)	2.376	-4.481	1.202
C(35)	1.298	-4.027	1.929
N(36)	-0.117	-5.045	-1.029
C(37)	0.782	-4.368	-1.814
N(38)	2.007	-4.436	-1.198
O(39)	1.341	-3.352	2.942
O(40)	0.54	-3.81	-2.88
N(41)	5.56	-1.314	1.047
C(42)	5.748	-1.83	-0.287
C(43)	4.981	-3.191	-0.252
N(44)	4.482	-3.255	1.098
C(45)	4.825	-2.155	1.851
N(46)	5.078	-1.105	-1.346
C(47)	4.009	-1.786	-1.851
N(48)	3.969	-3.027	-1.27
O(49)	4.582	-1.995	3.034
O(50)	3.225	-1.387	-2.709
C(51)	-5.285	-2.119	1.882
C(52)	3.75	4.64	-1.528
C(53)	-5.327	-2.517	-1.605
C(54)	3.407	3.924	1.954
N(55)	-2.349	4.445	1.168
C(56)	-2.923	4.94	-0.07
C(57)	-4.182	4.053	-0.233
N(58)	-4.342	3.457	1.063
C(59)	-3.247	3.666	1.874
N(60)	-2.164	4.66	-1.257
C(61)	-2.652	3.577	-1.95
N(62)	-3.789	3.138	-1.29
O(63)	-3.109	3.269	3.017
O(64)	-2.192	3.108	-2.975
C(65)	-1.286	5.137	1.855
C(66)	-1.057	5.454	-1.72
C(67)	-4.742	2.293	-1.96
C(68)	-5.517	2.745	1.491
C(69)	6.142	-0.098	1.549
C(70)	5.554	0.124	-1.925
C(71)	3.746	-4.359	1.648
C(72)	3.235	-4.108	-1.87
N(73)	-2.505	-4.633	-0.971
C(74)	-3.002	-4.681	0.379
C(75)	-4.317	-3.859	0.301
N(76)	-4.24	-3.251	-1.012

C(77)	-3.233	-3.796	-1.781
N(78)	-2.212	-3.952	1.355
C(79)	-2.965	-2.986	2
N(80)	-4.204	-2.943	1.403
O(81)	-3.037	-3.586	-2.966
O(82)	-2.598	-2.306	2.943
C(83)	-1.428	-5.439	-1.474
C(84)	-1.095	-4.561	2.041
H(85)	0.352	6.702	0.301
H(86)	2.721	6.17	0.556
H(87)	5.682	4.023	0.374
H(88)	6.828	1.933	-0.218
H(89)	-6.951	1.377	-0.516
H(90)	-7.113	-1.027	-0.012
H(91)	0.174	-6.446	0.5
H(92)	2.547	-6.132	-0.075
H(93)	6.814	-1.927	-0.515
H(94)	5.61	-4.059	-0.476
H(95)	-6.217	-2.685	1.78
H(96)	-5.104	-1.907	2.936
H(97)	3.702	4.64	-2.618
H(98)	4.388	5.463	-1.19
H(99)	-5.182	-2.55	-2.686
H(100)	-6.281	-2.99	-1.353
H(101)	3.17	3.539	2.947
H(102)	4.034	4.821	2.051
H(103)	-3.14	6.011	0.005
H(104)	-5.083	4.608	-0.518
H(105)	-1.293	4.789	2.889
H(106)	-1.478	6.217	1.833
H(107)	-0.94	5.277	-2.789
H(108)	-1.3	6.509	-1.549
H(109)	-4.328	2.049	-2.939
H(110)	-5.688	2.836	-2.091
H(111)	-5.527	2.754	2.581
H(112)	-6.4	3.269	1.113
H(113)	6.106	-0.157	2.637
H(114)	7.185	-0.035	1.222
H(115)	5.188	0.18	-2.951
H(116)	6.65	0.093	-1.933
H(117)	3.736	-4.22	2.729
H(118)	4.258	-5.296	1.406
H(119)	3.881	-4.994	-1.892
H(120)	2.979	-3.822	-2.891
H(121)	-3.149	-5.718	0.699
H(122)	-5.224	-4.465	0.393

H(123)	-1.452	-5.364	-2.561
H(124)	-1.589	-6.48	-1.176
H(125)	-1.339	-5.61	2.258
H(126)	-0.951	-4.022	2.978
C(127)	0.178	-0.343	0.99
C(128)	1.387	-0.834	0.216
N(129)	0.891	-1.325	-0.986
C(130)	-0.454	-1.097	-1.078
N(131)	-0.902	-0.521	0.032
C(132)	-2.283	-0.192	0.32
N(133)	-1.16	-1.432	-2.137
O(134)	2.546	-0.808	0.546
H(135)	0.299	0.701	1.291
H(136)	0.015	-0.965	1.877
H(137)	-2.934	-0.975	-0.076
H(138)	-2.556	0.778	-0.106
H(139)	-2.412	-0.165	1.403
H(140)	1.501	-1.535	-1.783
H(141)	-2.136	-1.156	-2.264
H(142)	-0.768	-2.115	-2.781
H(143)	-1.279	-1.185	-1.82

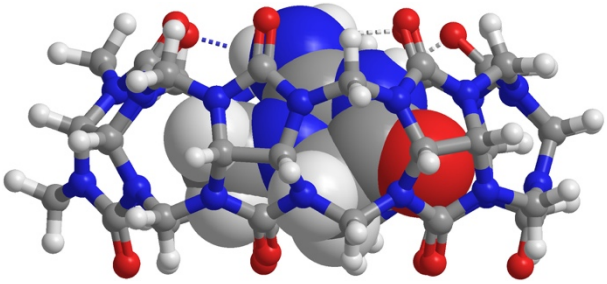

Table S3. Coordinates of the [CB7-CRN-H]$^+$ inclusion complex in gas phase, geometry-optimised at the wB97X-D/6-31G* level of theory. Energy = −4607.6597 hartree.

Atom (Centre Nr.)	Coordinates (Å)		
	X	Y	Z
N(1)	-0.907	4.745	1.359
C(2)	-0.428	5.585	0.3
C(3)	1.119	5.429	0.395
N(4)	1.284	4.315	1.305
C(5)	0.083	3.938	1.888
N(6)	-0.715	5.127	-1.039
C(7)	0.433	5.001	-1.812
N(8)	1.51	5.192	-0.965
O(9)	-0.069	3.085	2.735
O(10)	0.476	4.814	-3.005
N(11)	3.486	3.309	1.285
C(12)	4.297	3.871	0.226
C(13)	5.319	2.734	-0.031
N(14)	5.26	1.962	1.171
C(15)	4.135	2.255	1.925
N(16)	3.651	4.028	-1.044
C(17)	3.889	2.954	-1.887
N(18)	4.78	2.118	-1.226
O(19)	3.808	1.742	2.967
O(20)	3.449	2.801	-3.001
N(21)	-5.866	0.445	0.993
C(22)	-6.094	-0.106	-0.311
C(23)	-5.883	-1.635	-0.092
N(24)	-5.165	-1.667	1.165
C(25)	-5.274	-0.462	1.855
N(26)	-5.09	0.2	-1.317
C(27)	-4.529	-0.935	-1.85
N(28)	-5.124	-2.021	-1.248
O(29)	-4.946	-0.266	2.999
O(30)	-3.669	-0.981	-2.714
N(31)	0.963	-4.298	1.294
C(32)	1.39	-5.233	0.275

C(33)	2.861	-4.808	0.035
N(34)	3.184	-4.047	1.203
C(35)	2.053	-3.668	1.902
N(36)	0.776	-5.039	-1.008
C(37)	1.525	-4.194	-1.802
N(38)	2.751	-4.048	-1.195
O(39)	2.003	-2.958	2.877
O(40)	1.173	-3.691	-2.855
N(41)	5.817	-0.405	0.999
C(42)	6.037	-0.865	-0.345
C(43)	5.505	-2.338	-0.307
N(44)	5.064	-2.498	1.049
C(45)	5.256	-1.363	1.825
N(46)	5.24	-0.258	-1.389
C(47)	4.275	-1.097	-1.872
N(48)	4.463	-2.337	-1.304
O(49)	5.053	-1.27	3.01
O(50)	3.417	-0.832	-2.701
C(51)	-4.814	-2.867	1.882
C(52)	2.868	5.167	-1.44
C(53)	-4.771	-3.368	-1.61
C(54)	2.521	4.083	2.013
N(55)	-3.201	3.979	1.163
C(56)	-3.807	4.412	-0.079
C(57)	-4.891	3.325	-0.303
N(58)	-5.056	2.751	0.998
C(59)	-4.021	3.099	1.857
N(60)	-2.991	4.306	-1.253
C(61)	-3.207	3.127	-1.936
N(62)	-4.266	2.475	-1.298
O(63)	-3.888	2.737	3.001
O(64)	-2.626	2.739	-2.922
C(65)	-2.241	4.774	1.888
C(66)	-2.001	5.268	-1.666
C(67)	-4.997	1.464	-2.008
C(68)	-6.083	1.82	1.376
C(69)	6.161	0.894	1.512
C(70)	5.443	1.062	-1.931
C(71)	4.524	-3.695	1.617
C(72)	3.89	-3.511	-1.894
N(73)	-1.656	-4.983	-0.924
C(74)	-2.115	-5.028	0.436
C(75)	-3.556	-4.45	0.341
N(76)	-3.577	-3.866	-0.983
C(77)	-2.499	-4.273	-1.753
N(78)	-1.457	-4.12	1.352

C(79)	-2.37	-3.283	1.988
N(80)	-3.613	-3.522	1.429
O(81)	-2.345	-4.072	-2.937
O(82)	-2.122	-2.505	2.881
C(83)	-0.469	-5.621	-1.422
C(84)	-0.246	-4.489	2.051
H(85)	-0.778	6.617	0.443
H(86)	1.627	6.32	0.79
H(87)	4.758	4.818	0.541
H(88)	6.344	3.09	-0.207
H(89)	-7.095	0.156	-0.675
H(90)	-6.816	-2.209	-0.035
H(91)	1.272	-6.273	0.608
H(92)	3.558	-5.647	-0.088
H(93)	7.1	-0.788	-0.606
H(94)	6.267	-3.087	-0.561
H(95)	-5.636	-3.594	1.824
H(96)	-4.661	-2.57	2.922
H(97)	2.816	5.167	-2.531
H(98)	3.382	6.073	-1.093
H(99)	-4.593	-3.394	-2.687
H(100)	-5.625	-4.013	-1.365
H(101)	2.288	3.522	2.922
H(102)	2.954	5.06	2.287
H(103)	-4.212	5.429	0.014
H(104)	-5.846	3.723	-0.675
H(105)	-2.213	4.371	2.904
H(106)	-2.57	5.823	1.918
H(107)	-1.837	5.143	-2.739
H(108)	-2.409	6.27	-1.47
H(109)	-4.468	1.286	-2.948
H(110)	-6.017	1.819	-2.22
H(111)	-6.142	1.837	2.466
H(112)	-7.035	2.153	0.948
H(113)	6.165	0.799	2.6
H(114)	7.163	1.172	1.162
H(115)	5.05	1.071	-2.95
H(116)	6.527	1.246	-1.955
H(117)	4.508	-3.537	2.697
H(118)	5.173	-4.548	1.379
H(119)	4.669	-4.285	-1.954
H(120)	3.551	-3.256	-2.9
H(121)	-2.079	-6.057	0.819
H(122)	-4.345	-5.209	0.44
H(123)	-0.52	-5.565	-2.511
H(124)	-0.472	-6.672	-1.107

H(125)	-0.323	-5.545	2.361
H(126)	-0.173	-3.856	2.938
C(127)	0.371	-0.197	1.005
C(128)	1.622	-0.517	0.206
N(129)	1.173	-1.131	-0.968
C(130)	-0.19	-1.094	-1.034
N(131)	-0.695	-0.55	0.07
C(132)	-2.108	-0.4	0.361
N(133)	-0.864	-1.576	-2.059
O(134)	2.772	-0.305	0.482
H(135)	0.34	0.855	1.307
H(136)	0.327	-0.823	1.905
H(137)	-2.645	-1.292	0.027
H(138)	-2.522	0.485	-0.132
H(139)	-2.237	-0.312	1.441
H(140)	1.787	-1.228	-1.786
H(141)	-1.858	-1.398	-2.217
H(142)	-0.375	-2.153	-2.739
H(143)	-0.997	-1.226	-1.788

3. NMR and energy-minimised model of [CB7-CRN-H]$^+$

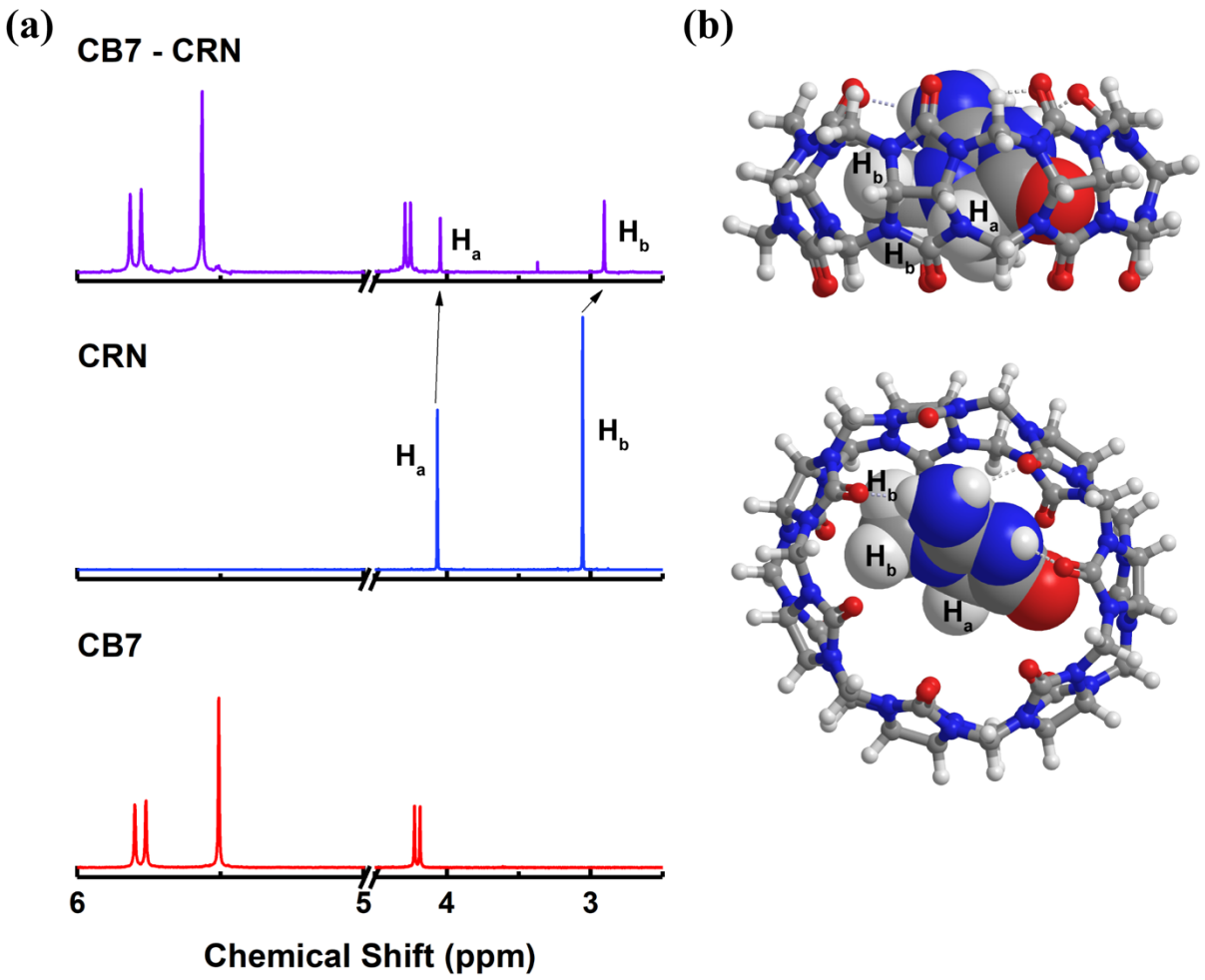

Figure S1. (a) ^{1}H NMR spectra of CB7, CRN and CB7-CRN inclusion complex with 1:1 stoichiometry in D_2O. Characteristic upfield shifts of CRN protons were observed. (b) Side and top views of an energy-minimised [CB7-CRN-H]$^+$ inclusion complex in water modelled at CPCM/wB97XD/6-31G* level of theory.

4. UV-Vis titration of CB7-CRN

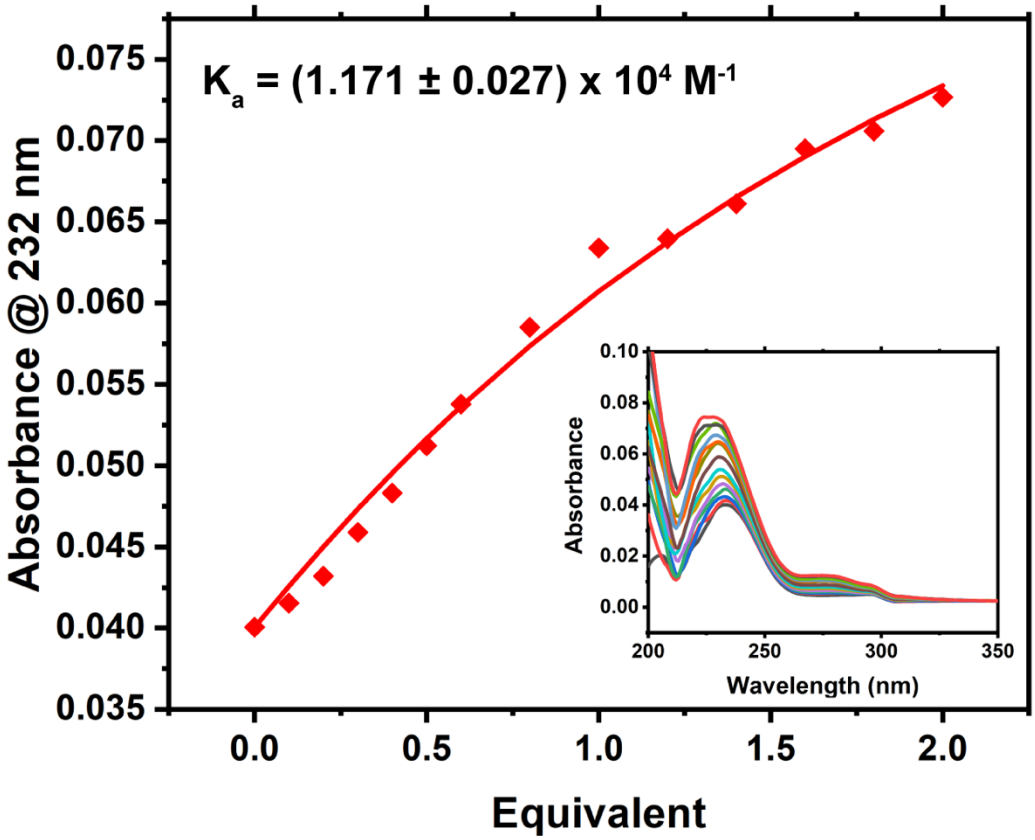

Figure S2. UV-Vis titration of 50 µM CRN with up to 2 equivalents of CB7. The binding curve was fitted by assuming a 1:1 binding model from which the binding constant was derived. Inset: UV-Vis spectra of CB7-CRN with concentrations of CB7 from 0 to 100 µM.

5. UV-Vis spectra of Au NP-CB7-CRN in SU after 5000x dilution

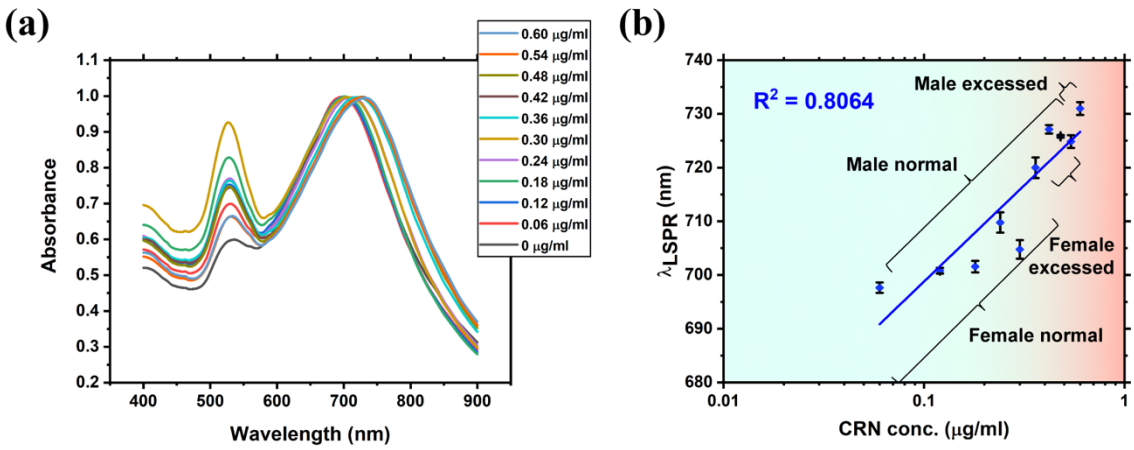

Figure S3. (a) UV-Vis spectra of CRN in SU with concentrations from 0 to 0.60 μg/ml after 5000x dilution with aggregation of Au NPs triggered by 10 μM CB7. (b) Corresponding plot of λ_{LSPR} in (a) against CRN concentration. Logarithmic fitting was performed to reveal correlation between λ_{LSPR} and CRN concentration. (Note: 1 μg/ml in measurement samples corresponds to 5000 μg/ml of the actual CRN concentration in undiluted patient samples.)

6. Size and zeta potential of Au NP-CRN and Au NP-CB7-CRN

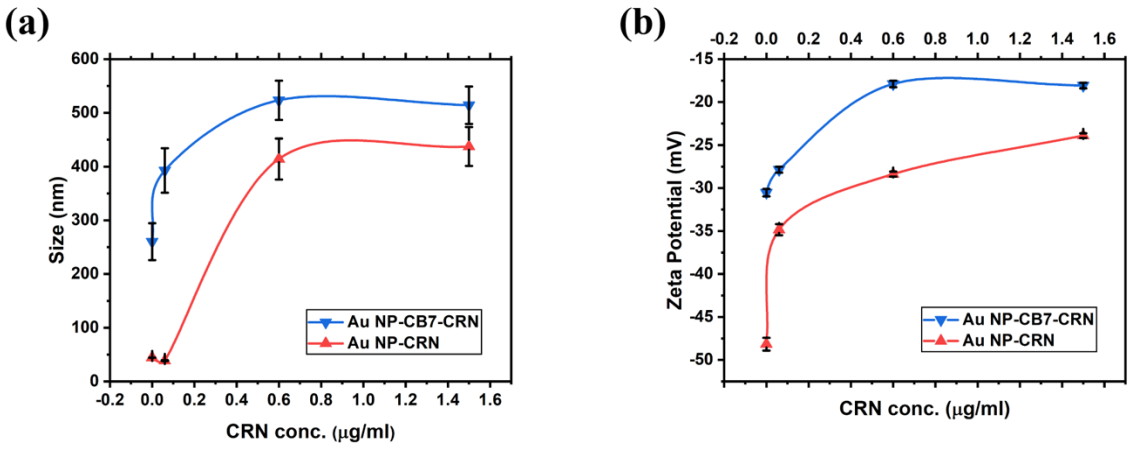

Figure S4. (a) Size and (b) zeta potential of Au NP-CRN and Au NP-CB7-CRN at different concentrations of CRN from 0 to 1.50 μg/ml. (Note: solid lines are to guide the eyes.)

7. UV-Vis spectra of Au NP-CB7-CRN in water

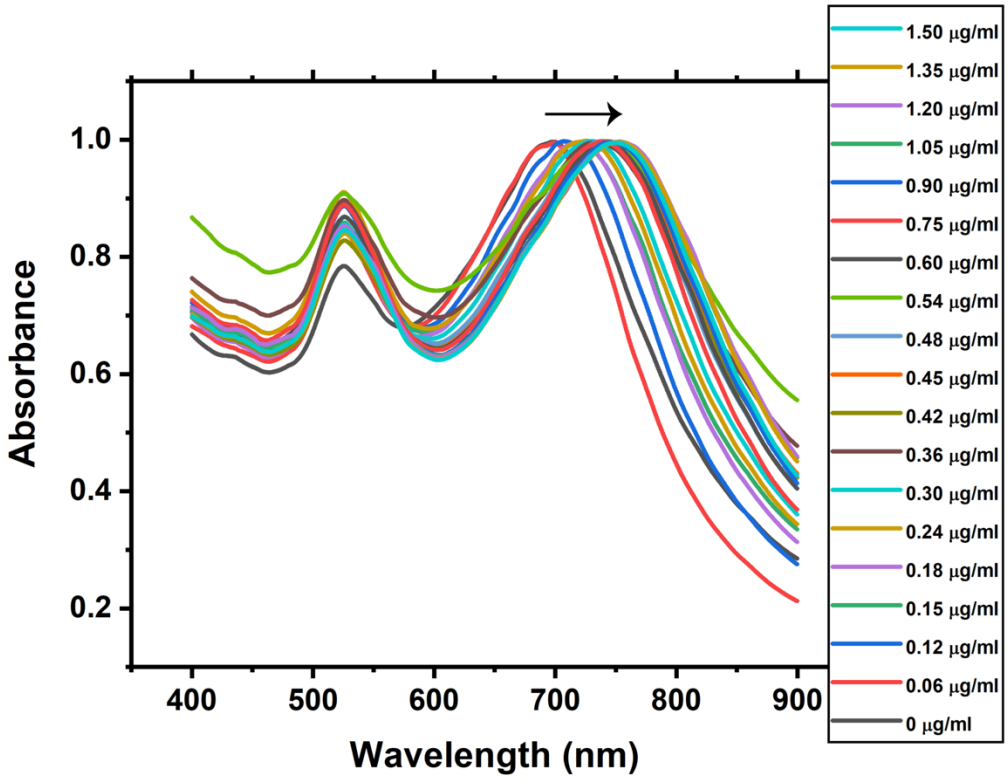

Figure S5. Full UV-Vis spectra of AuNP-CRN in water with CRN concentration from 0 to 1.50 μg/ml in the presence of CB7, with an arrow indicating the shifting of the LSPR peaks.

8. UV-Vis spectra of Au NP-CRN

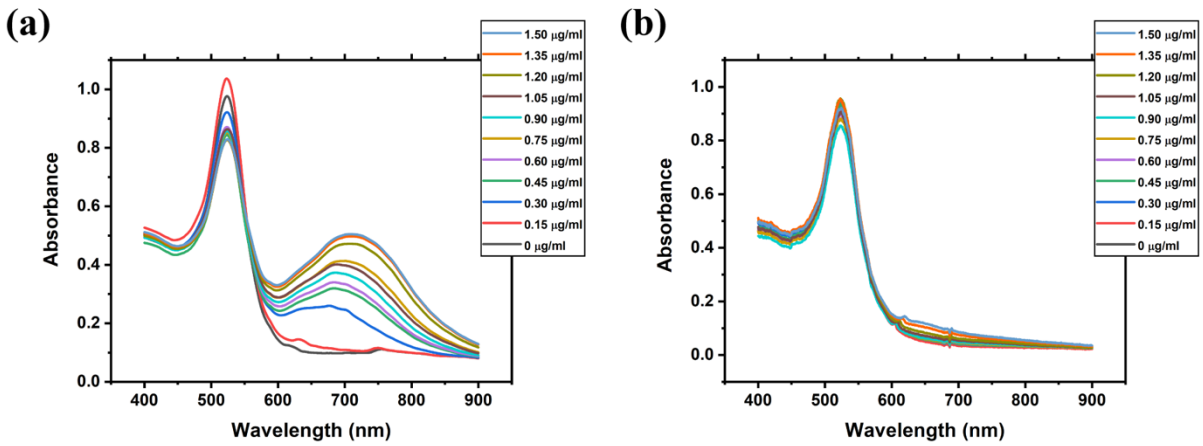

Figure S6. UV-Vis spectra of Au NP-CRN in (a) water and (b) SU after 2000x dilution, with CRN concentration from 0 to 1.50 μg/ml in the absence of CB7.

9. Raman spectra of CRN and CB7 powder

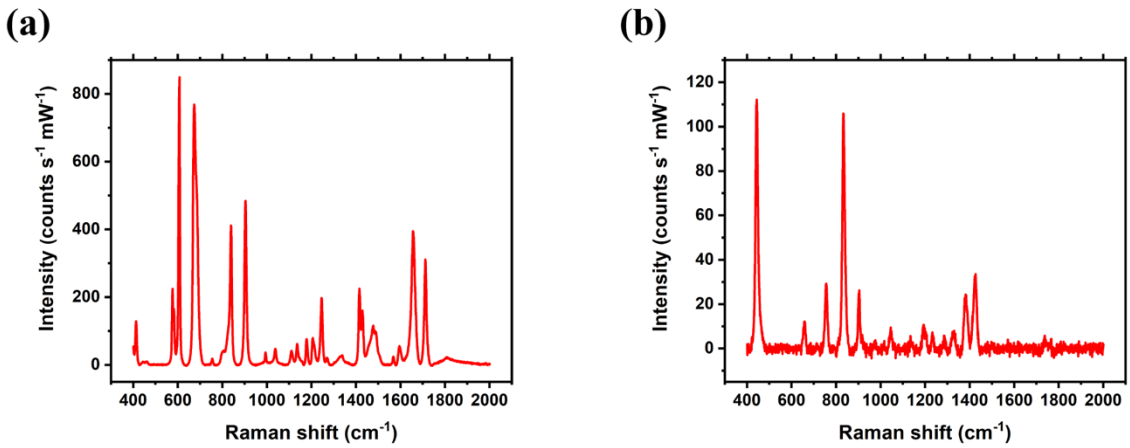

Figure S7. Raman spectra of (a) CRN powder and (b) CB7 powder respectively.

10. Raman and SERS spectra of CB7, CRN and CB7-CRN

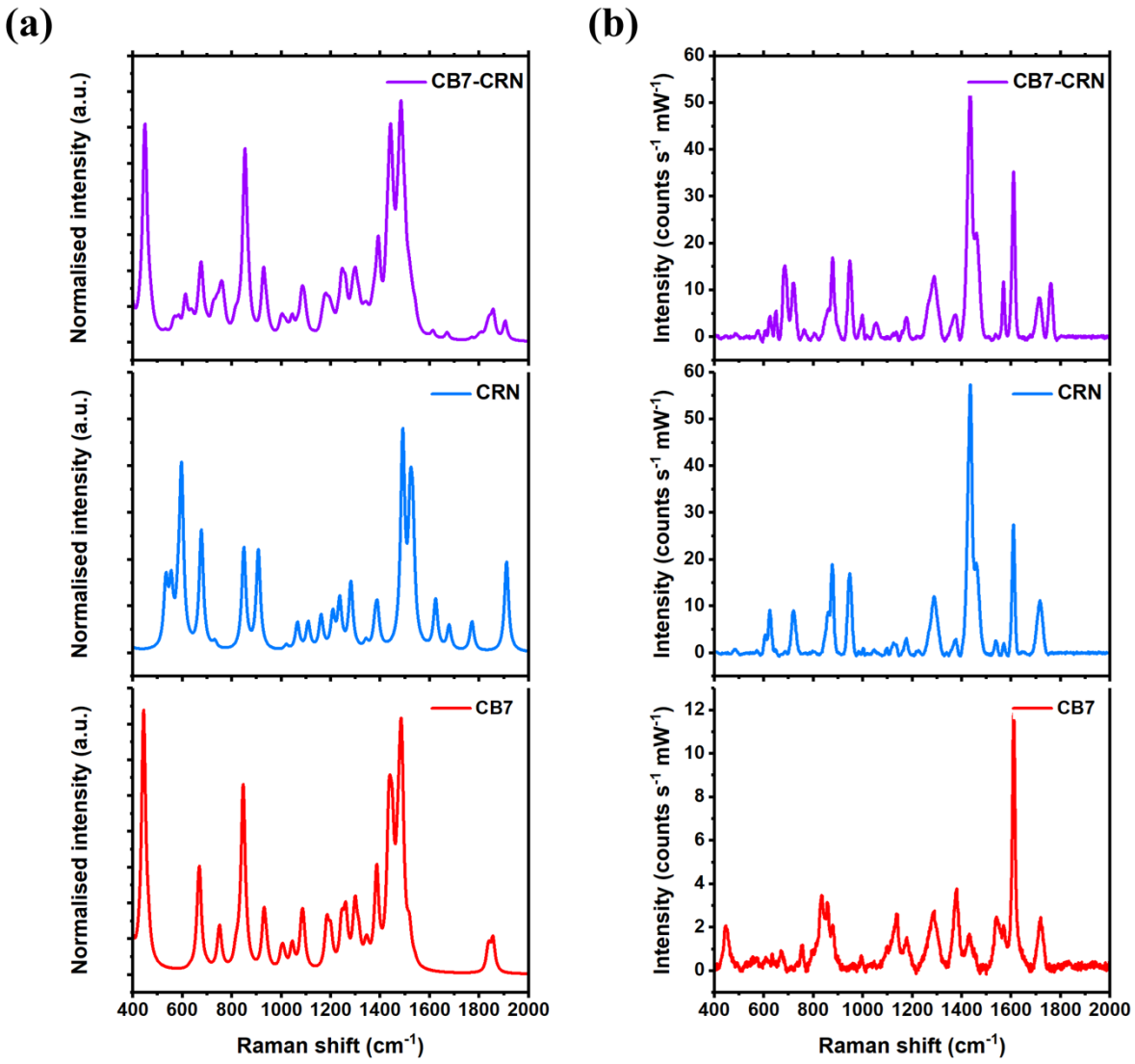

Figure S8. (a) Simulated Raman spectra of CB7, CRN and 1:1 CB7-CRN inclusion complex in water at CPCM/wB97XD/6-31G* level of theory. (b) Experimental SERS spectra of CB7, CRN and CB-CRN inclusion complex with 40 nm Au NPs in water, showing general consistency with the simulated data.

11. SERS spectra of Au NP-CB7-CRN in water

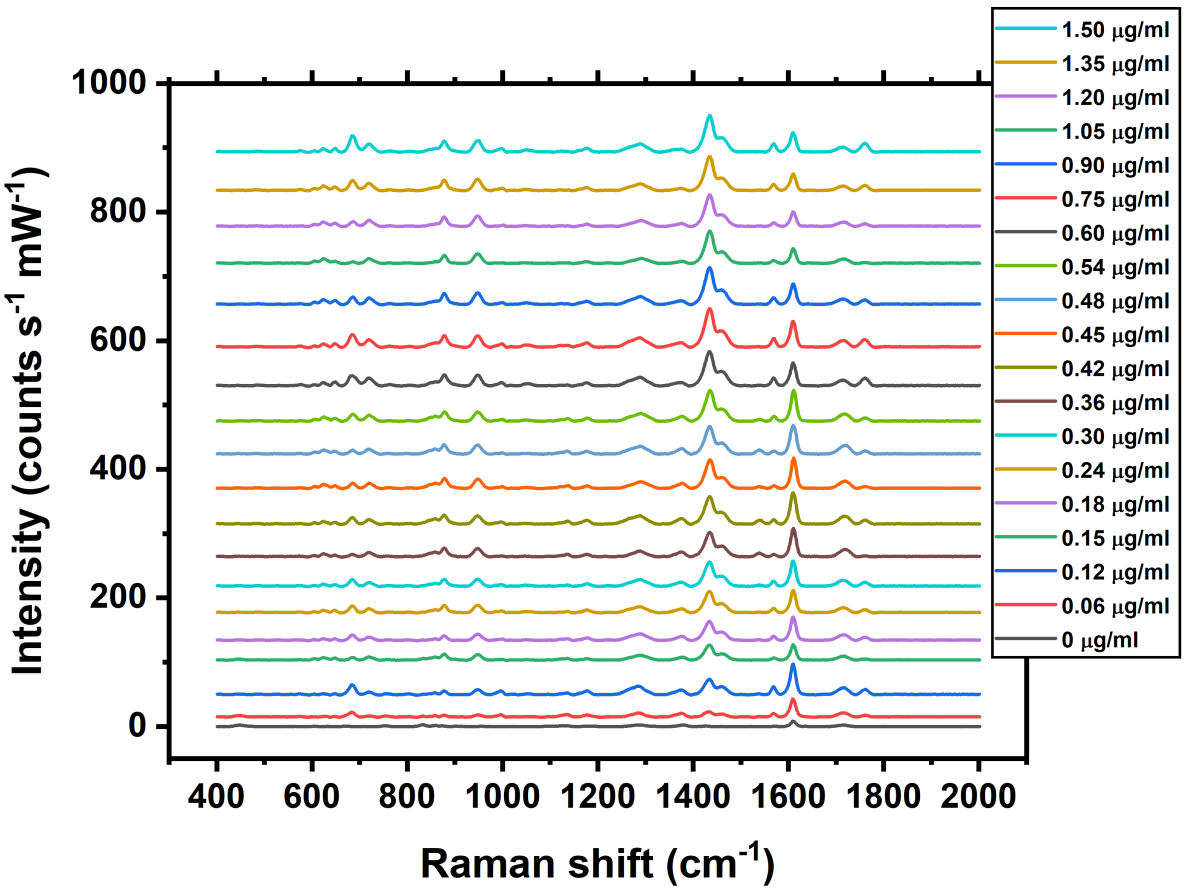

Figure S9. Full SERS spectra of CRN in water with concentrations from 0 to 1.50 μg/ml with aggregation of Au NPs triggered by 10 μM CB7.

12. SERS spectra of Au NP-CRN in water and SU and Raman spectrum of SU

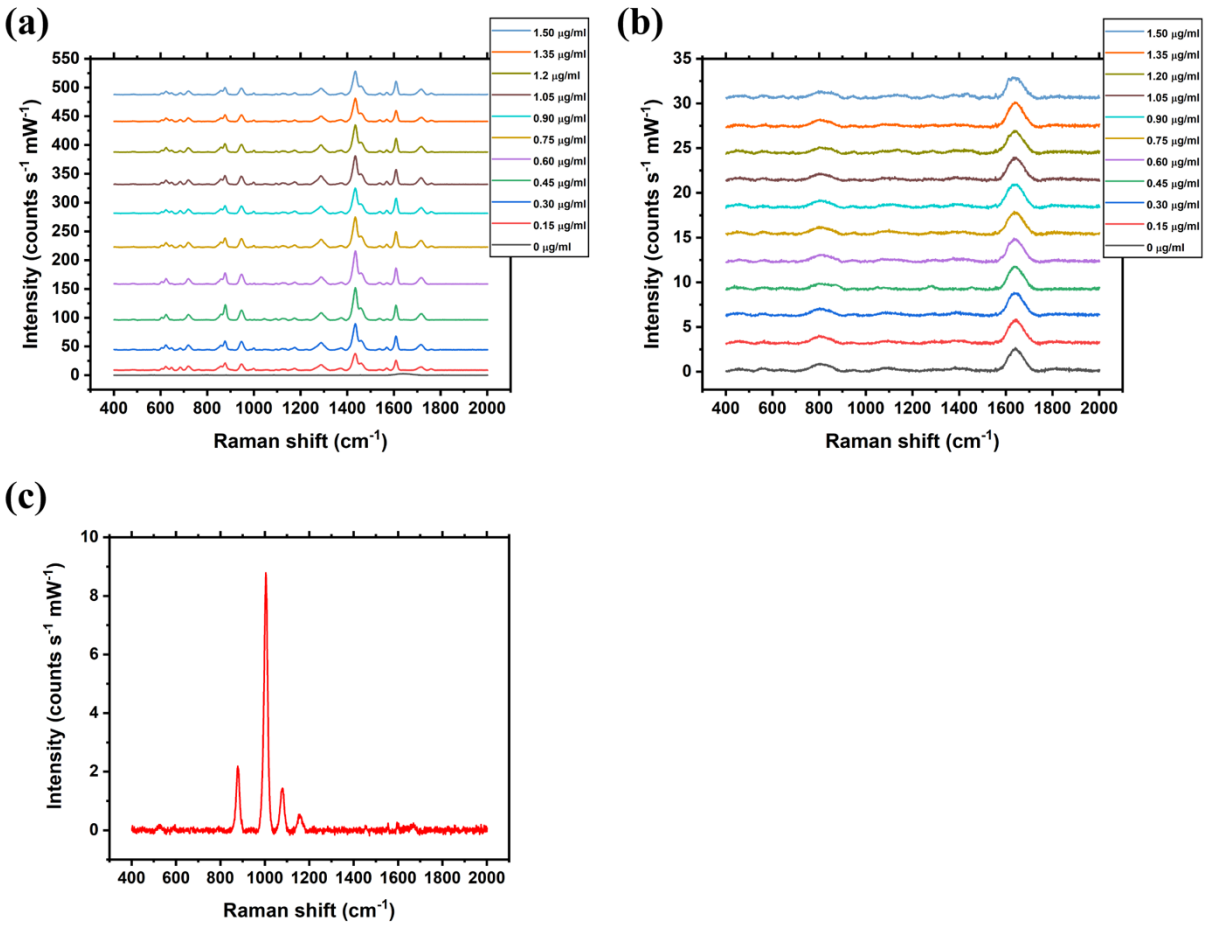

Figure S10. (a-b) SERS spectra of Au NP-CRN in (a) water and (b) SU after 2000x dilution, with CRN concentration from 0 to 1.50 μg/ml in the absence of CB7. (c) Raman spectrum of SU.

13. SERS of Au NP-CB7-CRN in SU after 1000x dilution

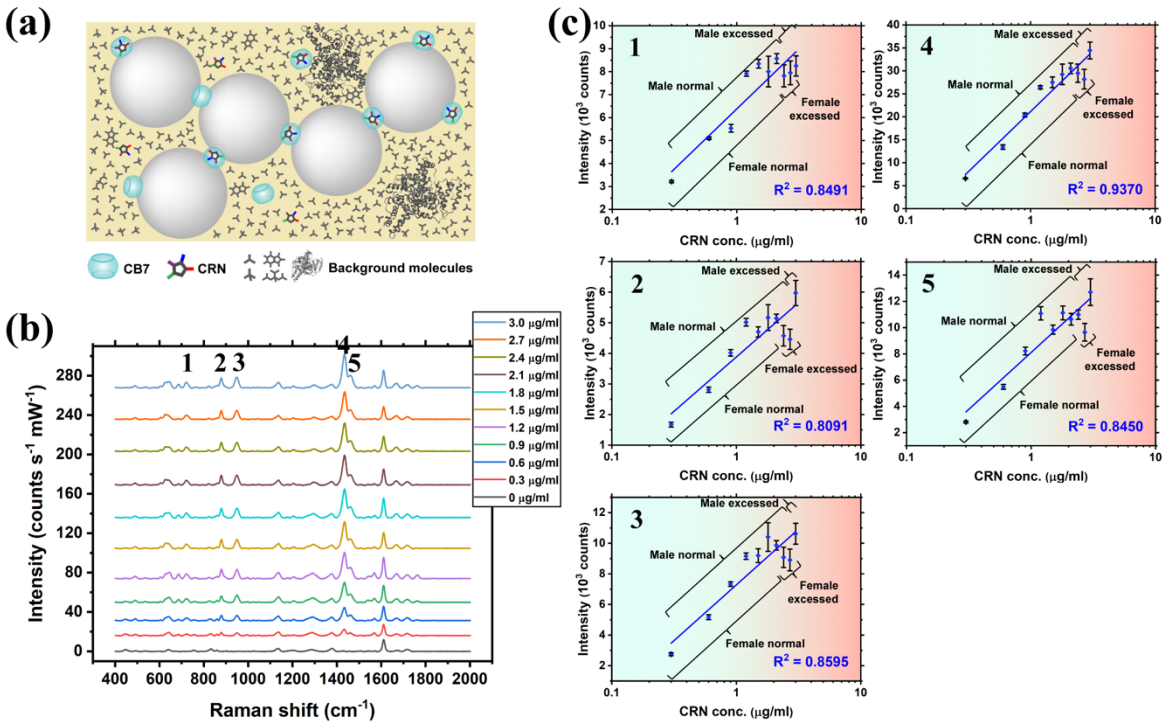

Figure S11. (a) Schematic illustration of the precise plasmonic hotspots within dynamic aggregates of Au NPs formed by 10 μM CB7 for CRN detection in SU after 1000x dilution with water (not to scale). (b) SERS spectra of CRN in SU with concentrations from 0 to 3.0 μg/ml with aggregation of Au NPs triggered by 10 μM CB7. Spectra were baseline corrected and offset for clarity. (c) Corresponding plots of SERS intensity of the five characteristic CRN peaks in (b) against CRN concentration. Logarithmic fittings were performed to reveal correlation between SERS intensity and CRN concentration. (Note: 1 μg/ml in measurement samples corresponds to 1000 μg/ml of the actual CRN concentration in undiluted patient samples.)

14. SERS of Au NP-CB7-CRN in SU after 5000x dilution

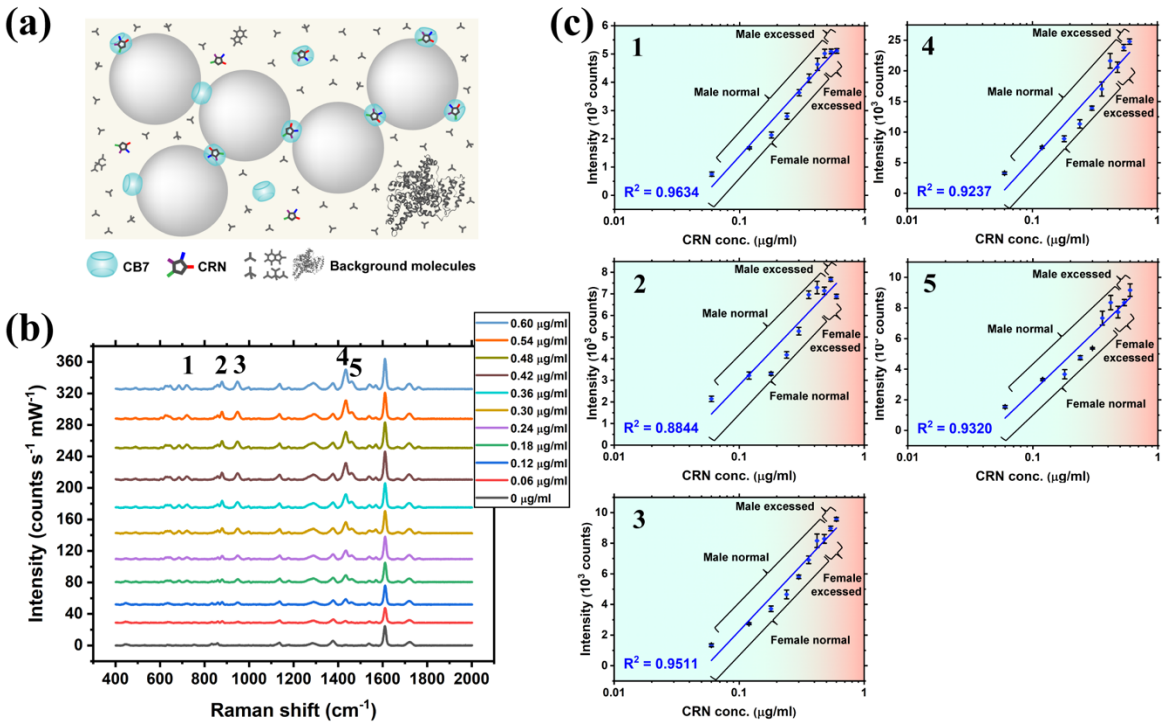

Figure S12. (a) Schematic illustration of the precise plasmonic hotspots within dynamic aggregates of Au NPs formed by 10 μM CB7 for CRN detection in SU after 5000x dilution with water (not to scale). (b) SERS spectra of CRN in SU with concentrations from 0 to 0.60 μg/ml with aggregation of Au NPs triggered by 10 μM CB7. Spectra were baseline corrected and offset for clarity. (c) Corresponding plots of SERS intensity of the five characteristic CRN peaks in (b) against CRN concentration. Logarithmic fittings were performed to reveal correlation between SERS intensity and CRN concentration. (Note: 1 μg/ml in measurement samples corresponds to 5000 μg/ml of the actual CRN concentration in undiluted patient samples.)