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Supplementary information

Identifying a Selective Oligopeptide Clamp in Gas Phase

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Materials

The non-capped pentapeptide (SIVSF) was purchased from Shanghai Yubo Biological Technology Co., LTD (Shanghai, China). The four β_2-blockers and solvents were purchased from Sigma (Shanghai, China). SIVSF was dissolved in methanol containing 0.5% formic acid to a concentration of 0.2 mM. Each β_2-blocker was dissolved in the same solvent to a concentration of 20 mM. Then, the SIVSF solution and the β_2-blocker solutions were mixed, and diluted with methanol to prepare the working solutions. SIVSF and β_2-blocker were both 0.02mM in each working solution.

Collision-induced dissociation

Collision-induced dissociation (CID) was conducted in a triple-quadrupole mass spectrometer (AB Sciex Triple Quad 4500, MA, USA). The working solutions were injected by an injection pump (7 μL min^{-1}) to an electrospray ionization (ESI) source at positive mode. Compared to the ordinary electrospray ionization (ESI) source, the nanoESI source is more prone to retain the solution-phase conformations of peptides, and to achieve high detection sensitivity.[1] The desorption ESI source is especially suitable for the analysis of complex samples with no need of tedious sample preparation.[1] Herein, since the ordinary ESI source is much more widely equipped in academic laboratories and cheaper than other two sources, it was used in the current study. In addition, the pentapeptide was not required to maintain its solution-phase conformation. It was supposed that the pentapeptide could flow to local minima during the ionization processes.[2] The obtained gas-phase conformations were the targets of interest. The collision gas was N_2 in the mass spectrometer. The CID curves were drawn by recording the dissociated ratios of the complex cations along with the center-of-mass collision energy (E_{cm}),

$$E_{cm} = \frac{m}{m+M}E_k$$

where E_{cm} is the center-of-mass collision energy, E_k is the kinetic energy of the complex anions in the collision cell. m and M are the molecular weights of the collision gas and the complex anions. The CID curves were further fit with the Boltzmann function. The data points at the low energy stages were excluded for fitting, as the exotically low abundances of the complex cations might be attributed to the low transportation efficiencies through the collision cell, other than the high fragmentation. The fitting was started from the lowest E_{cm} where the nominal dissociation ratios smaller than 5%.

Infrared multiple photon dissociation (IRMPD) spectroscopy

The IRMPD spectra[3,4] were measured by using a 7 T Fourier Transform Ion Cyclotron Resonance (FT ICR) Mass Spectrometer (IonSpec, Varian Inc., Lake Forest, CA, USA). A Zspray electrospray ionization (ESI) source was used.[5] After passing through the differentially pumped region, ions were accumulated in the hexapole ion trap and finally pulsed into the ICR cell. The pre-selected ions were then isolated in the cell using the stored waveform inverse Fourier-transform (SWIFT) method.[6] The spectra were obtained by manually scanning wavelength in the range from 2895 cm^{-1} to 3720 cm^{-1} in a step width of 5 cm^{-1}. The spectral intensity at each wavelength was calculated as,

$$Intensity = \ln \frac{I_p + \sum I_d}{I_p}$$

where I_p and I_d are the intensities of the parent ion and the daughter ions, respectively.

Theoretical calculations

The pentapeptide-propranolol complex cation was selected for calculating the interaction mode. The search of initial conformers was performed on the Autodock package. Next, molecular mechanisms (MM) calculations were conducted with the Amber package, where the protonated SIVSF was treated with the protein.ff14SB forcefield and the β_2-blockers were treated with the GAFF forcefield. Calculations were performed in a cube with the side length of 30 Å and with 1 fs integration per step. The systems were first heated from 0 K to 1000 K within 7ps, kept at 1000 K for 20 ps, and then annealed to 298 K within 13 ps. Finally, 100 ps of equilibration was performed at 1.0 atm and 298 K. Fifty-eight low-energy conformers were screened from 1000 conformers for further density function theory (DFT) calculations.

All DFT calculations were performed with the Gaussian09 package. Geometry optimizations were performed with the dispersion-corrected density functional method B3LYP-D3 with a Becke-Johnson (BJ) damping function and the 6-31G(d,p) basis set. Normal fundamental vibrational frequencies were scaled by 0.952 to get the harmonic IR spectrums.[7]

References

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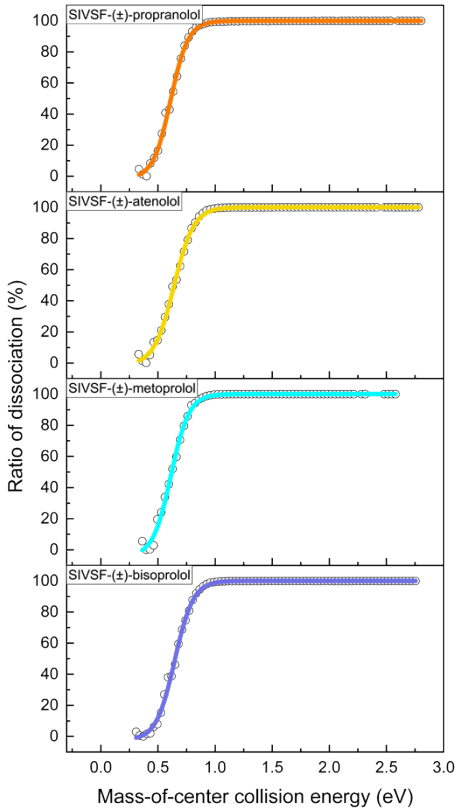

Fig. S1 Collision-induced dissociation curves of the complex cations. All the curves are fit with the Boltzmann function ($y = \frac{A_1 - A_2}{1 + e^{(x - x_0)/dx}} + A_2$, A_1, A_2, x_0 and d are constants).

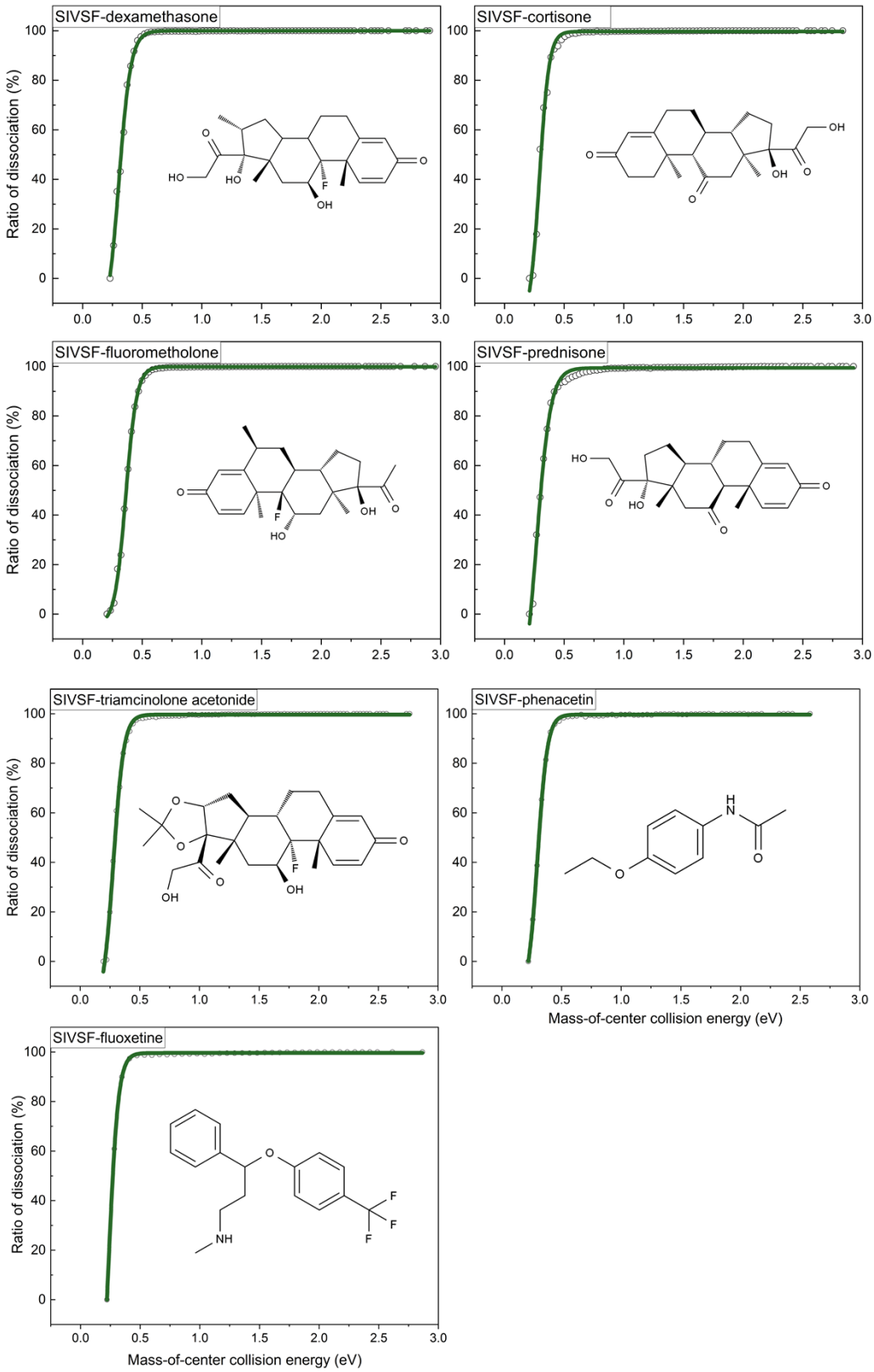

Fig. S2 CID curves of the complex cations formed between SIVSF and other drug molecules.

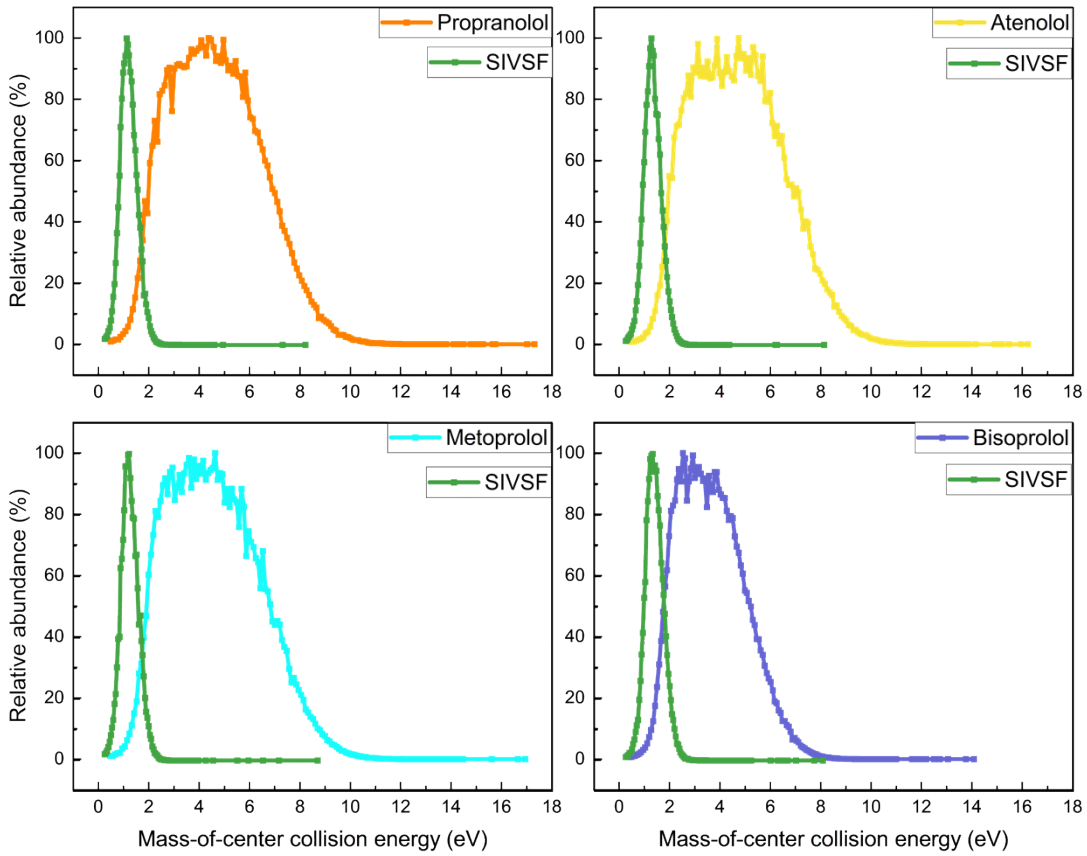

Fig. S3 The relative abundances of the daughter cations during CID at different center-of-mass collision energies.

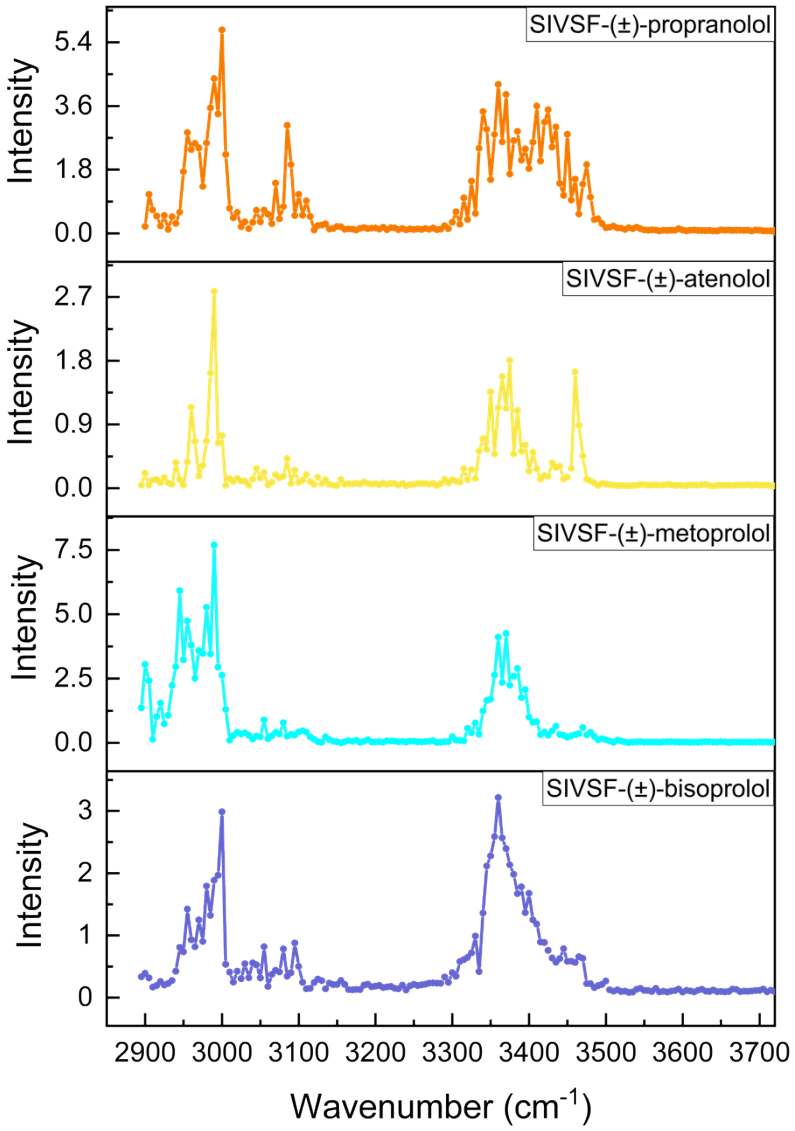

Fig. S4 Experimental IRMPD spectra of the complex cations in the range from 2895 cm^{-1} to 3720 cm^{-1}. The absorption bands of the SIVSF-propranolol complex cation in the region from 3000 cm^{-1} to 3150 cm^{-1} were observed relatively more intensive than the other complex cations. These bands were mainly assigned to the stretches of C-H bonds on aromatic rings. The more intensive absorption bands in this region were attributed to the larger number of C-H bonds on the naphthyl group of propranolol compared with those on the benzene rings of atenolol, bisoprolol and metoprolol. The absorption bands of all the four complex cations in the range from 2900 cm^{-1} to 3000 cm^{-1} were attributed to the aliphatic C-H groups.

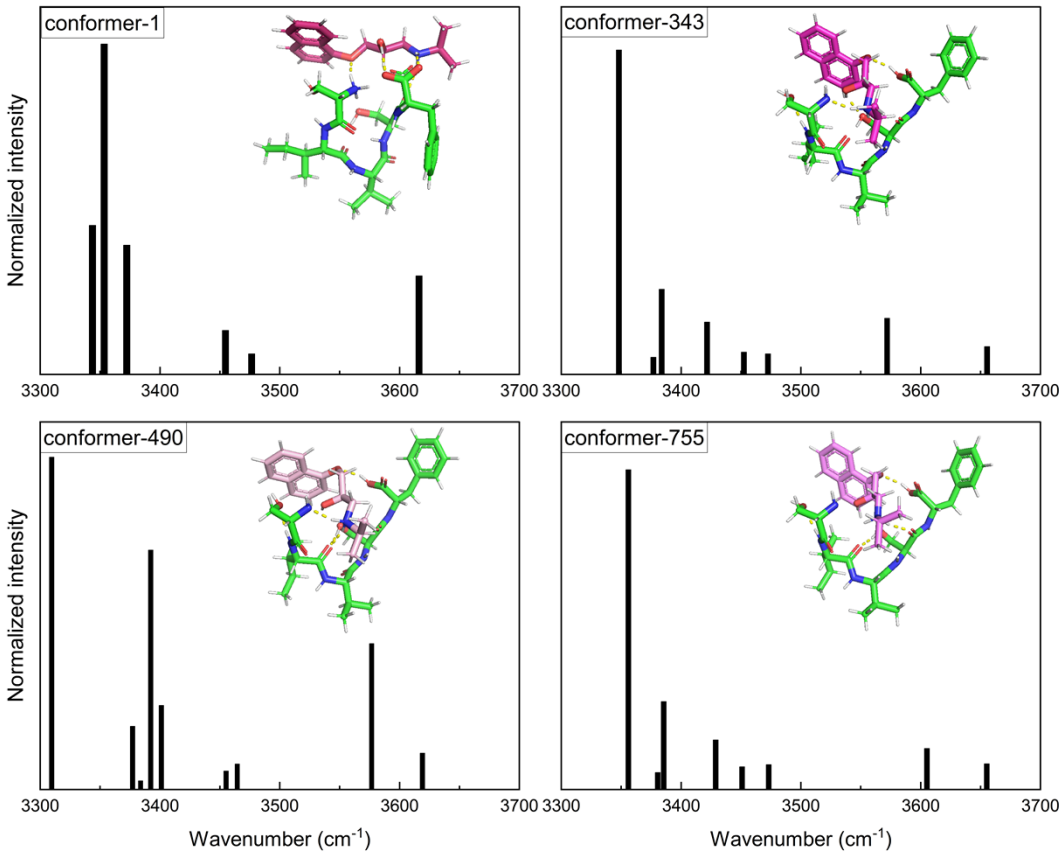

Fig. S5 The calculated IR spectra of four conformers with the energies lower than conformer-76.

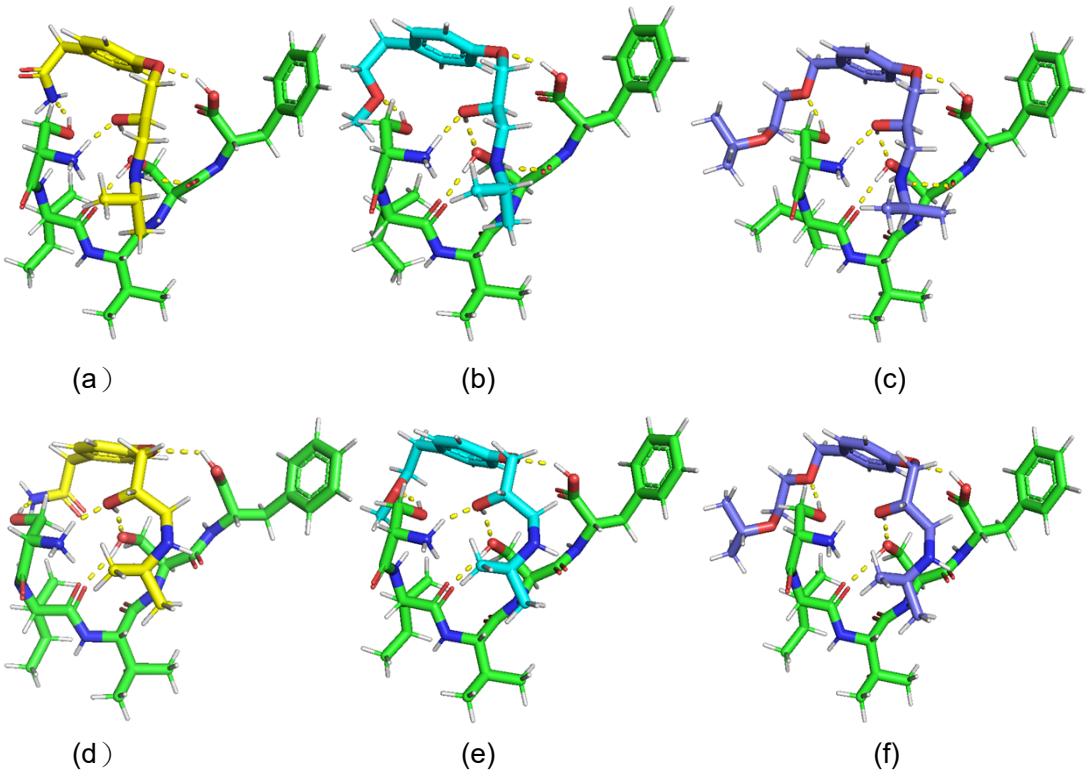

Fig. S6 The calculated conformations of (a) SIVSF-(R)-atenolol, (b) SIVSF-(R)-metoprolol, (c) SIVSF-(R)-bisoprolol, (d) SIVSF-(S)-atenolol, (e) SIVSF-(S)-metoprolol, and (f) SIVSF-(S)-bisoprolol.

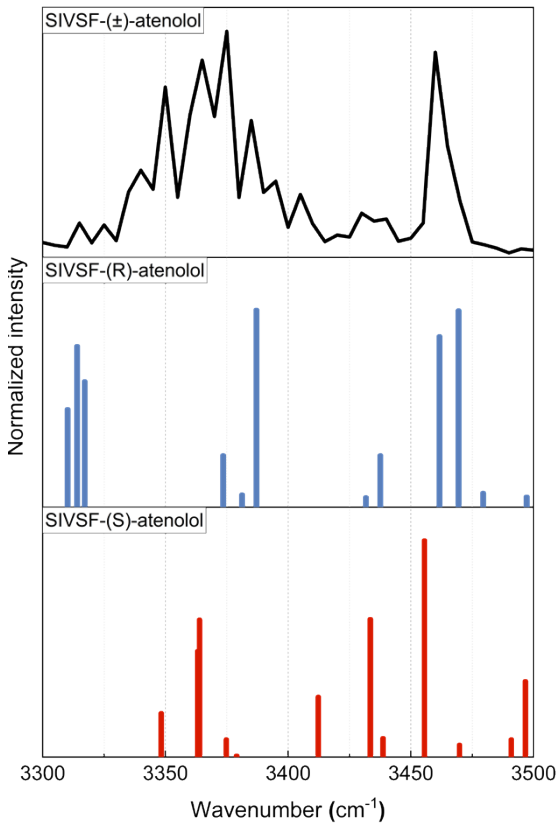

Fig. S7 The comparison between the experimental IRMPD spectrum of SIVSF-(±)-atenolol, and the calculated IR spectra of SIVSF-(R)-atenolol and SIVSF-(S)-atenolol in the range from 3300 cm^{-1} to 3500 cm^{-1}. The principal stretching frequencies of S1-OH in SIVSF-(R)-atenolol and the SIVSF-(S)-atenolol were located at 3462 cm^{-1} and 3434 cm^{-1}, respectively.

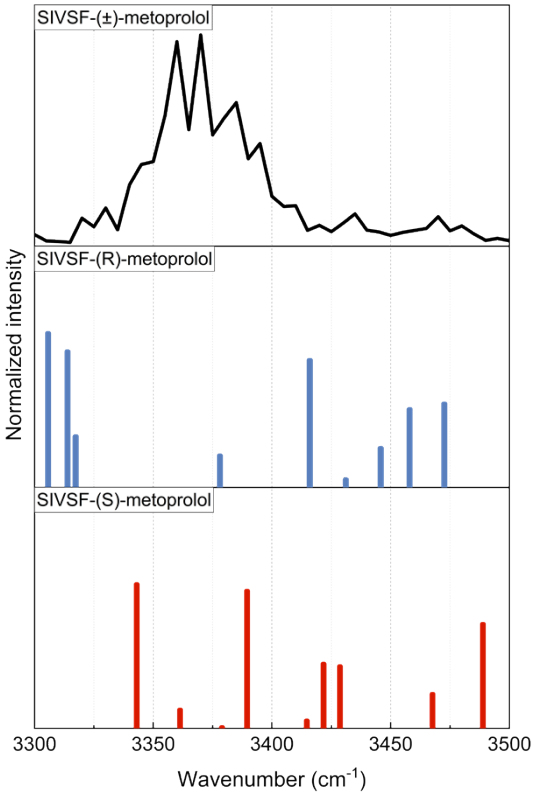

Fig. S8 The comparison between the experimental IRMPD spectrum of SIVSF-(±)-metoprolol, and the calculated IR spectra of SIVSF-(R)-metoprolol and SIVSF-(S)-metoprolol in the range from 3300 cm^{-1} to 3500 cm^{-1}. The principal stretching frequencies of S1-OH in SIVSF-(R)-metoprolol and the SIVSF-(S)-metoprolol were located at 3314 cm^{-1} and 3343 cm^{-1}, respectively.

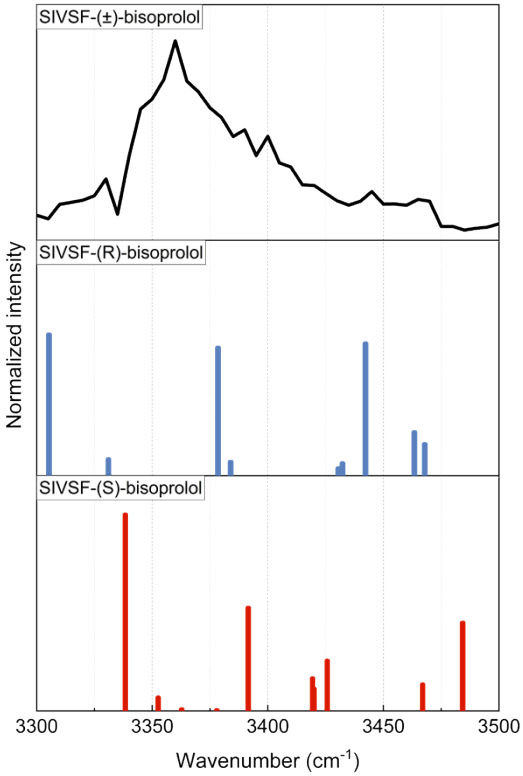

Fig. S9 The comparison between the experimental IRMPD spectrum of SIVSF-(±)-bisoprolol, and the calculated IR spectra of SIVSF-(R)-bisoprolol and SIVSF-(S)-bisoprolol in the range from 3300 cm^{-1} to 3500 cm^{-1}. The principal stretching frequencies of S1-OH in SIVSF-(R)-bisoprolol and the SIVSF-(S)-bisoprolol were located at 3378 cm^{-1} and 3338 cm^{-1}, respectively.

Table S1. Stabilities of the complex cations

Complex cation	$E_{cm,1/2}$
SIVSF-propranolol	1.84
SIVSF-atenolol	1.90
SIVSF-metoprolol	1.85
SIVSF-bisoprolol	1.91
SIVSF-dexamethasone	1.36
SIVSF-cortisone	1.34
SIVSF-fluorometholone	1.44
SIVSF-prednisone	1.31
SIVSF-triamcinolone acetonide	1.32
SIVSF-phenacetin	1.35
SIVSF-fluoxetine	1.26

* $E_{cm,1/2}$ is the center-of-mass collision energy when the ratio of dissociation is 50%. The values are derived from the Boltzmann function.

Table S2. Conformers obtained from MM calculation and their energies obtained from DFT calculation.

Conformer	E* (Hartree)	ΔE (kJ mol^{-1})	Conformer	E* (Hartree)	ΔE (kJ mol^{-1})
1	-2718.55777	-66.15	78	-2718.526119	16.94
755	-2718.545404	-33.69	337	-2718.526115	16.96
490	-2718.543080	-27.59	151	-2718.526114	16.96
343	-2718.541901	-24.50	163	-2718.526113	16.96
76	-2718.532573	0	290	-2718.526113	16.96
495	-2718.531068	3.959	170	-2718.526111	16.97
488	-2718.531051	4.00	112	-2718.526110	16.97
489	-2718.531013	4.10	113	-2718.526109	16.97
514	-2718.530986	4.17	109	-2718.526108	16.97
428	-2718.530694	4.93	333	-2718.526107	16.98
273	-2718.530225	6.16	386	-2718.526107	16.98
326	-2718.530220	6.18	401	-2718.526107	16.98
120	-2718.530219	6.18	227	-2718.526106	16.98
19	-2718.530217	6.19	306	-2718.526106	16.98
166	-2718.530217	6.19	429	-2718.526106	16.98
416	-2718.530217	6.19	171	-2718.526104	16.98
380	-2718.530216	6.19	342	-2718.526104	16.98
188	-2718.530213	6.20	156	-2718.526102	16.99
121	-2718.530211	6.20	697	-2718.525768	17.87
154	-2718.530202	6.23	246	-2718.524920	20.09
220	-2718.530190	6.26	222	-2718.524695	20.68
97	-2718.530171	6.31	111	-2718.524694	20.69
221	-2718.529466	8.16	223	-2718.524693	20.69
45	-2718.529030	9.30	75	-2718.524666	20.76
228	-2718.529023	9.32	243	-2718.524445	21.34
434	-2718.528702	10.16	74	-2718.523648	23.43
432	-2718.528701	10.17	77	-2718.523648	23.43
857	-2718.528349	11.09	224	-2718.523582	23.61
464	-2718.526495	15.96	226	-2718.523345	24.23

*Electronic energy plus thermal free energy correction. Hartree is the unit of Hartree-Fock (HF) energy, 1 Hartree = 2625.5 kJ mol^{-1}.

Table S3. Hydrogen bonds in the complex cations.

			R-enantiomers							
			Propranolol		Atenolol		Metoprolol		Bisoprolol	
No.	donor	acceptor	Length (Å)	Angle (°)	Length (Å)	Angle (°)	Length (Å)	Angle (°)	Length (Å)	Angle (°)
1	S1-OH	A-R[a]	3.20	170.1	2.94	152.8	2.71	154.5	2.76	165.5
2	F-COOH	A-O	2.79	142.0	2.74	145.8	2.73	145.5	2.74	146.2
3	A-OH	S2-OH	2.73	157.0	2.73	153.0	2.77	150.6	2.77	144.0
4	S2-OH	I-amido-V[b]	2.77	170.1	2.80	171.7	2.80	172.9	2.76	170.1
5	S1-NH_3^+	A-OH	2.65	162.7	2.66	163.3	2.64	164.7	2.66	161.6
6	S1-NH_3^+	I-amido-V	2.82	164.2	2.84	164.4	2.81	164.1	2.83	163.8
7	A-NH	S2-amido-F	3.01	160.0	3.07	163.0	3.04	163.3	3.09	148.4
			S-enantiomers							
			Propranolol		Atenolol		Metoprolol		Bisoprolol	
No.	donor	acceptor	Length (Å)	Angle (°)	Length (Å)	Angle (°)	Length (Å)	Angle (°)	Length (Å)	Angle (°)
1	S1-OH	A-R	3.12	166.3	2.95	165.1	2.71	150.8	2.73	171.2
2	F-COOH	A-O	2.80	145.8	2.86	127.9	2.75	141.3	2.77	142.7
3	A-OH	S2-OH	2.88	158.1	2.79	157.6	2.86	153.2	2.86	154.6
4	S2-OH	I-amido-V	2.80	170.1	2.77	167.5	2.81	171.7	2.80	171.7
5	S1-NH_3^+	A-OH	2.65	156.1	2.67	150.7	2.65	152.9	2.66	141.5
6	S1-NH_3^+	I-amido-V	2.76	170.6	2.84	149.0	2.77	172.2	2.770	163.7
7	A-NH	S2-amido-F	3.10	112.3	3.18	108.7	3.15	109.2	3.17	107.4

[a]A-R represents the different moieties on the β_2-blockers for performing as hydrogen bond donors, i.e. the naphthyl group of propranolol, the amido group of atenolol, and the ether O atoms of metoprolol and bisoprolol. A represents the β_2-blockers.

[b]I-amido-V represents the amido bond between I and V amino acid residues.