Molecular-Level Understanding of the hTAS2R1 Receptor-Bitter Tasting Tetra-Peptides Binding: A Structural Biology Study Based on Computational Approaches

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Table S1

Summary of QSAR results for bitter-tasting tetra-peptides based on Alignment 1.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	0.533	0.560	0.072	0.606	0.019	-0.148	0.636	0.6	0.543
R^2_{ncv}	0.995	0.984	0.582	0.998	0.528	0.379	0.988	0.998	0.998
SEE	0.074	0.128	0.600	0.041	0.614	0.705	0.117	0.047	0.047
F	335.267	133.344	6.033	1087.68	7.845	4.265	135.616	848.899	626.269
R^2_{pred}	0.6601	0.828	0.1609	0.2987	0.2097	0.2312	0.9123	0.6476	0.8238
SEP	0.723	0.669	0.894	0.664	0.885	0.958	0.638	0.669	0.799
N_C	6	5	3	6	2	2	6	6	8
Field contribution									
S	0.774	1.000	-	-	-	-	0.607	0.385	0.546
E	0.226	-	1.000	-	-	-	0.393	-	-
H	-	-	-	1.000	-	-	-	0.616	-
D	-	-	-	-	1.000	-	-	-	0.454
A	-	-	-	-	-	1.000	-	-	-
CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	0.535	0.613	0.06	-0.029	0.576	0.526	-0.023	0.612	0.552
R^2_{ncv}	0.989	0.995	0.995	0.429	0.999	0.999	0.538	0.989	0.997
SEE	0.110	0.076	0.099	0.676	0.039	0.032	0.608	0.105	0.063
F	153.128	323.337	114.442	5.258	1042.172	1516.157	8.150	199.207	350.651

R^2_{pred}	0.7181	0.2699	0.119	0.3563	0.2278	0.1866	0.3291	0.7433	0.9272
SEP	0.721	0.658	1.324	0.907	0.726	0.768	0.904	0.628	0.792
N_C	6	6	10	2	7	7	2	5	8
Field contribution									
S	0.721	-	-	-	-	-	-	0.289	0.416
E	-	0.319	0.423	0.625	-	-	-	0.248	0.252
H	-	0.681	-	-	0.610	0.791	-	0.463	-
D	-	-	0.577	-	0.390	-	0.717	-	0.332
A	0.279	-	-	0.375	-	0.209	0.283	-	-

CoMSIA

	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.581	0.603	0.571	0.447	0.567	0.570	-0.063	0.507	0.597
R^2_{ncv}	0.997	0.999	0.998	0.997	0.999	0.998	0.602	1.000	1.000
SEE	0.069	0.026	0.047	0.064	0.027	0.051	0.585	0.026	0.018
F	294.058	2323.592	852.471	339.851	1954.199	609.322	6.550	2114.333	4187.946
R^2_{pred}	0.8219	0.5943	0.5388	0.7332	0.2720	0.1854	0.2203	0.2575	0.6269
SEP	0.765	0.703	0.693	0.879	0.779	0.731	0.956	0.830	0.751
N_C	8	7	6	8	8	7	3	8	8
Field contribution									
S	0.533	0.260	0.331	0.466	-	-	-	-	0.221
E	0.295	-	-	-	0.195	0.260	0.321	-	0.163
H	-	0.437	0.516	-	0.504	0.605	-	0.549	0.373
D	-	0.303	-	0.370	0.301	-	0.489	0.329	0.243
A	0.172	-	0.152	0.164	-	0.135	0.189	0.122	-

CoMSIA

	SEHA	SEDA	SHDA	EHDA	SEHDA
R^2_{cv}	0.589	0.490	0.561	0.521	0.565
R^2_{ncv}	0.999	0.998	0.999	0.999	0.998
SEE	0.041	0.051	0.041	0.038	0.055
F	935.882	540.439	972.431	953.833	531.757
R^2_{pred}	0.5027	0.8989	0.6077	0.2673	0.6172
SEP	0.715	0.845	0.739	0.819	0.735
N_C	7	8	7	8	7
Field contribution					
S	0.266	0.371	0.237	-	0.209
E	0.200	0.214	-	0.173	0.144
H	0.427	-	0.401	0.472	0.355
D	-	0.298	0.263	0.264	0.217
A	0.107	0.117	0.099	0.092	0.076

Table S2

Summary of QSAR results for bitter-tasting tetra-peptides based on Alignment 2.

	CoMFA	CoMSIA							
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	-0.062	0.157	0.049	-0.039	0.158	-0.169	0.080	0.027	0.105
R^2_{ncv}	0.602	0.995	1.000	0.648	0.992	0.997	1.000	0.727	0.999
SEE	0.545	0.074	0.020	0.512	0.084	0.056	0.013	0.451	0.034
F	22.662	342.021	4656.53	27.603	390.717	585.291	10747.363	39.909	1912.074
R^2_{pred}	0.0634	0.0061	0.1862	0.2541	0.1869	0.2794	0.0033	0.2372	0.0156
SEP	0.891	0.971	1.031	0.880	0.886	0.955	1.014	0.852	0.954
N_C	1	6	6	1	4	6	6	1	5
Field contribution									
S	0.333	1.000	-	-	-	-	0.364	0.374	0.338
E	0.667	-	1.000	-	-	-	0.636	-	-
H	-	-	-	1.000	-	-	-	0.626	-
D	-	-	-	-	1.000	-	-	-	0.662
A	-	-	-	-	-	1.000	-	-	-

CoMSIA									
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	-0.102	0.081	0.047	-0.110	-0.024	-0.001	-0.068	0.043	0.072
R^2_{ncv}	0.670	0.998	0.996	1.000	0.767	0.998	1.000	0.998	1.000
SEE	0.496	0.039	0.064	0.020	0.417	0.037	0.008	0.042	0.007
F	30.445	1819.393	676.973	5501.979	49.308	1986.759	26521.825	1553.976	41932。475
R^2_{pred}	0.0181	0.0728	0.0025	0.0117	0.3270	0.1070	0.0584	0.0252	0.0034
SEP	0.907	0.926	0.943	0.917	0.874	0.875	0.929	0.944	1.019
N_C	1	4	4	5	1	4	6	4	6
Field contribution									
S	0.429	-	-	-	-	-	-	0.207	0.237
E	-	0.496	0.501	0.548	-	-	-	0.402	0.362
H	-	0.504	-	-	0.528	0.552	-	0.390	-
D	-	-	0.499	-	0.472	-	0.553	-	0.401
A	0.571	-	-	0.452	-	0.448	0.447	-	-

CoMSIA									
	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	0.010	0.004	-0.001	-0.025	0.060	0.093	-0.064	0.028	0.045
R^2_{ncv}	1.000	0.780	0.752	1.000	1.000	1.000	1.000	0.999	0.999
SEE	0.004	0.405	0.430	0.010	0.005	0.006	0.022	0.024	0.023
F	118.129	53.160	45.505	17544.863	643.86	58658.241	4628.337	4842.346	5065.479
R^2_{pred}	0.0105	0.2567	0.1342	0.0478	0.0123	0.0729	0.0029	0.0383	0.0003
SEP	1.053	0.862	0.864	0.903	1.025	1.0087	0.911	0.952	0.944
N_C	6	1	1	6	6	5	5	4	4

Field contribution									
S	0.241	0.240	0.250	0.236	-	-	-	-	0.154
E	0.422	-	-	-	0.329	0.342	0.359	-	0.285
H	-	0.401	0.418	-	0.352	0.371	-	0.372	0.291
D	-	0.359	-	0.425	0.319	-	0.343	0.339	0.270
A	0.337	-	0.332	0.338	-	0.287	0.298	0.289	-

CoMSIA				
	SEHA	SEDA	SHDA	EHDA	SEHDA
R^2_{cv}	0.069	0.006	0.009	0.056	0.049
R^2_{ncv}	1.000	1.000	1.000	1.000	1.000
SEE	0.011	0.014	0.007	0.003	0.009
F	19009.173	10841.015	41718.111	168101.932	28246.17
R^2_{pred}	0.0495	0.0029	0.0618	0.0211	0.0164
SEP	0.973	1.006	1.053	1.027	1.031
N_C	5	5	6	6	5

Field contribution				
S	0.154	0.177	0.155	-	0.124
E	0.298	0.300	-	0.257	0.231
H	0.304	-	0.309	0.287	0.243
D	-	0.281	0.289	0.239	0.212
A	0.245	0.242	0.247	0.216	0.190

Table S3

Summary of QSAR results for bitter-tasting tetra-peptides based on Alignment 3.

	CoMFA	CoMSIA								
	SE	S	E	H	D	A	SE	SH	SD
R^2_{cv}	-0.054	0.041	-1.159	-0.379	-0.141	-0.954	-0.561	-0.123	0.010
R^2_{ncv}	0.525	0.676	0.454	0.787	0.705	0.508	0.683	0.780	0.784
SEE	0.595	0.492	0.638	0.399	0.469	0.606	0.486	0.405	0.402
F	16.602	31.242	12.464	55.371	35.851	15.492	32.344	53.245	54.367
R^2_{pred}	0.5603	0.4504	0.0256	0.0532	0.4053	0.2518	0.2067	0.2953	0.7550
SEP	0.887	0.846	1.269	1.014	0.923	1.207	1.079	0.915	0.859
N_C	1	1	1	1	1	1	1	1	1
Field contribution									
S	0.555	1.000	-	-	-	-	0.489	0.413	0.327
E	0.445	-	1.000	-	-	-	0.511	-	-
H	-	-	-	1.000	-	-	-	0.587	-
D	-	-	-	-	1.000	-	-	-	0.673
A	-	-	-	-	-	1.000	-	-	-

CoMSIA								
	SA	EH	ED	EA	HD	HA	DA	SEH	SED
R^2_{cv}	-0.300	-0.840	-0.540	-1.231	-0.188	-0.743	-0.508	-0.494	-0.270
R^2_{ncv}	0.892	0.718	0.705	0.572	0.796	0.713	0.700	0.761	0.953

SEE	0.294	0.458	0.469	0.565	0.391	0.462	0.473	0.422	0.194
F	57.516	38.238	35.766	20.031	58.352	37.344	35.056	47.750	140.904
R^2_{pred}	0.1407	0.0218	0.2346	0.1313	0.2629	0.0326	0.1477	0.1678	0.4842
SEP	1.050	1.172	1.072	1.290	0.942	1.140	1.061	1.056	0.993
N_C	2	1	1	1	1	1	1	1	2
Field contribution									
S	0.403	-	-	-	-	-	-	0.288	0.268
E	-	0.424	0.337	0.431	-	-	-	0.302	0.229
H	-	0.576	-	-	0.409	0.507	-	0.410	-
D	-	-	0.663	-	0.591	-	0.598	-	0.503
A	0.597	-	-	0.569	-	0.493	0.402	-	-

CoMSIA

	SEA	SHD	SHA	SDA	EHD	EHA	EDA	HDA	SEHD
R^2_{cv}	-0.707	-0.075	-0.393	-0.307	-0.479	-0.970	-0.734	-0.458	-0.294
R^2_{ncv}	0.976	0.817	0.935	0.767	0.774	0.702	0.701	0.766	0.958
SEE	0.144	0.370	0.227	0.417	0.411	0.472	0.472	0.418	0.183
F	176.546	66.833	101.151	49.394	51.324	35.327	35.171	49.015	160.392
R^2_{pred}	0.0044	0.4665	0.0276	0.3944	0.1799	0.0180	0.0616	0.0979	0.3864
SEP	1.153	0.895	1.037	0.987	1.050	1.212	1.137	1.043	0.993
N_C	3	1	2	1	1	1	1	1	2
Field contribution									
S	0.319	0.223	0.273	0.225	-	-	-	-	0.192
E	0.299	-	-	-	0.231	0.272	0.233	-	0.168
H	-	0.317	0.382	-	0.314	0.369	-	0.292	0.269
D	-	0.459	-	0.463	0.455	-	0.459	0.423	0.371
A	0.382	-	0.345	0.311	-	0.359	0.308	0.284	-

CoMSIA

	SEHA	SEDA	SHDA	EHDA	SEHDA
R^2_{cv}	-0.673	-0.523	-0.309	-0.647	-0.487
R^2_{ncv}	0.752	0.756	0.796	0.754	0.784
SEE	0.430	0.426	0.390	0.428	0.402
F	45.480	46.553	58.600	46.093	54.407
R^2_{pred}	0.0157	0.2336	0.2458	0.0633	0.1746
SEP	1.117	1.066	0.988	1.108	1.053
N_C	1	1	1	1	1
Field contribution					
S	0.206	0.182	0.170	-	0.145
E	0.216	0.191	-	0.177	0.151
H	0.293	-	0.243	0.241	0.206
D	-	0.375	0.351	0.348	0.298
A	0.285	0.252	0.236	0.234	0.200

Table S4 Actual and predicted activity values derived from the developed 3D-QSAR models.

Compound	Actual values (Log 1/T)	Predicted values ((Log 1/T)	
		CoMFA	CoMSIA
1	1.60	1.576	1.646
2	1.70	1.623	1.571
3	1.90	2.014	2.11
4	2.34	2.27	2.274
5	2.34	3.126	2.886
6	2.52	3.122	3.102
7	2.52	2.541	2.551
8	2.52	2.605	2.401
9	2.70	2.687	2.716
10	2.76	2.724	3.034
11	2.85	2.93	2.945
12	2.90	2.867	2.904
13	3.23	3.241	3.249
14	3.41	3.635	3.371
15	3.52	3.422	3.401
16	3.52	3.539	3.563
17	3.52	3.478	3.441
18	3.80	3.571	3.78
19	3.80	3.762	3.307
20	3.80	3.805	3.866
21	3.92	3.952	3.963
22	4.00	4.031	3.985
23	4.40	4.358	4.356

Table S5 The binding free energy between the **Pep23/Pep01** and hTAS2R1 based on the MD simulation (150 frame, respectively) from the lowest kinetics free energy landscape

Energy	Energy Terms	Pep01		Pep23	
		average	Std.Err.of Mean	average	Std.Err.of Mean
GBSA	VDWAALS	-34.2811	0.5186	-47.6254	1.1818
	EEL	-172.0266	6.4774	26.7793	6.489
	EGB	188.4109	5.646	-6.8392	5.833
	ESURF	-5.6819	0.0701	-7.5186	0.1236
	DELTA G gas	-206.3077	6.5755	-20.8461	6.0348
	DELTA G solv	182.729	5.5909	-14.3578	5.8553
	TS	-28.6457	2.5645	-29.6274	2.312
	DELTA GBSA	-23.5786	1.2338	-35.2038	1.3701
	DELTA G total	5.0671	3.7983	-5.5764	3.6821
PBSA	VDWAALS	-34.2811	0.5186	-47.6254	1.1818
	EEL	-172.0266	6.4774	26.7793	6.489
	EPB	186.8132	5.7815	-7.2668	5.4491
	ENPOLAR	-4.0201	0.0259	-5.912	0.0557
	DELTA G gas	-206.3077	6.5755	-20.8461	6.0348
	DELTA G solv	182.793	5.7696	-13.1788	5.4502
	TS	-28.6457	2.5645	-29.6274	2.312
	DELTA PBSA	-23.5146	1.5879	-34.0249	1.6613
	DELTA G total	5.1311	4.1524	-4.3975	3.9733

Figure S1. (A) Present the alignments for bitter peptides from Alignment 2. (B) Present the alignments for bitter peptides from Alignment 3.
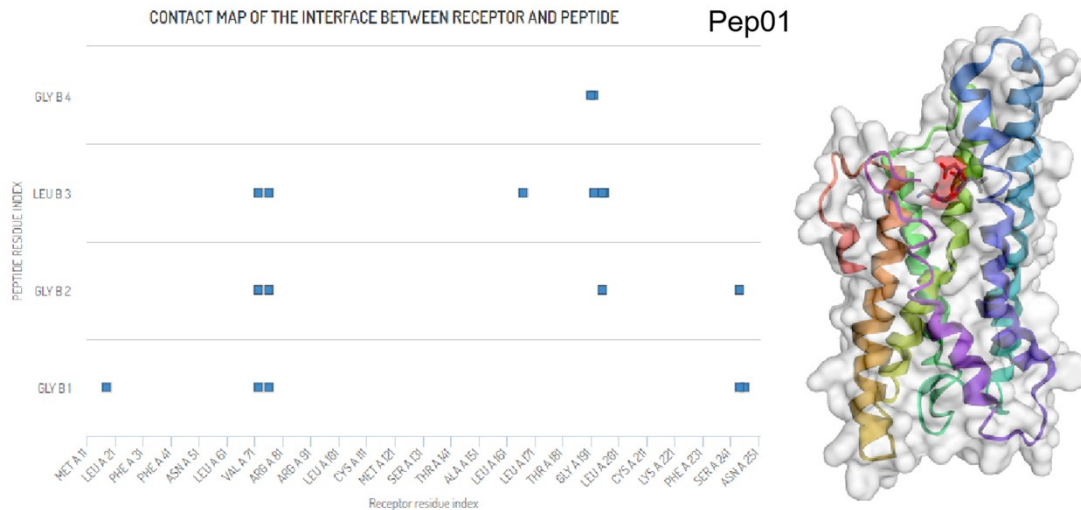
Figure S2. The binding interactions between **Pep01** and hTAS2R1. (A) The contact map of the interface between receptor hTAS2R1 and the **Pep01**. (B) The 3D complex structure of hTAS2R1-**Pep01**. The **Pep01** was shown as red stick and red transparent sphere.
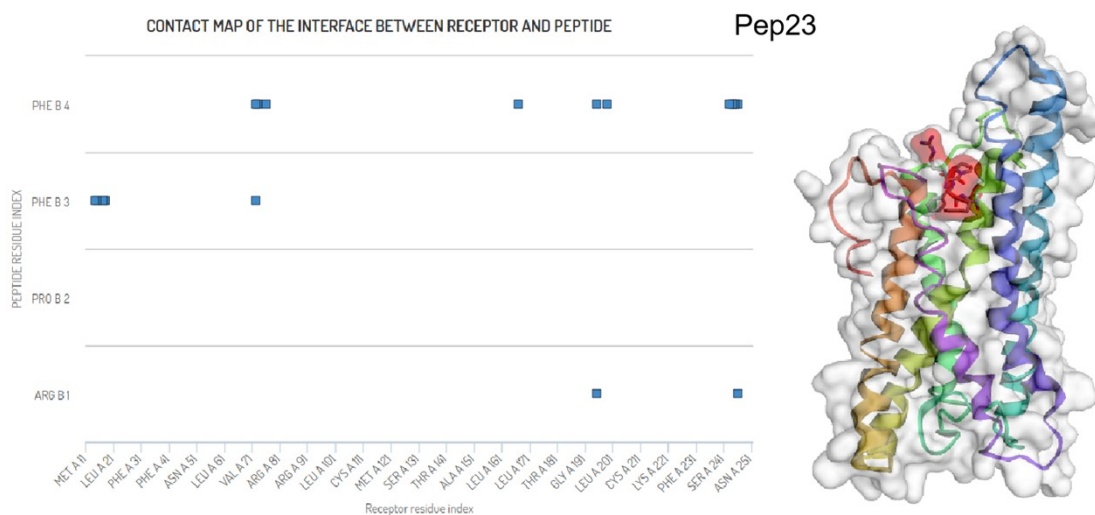

Figure S3. The binding interactions between **Pep23** and hTAS2R1. (A) The contact map of the interface between receptor hTAS2R1 and the **Pep23**. (B) The 3D complex structure of hTAS2R1-**Pep23**. The **Pep23** was shown as red stick and red transparent sphere.
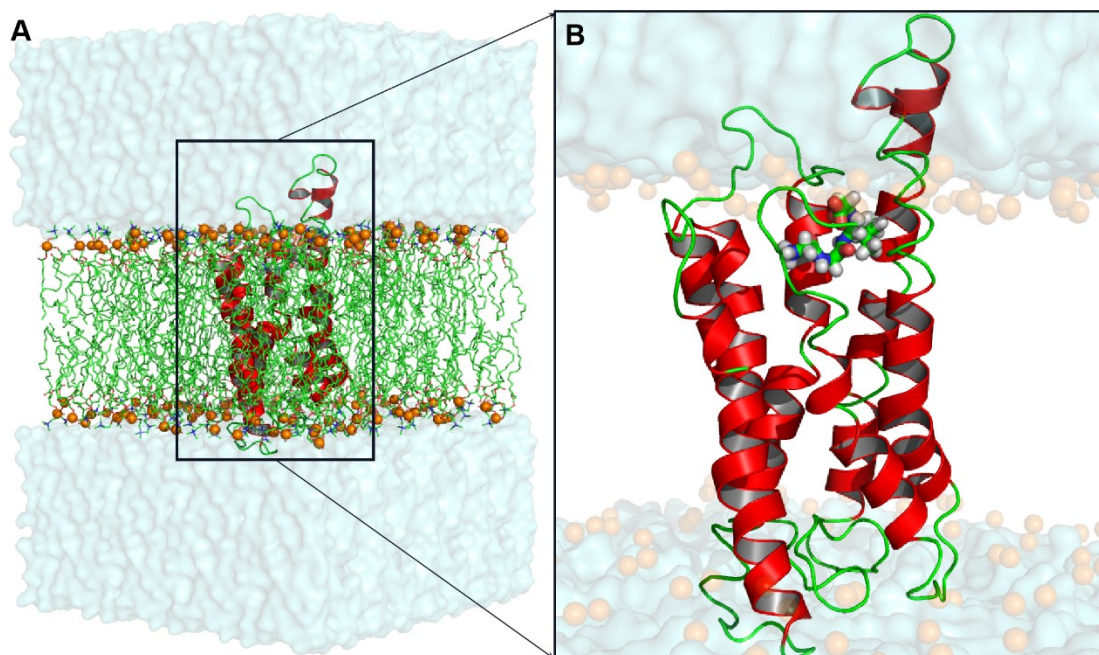
Figure S4. 3D structure for the MD input. (A) The overall structure of the hTAS2R1-peptide-membrane system. (B) The zoom-in structure of the hTAS2R1-peptide, where lipids were hidden.
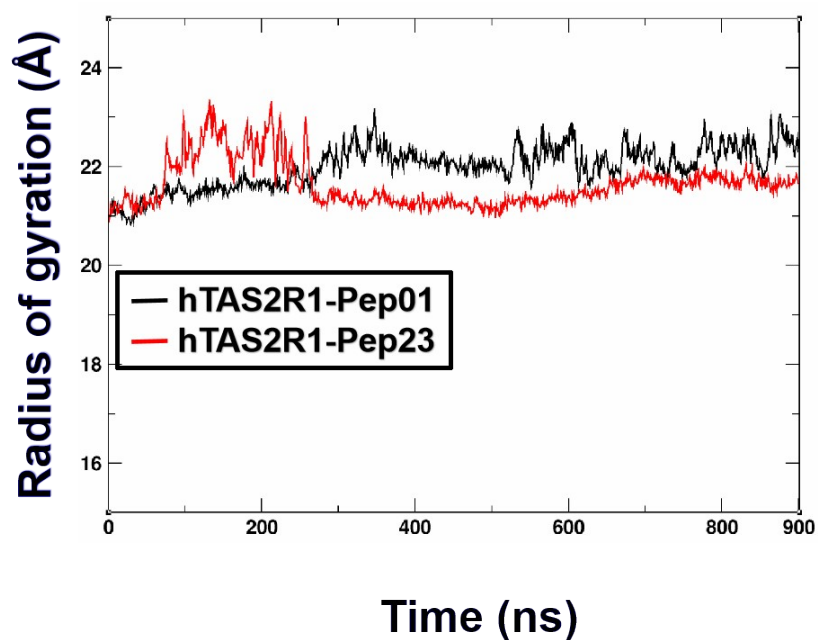

Figure S5. The Rg plot for heavy atoms in the hTAS2R1 protein along the MD trajectories.