

环肽化合物及其应用

相关申请的引用

本申请要求 2023 年 09 月 25 日提交的中国专利申请 CN202311247312.8 和 2024 年 9 月 19 日提交的中国专利申请 CN202411310856.9 的优先权，通过援引加入的方式将其内容整体并入本申请，并用于所有目的。

技术领域

本发明涉及生物医药领域或美容产品领域，具体涉及环肽化合物及其应用。

背景技术

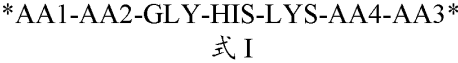
GHK 是一个三肽分子，也称为三胜肽或三肽-1，序列是 glycyl-histidyl-lysine，是胶原蛋白水解产物。它自然存在于人的血液、唾液和尿液当中。GHK 可以促进 I 型胶原片段而闻名。其作用机制可以简单理解为，当胶原蛋白在皮肤中自然分解时，产生的肽片段向皮肤发出信号，表明它应该开始工作，并产生一些漂亮的新胶原蛋白。

GHK 和二价铜离子有高度亲和性，能够自发地与其结合形成络合物 GHK-Cu，后者因水溶液呈蓝色也被称为蓝铜肽，是 GHK 在体内发挥功效的主要形式。它的功能主要包括：(1) 修复细胞的趋化作用，如巨噬细胞、肥大细胞、毛细血管细胞；(2) 抗炎作用(抑制自由基、血栓素形成、转化生长因子 β -1、肿瘤坏死因子 α 和蛋白糖化，同时增加超氧化物歧化酶、扩张血管、阻断紫外线对皮肤角质形成细胞的损伤和改善 X 射线治疗后成纤维细胞的恢复等)；(3) 增加胶原蛋白、弹性蛋白、透明质酸、金属蛋白酶、抗蛋白酶、血管内皮生长因子、成纤维细胞生长因子 2、神经生长因子、中性粒细胞 3 和 4 以及促红细胞生成素的蛋白质合成；(4) 增加成纤维细胞和角质形成细胞的增殖；神经生长、血管生成、和毛囊大小。老化皮肤的对照研究表明，GHK-Cu 可以收紧皮肤，提高弹性和紧致度，减少细纹、皱纹、光损伤和色素沉着过度，还可以促进生发、提高毛发移植的成功率。

发明内容

本发明提供了结构新颖同时功效与 GHK 三肽相当甚至更优的环肽化合物及其在刺激毛发生长或皮肤抗衰老的皮肤病学或美容学组合物中的应用。

为此，在本发明的第一方面，本发明提供了式 I 所示的环肽化合物或其立体异构体，



其中：

AA1 为氨基酸残基；

AA2 不存在或为氨基酸残基；

AA3 为氨基酸残基；

AA4 不存在或为氨基酸残基；

*表示式 I 的 N 端与 C 端相连形成环肽；

所述氨基酸为天然氨基酸或非天然氨基酸；

所述氨基酸为 D 型或 L 型。

需要说明的是，式 I 的左边为 N 端，右边为 C 端。

在一些实施方案中，所述氨基酸为 L 型。

在一些实施方案中，所述氨基酸为天然氨基酸。

在一些实施方案中，所述氨基酸为疏水性天然氨基酸。

5 在一些实施方案中，所述氨基酸选自丙氨酸 (ALA; A)、甘氨酸 (GLY; G)、异亮氨酸 (ILE; I)、亮氨酸 (LEU; L)、甲硫氨酸 (MET; M)、苯丙氨酸 (PHE; F)、脯氨酸 (PRO; P)、色氨酸 (TRP; W)、缬氨酸 (VAL; V)。

10 在一些实施方案中，AA1 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基。

在一些实施方案中，AA1 选自丙氨酸残基、甲硫氨酸残基、苯丙氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基。

在一些实施方案中，AA1 选自甲硫氨酸残基、丙氨酸残基、苯丙氨酸残基、甘氨酸残基、脯氨酸残基。

15 在一些实施方案中，AA2 为氨基酸残基。

在一些实施方案中，AA2 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基。

20 在一些实施方案中，AA2 选自缬氨酸残基、脯氨酸残基、亮氨酸残基、丙氨酸残基、异亮氨酸残基、甲硫氨酸残基、色氨酸残基。

在一些实施方案中，AA2 选自脯氨酸残基、亮氨酸残基、缬氨酸残基、异亮氨酸残基、色氨酸残基。

25 在一些实施方案中，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基。

在一些实施方案中，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、甘氨酸残基、缬氨酸残基。

在一些实施方案中，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、异亮氨酸残基、缬氨酸残基。

30 在一些实施方案中，AA3 选自异亮氨酸残基、亮氨酸残基、苯丙氨酸残基、甲硫氨酸残基、缬氨酸残基。

在一些实施方案中，AA4 不存在。

在一些实施方案中，所述环肽化合物具有式 I-1 所示的结构，

AA3-AA1-AA2-GLY-HIS-LYS

35 式 I-1

其中：

AA1 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

和/或

40 AA2 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

和/或

AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

- *表示式 I-1 的 N 端与 C 端相连形成环肽；
所述氨基酸为 D 型或 L 型。
需要说明的是，式 I-1 的左边为 N 端，右边为 C 端。
在一些实施方案中，所述氨基酸为 L 型。
- 5 在一些实施方案中，AA1 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基。
在一些实施方案中，AA1 选自甲硫氨酸残基、丙氨酸残基、苯丙氨酸残基、甘氨酸残基、脯氨酸残基。
- 10 在一些实施方案中，AA2 选自丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、缬氨酸残基。
在一些实施方案中，AA2 选自脯氨酸残基、亮氨酸残基、缬氨酸残基、异亮氨酸残基、色氨酸残基。
- 15 在一些实施方案中，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、甘氨酸残基、缬氨酸残基。
在一些实施方案中，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、异亮氨酸残基、缬氨酸残基。
在一些实施方案中，AA3 选自异亮氨酸残基、亮氨酸残基、苯丙氨酸残基、甲硫氨酸残基、缬氨酸残基。
- 20 在一些实施方案中，所述环肽化合物的结构式如表 A 所示。

表 A：环肽化合物结构式（所有氨基酸均为 L 型）

SEQ ID NO:	环肽化合物结构式
1	ALA ALA ALA GLY HIS LYS
2	ALA ALA GLY GLY HIS LYS
3	ALA ALA ILE GLY HIS LYS
4	ALA ALA LEU GLY HIS LYS
5	ALA ALA MET GLY HIS LYS
6	ALA ALA PHE GLY HIS LYS
7	ALA ALA PRO GLY HIS LYS
8	ALA ALA TRP GLY HIS LYS
9	ALA ALA VAL GLY HIS LYS
10	ALA GLY ALA GLY HIS LYS
11	ALA GLY GLY GLY HIS LYS
12	ALA GLY ILE GLY HIS LYS
13	ALA GLY LEU GLY HIS LYS
14	ALA GLY MET GLY HIS LYS
15	ALA GLY PHE GLY HIS LYS
16	ALA GLY PRO GLY HIS LYS
17	ALA GLY TRP GLY HIS LYS
18	ALA GLY VAL GLY HIS LYS
19	ALA ILE ALA GLY HIS LYS
20	ALA ILE GLY GLY HIS LYS
21	ALA ILE ILE GLY HIS LYS
22	ALA ILE LEU GLY HIS LYS

23	ALA ILE MET GLY HIS LYS
24	ALA ILE PHE GLY HIS LYS
25	ALA ILE PRO GLY HIS LYS
26	ALA ILE TRP GLY HIS LYS
27	ALA ILE VAL GLY HIS LYS
28	ALA LEU ALA GLY HIS LYS
29	ALA LEU GLY GLY HIS LYS
30	ALA LEU ILE GLY HIS LYS
31	ALA LEU LEU GLY HIS LYS
32	ALA LEU MET GLY HIS LYS
33	ALA LEU PHE GLY HIS LYS
34	ALA LEU PRO GLY HIS LYS
35	ALA LEU TRP GLY HIS LYS
36	ALA LEU VAL GLY HIS LYS
37	ALA MET ALA GLY HIS LYS
38	ALA MET GLY GLY HIS LYS
39	ALA MET ILE GLY HIS LYS
40	ALA MET LEU GLY HIS LYS
41	ALA MET MET GLY HIS LYS
42	ALA MET PHE GLY HIS LYS
43	ALA MET PRO GLY HIS LYS
44	ALA MET TRP GLY HIS LYS
45	ALA MET VAL GLY HIS LYS
46	ALA PHE ALA GLY HIS LYS
47	ALA PHE GLY GLY HIS LYS
48	ALA PHE ILE GLY HIS LYS
49	ALA PHE LEU GLY HIS LYS
50	ALA PHE MET GLY HIS LYS
51	ALA PHE PHE GLY HIS LYS
52	ALA PHE PRO GLY HIS LYS
53	ALA PHE TRP GLY HIS LYS
54	ALA PHE VAL GLY HIS LYS
55	ALA PRO ALA GLY HIS LYS
56	ALA PRO GLY GLY HIS LYS
57	ALA PRO ILE GLY HIS LYS
58	ALA PRO LEU GLY HIS LYS
59	ALA PRO MET GLY HIS LYS
60	ALA PRO PHE GLY HIS LYS
61	ALA PRO PRO GLY HIS LYS
62	ALA PRO TRP GLY HIS LYS
63	ALA PRO VAL GLY HIS LYS
64	ALA TRP ALA GLY HIS LYS
65	ALA TRP GLY GLY HIS LYS

66	ALA TRP ILE GLY HIS LYS
67	ALA TRP LEU GLY HIS LYS
68	ALA TRP MET GLY HIS LYS
69	ALA TRP PHE GLY HIS LYS
70	ALA TRP PRO GLY HIS LYS
71	ALA TRP TRP GLY HIS LYS
72	ALA TRP VAL GLY HIS LYS
73	ALA VAL ALA GLY HIS LYS
74	ALA VAL GLY GLY HIS LYS
75	ALA VAL ILE GLY HIS LYS
76	ALA VAL LEU GLY HIS LYS
77	ALA VAL MET GLY HIS LYS
78	ALA VAL PHE GLY HIS LYS
79	ALA VAL PRO GLY HIS LYS
80	ALA VAL TRP GLY HIS LYS
81	ALA VAL VAL GLY HIS LYS
82	GLY ALA ALA GLY HIS LYS
83	GLY ALA GLY GLY HIS LYS
84	GLY ALA ILE GLY HIS LYS
85	GLY ALA LEU GLY HIS LYS
86	GLY ALA MET GLY HIS LYS
87	GLY ALA PHE GLY HIS LYS
88	GLY ALA PRO GLY HIS LYS
89	GLY ALA TRP GLY HIS LYS
90	GLY ALA VAL GLY HIS LYS
91	GLY GLY ALA GLY HIS LYS
92	GLY GLY GLY GLY HIS LYS
93	GLY GLY ILE GLY HIS LYS
94	GLY GLY LEU GLY HIS LYS
95	GLY GLY MET GLY HIS LYS
96	GLY GLY PHE GLY HIS LYS
97	GLY GLY PRO GLY HIS LYS
98	GLY GLY TRP GLY HIS LYS
99	GLY GLY VAL GLY HIS LYS
100	GLY ILE ALA GLY HIS LYS
101	GLY ILE GLY GLY HIS LYS
102	GLY ILE ILE GLY HIS LYS
103	GLY ILE LEU GLY HIS LYS
104	GLY ILE MET GLY HIS LYS
105	GLY ILE PHE GLY HIS LYS
106	GLY ILE PRO GLY HIS LYS
107	GLY ILE TRP GLY HIS LYS
108	GLY ILE VAL GLY HIS LYS

109	GLY LEU ALA GLY HIS LYS
110	GLY LEU GLY GLY HIS LYS
111	GLY LEU ILE GLY HIS LYS
112	GLY LEU LEU GLY HIS LYS
113	GLY LEU MET GLY HIS LYS
114	GLY LEU PHE GLY HIS LYS
115	GLY LEU PRO GLY HIS LYS
116	GLY LEU TRP GLY HIS LYS
117	GLY LEU VAL GLY HIS LYS
118	GLY MET ALA GLY HIS LYS
119	GLY MET GLY GLY HIS LYS
120	GLY MET ILE GLY HIS LYS
121	GLY MET LEU GLY HIS LYS
122	GLY MET MET GLY HIS LYS
123	GLY MET PHE GLY HIS LYS
124	GLY MET PRO GLY HIS LYS
125	GLY MET TRP GLY HIS LYS
126	GLY MET VAL GLY HIS LYS
127	GLY PHE ALA GLY HIS LYS
128	GLY PHE GLY GLY HIS LYS
129	GLY PHE ILE GLY HIS LYS
130	GLY PHE LEU GLY HIS LYS
131	GLY PHE MET GLY HIS LYS
132	GLY PHE PHE GLY HIS LYS
133	GLY PHE PRO GLY HIS LYS
134	GLY PHE TRP GLY HIS LYS
135	GLY PHE VAL GLY HIS LYS
136	GLY PRO ALA GLY HIS LYS
137	GLY PRO GLY GLY HIS LYS
138	GLY PRO ILE GLY HIS LYS
139	GLY PRO LEU GLY HIS LYS
140	GLY PRO MET GLY HIS LYS
141	GLY PRO PHE GLY HIS LYS
142	GLY PRO PRO GLY HIS LYS
143	GLY PRO TRP GLY HIS LYS
144	GLY PRO VAL GLY HIS LYS
145	GLY TRP ALA GLY HIS LYS
146	GLY TRP GLY GLY HIS LYS
147	GLY TRP ILE GLY HIS LYS
148	GLY TRP LEU GLY HIS LYS
149	GLY TRP MET GLY HIS LYS
150	GLY TRP PHE GLY HIS LYS
151	GLY TRP PRO GLY HIS LYS

152	GLY TRP TRP GLY HIS LYS
153	GLY TRP VAL GLY HIS LYS
154	GLY VAL ALA GLY HIS LYS
155	GLY VAL GLY GLY HIS LYS
156	GLY VAL ILE GLY HIS LYS
157	GLY VAL LEU GLY HIS LYS
158	GLY VAL MET GLY HIS LYS
159	GLY VAL PHE GLY HIS LYS
160	GLY VAL PRO GLY HIS LYS
161	GLY VAL TRP GLY HIS LYS
162	GLY VAL VAL GLY HIS LYS
163	ILE ALA ALA GLY HIS LYS
164	ILE ALA GLY GLY HIS LYS
165	ILE ALA ILE GLY HIS LYS
166	ILE ALA LEU GLY HIS LYS
167	ILE ALA MET GLY HIS LYS
168	ILE ALA PHE GLY HIS LYS
169	ILE ALA PRO GLY HIS LYS
170	ILE ALA TRP GLY HIS LYS
171	ILE ALA VAL GLY HIS LYS
172	ILE GLY ALA GLY HIS LYS
173	ILE GLY GLY GLY HIS LYS
174	ILE GLY ILE GLY HIS LYS
175	ILE GLY LEU GLY HIS LYS
176	ILE GLY MET GLY HIS LYS
177	ILE GLY PHE GLY HIS LYS
178	ILE GLY PRO GLY HIS LYS
179	ILE GLY TRP GLY HIS LYS
180	ILE GLY VAL GLY HIS LYS
181	ILE ILE ALA GLY HIS LYS
182	ILE ILE GLY GLY HIS LYS
183	ILE ILE ILE GLY HIS LYS
184	ILE ILE LEU GLY HIS LYS
185	ILE ILE MET GLY HIS LYS
186	ILE ILE PHE GLY HIS LYS
187	ILE ILE PRO GLY HIS LYS
188	ILE ILE TRP GLY HIS LYS
189	ILE ILE VAL GLY HIS LYS
190	ILE LEU ALA GLY HIS LYS
191	ILE LEU GLY GLY HIS LYS
192	ILE LEU ILE GLY HIS LYS
193	ILE LEU LEU GLY HIS LYS
194	ILE LEU MET GLY HIS LYS

195	ILE LEU PHE GLY HIS LYS
196	ILE LEU PRO GLY HIS LYS
197	ILE LEU TRP GLY HIS LYS
198	ILE LEU VAL GLY HIS LYS
199	ILE MET ALA GLY HIS LYS
200	ILE MET GLY GLY HIS LYS
201	ILE MET ILE GLY HIS LYS
202	ILE MET LEU GLY HIS LYS
203	ILE MET MET GLY HIS LYS
204	ILE MET PHE GLY HIS LYS
205	ILE MET PRO GLY HIS LYS
206	ILE MET TRP GLY HIS LYS
207	ILE MET VAL GLY HIS LYS
208	ILE PHE ALA GLY HIS LYS
209	ILE PHE GLY GLY HIS LYS
210	ILE PHE ILE GLY HIS LYS
211	ILE PHE LEU GLY HIS LYS
212	ILE PHE MET GLY HIS LYS
213	ILE PHE PHE GLY HIS LYS
214	ILE PHE PRO GLY HIS LYS
215	ILE PHE TRP GLY HIS LYS
216	ILE PHE VAL GLY HIS LYS
217	ILE PRO ALA GLY HIS LYS
218	ILE PRO GLY GLY HIS LYS
219	ILE PRO ILE GLY HIS LYS
220	ILE PRO LEU GLY HIS LYS
221	ILE PRO MET GLY HIS LYS
222	ILE PRO PHE GLY HIS LYS
223	ILE PRO PRO GLY HIS LYS
224	ILE PRO TRP GLY HIS LYS
225	ILE PRO VAL GLY HIS LYS
226	ILE TRP ALA GLY HIS LYS
227	ILE TRP GLY GLY HIS LYS
228	ILE TRP ILE GLY HIS LYS
229	ILE TRP LEU GLY HIS LYS
230	ILE TRP MET GLY HIS LYS
231	ILE TRP PHE GLY HIS LYS
232	ILE TRP PRO GLY HIS LYS
233	ILE TRP TRP GLY HIS LYS
234	ILE TRP VAL GLY HIS LYS
235	ILE VAL ALA GLY HIS LYS
236	ILE VAL GLY GLY HIS LYS
237	ILE VAL ILE GLY HIS LYS

238	ILE VAL LEU GLY HIS LYS
239	ILE VAL MET GLY HIS LYS
240	ILE VAL PHE GLY HIS LYS
241	ILE VAL PRO GLY HIS LYS
242	ILE VAL TRP GLY HIS LYS
243	ILE VAL VAL GLY HIS LYS
244	LEU ALA ALA GLY HIS LYS
245	LEU ALA GLY GLY HIS LYS
246	LEU ALA ILE GLY HIS LYS
247	LEU ALA LEU GLY HIS LYS
248	LEU ALA MET GLY HIS LYS
249	LEU ALA PHE GLY HIS LYS
250	LEU ALA PRO GLY HIS LYS
251	LEU ALA TRP GLY HIS LYS
252	LEU ALA VAL GLY HIS LYS
253	LEU GLY ALA GLY HIS LYS
254	LEU GLY GLY GLY HIS LYS
255	LEU GLY ILE GLY HIS LYS
256	LEU GLY LEU GLY HIS LYS
257	LEU GLY MET GLY HIS LYS
258	LEU GLY PHE GLY HIS LYS
259	LEU GLY PRO GLY HIS LYS
260	LEU GLY TRP GLY HIS LYS
261	LEU GLY VAL GLY HIS LYS
262	LEU ILE ALA GLY HIS LYS
263	LEU ILE GLY GLY HIS LYS
264	LEU ILE ILE GLY HIS LYS
265	LEU ILE LEU GLY HIS LYS
266	LEU ILE MET GLY HIS LYS
267	LEU ILE PHE GLY HIS LYS
268	LEU ILE PRO GLY HIS LYS
269	LEU ILE TRP GLY HIS LYS
270	LEU ILE VAL GLY HIS LYS
271	LEU LEU ALA GLY HIS LYS
272	LEU LEU GLY GLY HIS LYS
273	LEU LEU ILE GLY HIS LYS
274	LEU LEU LEU GLY HIS LYS
275	LEU LEU MET GLY HIS LYS
276	LEU LEU PHE GLY HIS LYS
277	LEU LEU PRO GLY HIS LYS
278	LEU LEU TRP GLY HIS LYS
279	LEU LEU VAL GLY HIS LYS
280	LEU MET ALA GLY HIS LYS

281	LEU MET GLY GLY HIS LYS
282	LEU MET ILE GLY HIS LYS
283	LEU MET LEU GLY HIS LYS
284	LEU MET MET GLY HIS LYS
285	LEU MET PHE GLY HIS LYS
286	LEU MET PRO GLY HIS LYS
287	LEU MET TRP GLY HIS LYS
288	LEU MET VAL GLY HIS LYS
289	LEU PHE ALA GLY HIS LYS
290	LEU PHE GLY GLY HIS LYS
291	LEU PHE ILE GLY HIS LYS
292	LEU PHE LEU GLY HIS LYS
293	LEU PHE MET GLY HIS LYS
294	LEU PHE PHE GLY HIS LYS
295	LEU PHE PRO GLY HIS LYS
296	LEU PHE TRP GLY HIS LYS
297	LEU PHE VAL GLY HIS LYS
298	LEU PRO ALA GLY HIS LYS
299	LEU PRO GLY GLY HIS LYS
300	LEU PRO ILE GLY HIS LYS
301	LEU PRO LEU GLY HIS LYS
302	LEU PRO MET GLY HIS LYS
303	LEU PRO PHE GLY HIS LYS
304	LEU PRO PRO GLY HIS LYS
305	LEU PRO TRP GLY HIS LYS
306	LEU PRO VAL GLY HIS LYS
307	LEU TRP ALA GLY HIS LYS
308	LEU TRP GLY GLY HIS LYS
309	LEU TRP ILE GLY HIS LYS
310	LEU TRP LEU GLY HIS LYS
311	LEU TRP MET GLY HIS LYS
312	LEU TRP PHE GLY HIS LYS
313	LEU TRP PRO GLY HIS LYS
314	LEU TRP TRP GLY HIS LYS
315	LEU TRP VAL GLY HIS LYS
316	LEU VAL ALA GLY HIS LYS
317	LEU VAL GLY GLY HIS LYS
318	LEU VAL ILE GLY HIS LYS
319	LEU VAL LEU GLY HIS LYS
320	LEU VAL MET GLY HIS LYS
321	LEU VAL PHE GLY HIS LYS
322	LEU VAL PRO GLY HIS LYS
323	LEU VAL TRP GLY HIS LYS

324	LEU VAL VAL GLY HIS LYS
325	MET ALA ALA GLY HIS LYS
326	MET ALA GLY GLY HIS LYS
327	MET ALA ILE GLY HIS LYS
328	MET ALA LEU GLY HIS LYS
329	MET ALA MET GLY HIS LYS
330	MET ALA PHE GLY HIS LYS
331	MET ALA PRO GLY HIS LYS
332	MET ALA TRP GLY HIS LYS
333	MET ALA VAL GLY HIS LYS
334	MET GLY ALA GLY HIS LYS
335	MET GLY GLY GLY HIS LYS
336	MET GLY ILE GLY HIS LYS
337	MET GLY LEU GLY HIS LYS
338	MET GLY MET GLY HIS LYS
339	MET GLY PHE GLY HIS LYS
340	MET GLY PRO GLY HIS LYS
341	MET GLY TRP GLY HIS LYS
342	MET GLY VAL GLY HIS LYS
343	MET ILE ALA GLY HIS LYS
344	MET ILE GLY GLY HIS LYS
345	MET ILE ILE GLY HIS LYS
346	MET ILE LEU GLY HIS LYS
347	MET ILE MET GLY HIS LYS
348	MET ILE PHE GLY HIS LYS
349	MET ILE PRO GLY HIS LYS
350	MET ILE TRP GLY HIS LYS
351	MET ILE VAL GLY HIS LYS
352	MET LEU ALA GLY HIS LYS
353	MET LEU GLY GLY HIS LYS
354	MET LEU ILE GLY HIS LYS
355	MET LEU LEU GLY HIS LYS
356	MET LEU MET GLY HIS LYS
357	MET LEU PHE GLY HIS LYS
358	MET LEU PRO GLY HIS LYS
359	MET LEU TRP GLY HIS LYS
360	MET LEU VAL GLY HIS LYS
361	MET MET ALA GLY HIS LYS
362	MET MET GLY GLY HIS LYS
363	MET MET ILE GLY HIS LYS
364	MET MET LEU GLY HIS LYS
365	MET MET MET GLY HIS LYS
366	MET MET PHE GLY HIS LYS

367	MET MET PRO GLY HIS LYS
368	MET MET TRP GLY HIS LYS
369	MET MET VAL GLY HIS LYS
370	MET PHE ALA GLY HIS LYS
371	MET PHE GLY GLY HIS LYS
372	MET PHE ILE GLY HIS LYS
373	MET PHE LEU GLY HIS LYS
374	MET PHE MET GLY HIS LYS
375	MET PHE PHE GLY HIS LYS
376	MET PHE PRO GLY HIS LYS
377	MET PHE TRP GLY HIS LYS
378	MET PHE VAL GLY HIS LYS
379	MET PRO ALA GLY HIS LYS
380	MET PRO GLY GLY HIS LYS
381	MET PRO ILE GLY HIS LYS
382	MET PRO LEU GLY HIS LYS
383	MET PRO MET GLY HIS LYS
384	MET PRO PHE GLY HIS LYS
385	MET PRO PRO GLY HIS LYS
386	MET PRO TRP GLY HIS LYS
387	MET PRO VAL GLY HIS LYS
388	MET TRP ALA GLY HIS LYS
389	MET TRP GLY GLY HIS LYS
390	MET TRP ILE GLY HIS LYS
391	MET TRP LEU GLY HIS LYS
392	MET TRP MET GLY HIS LYS
393	MET TRP PHE GLY HIS LYS
394	MET TRP PRO GLY HIS LYS
395	MET TRP TRP GLY HIS LYS
396	MET TRP VAL GLY HIS LYS
397	MET VAL ALA GLY HIS LYS
398	MET VAL GLY GLY HIS LYS
399	MET VAL ILE GLY HIS LYS
400	MET VAL LEU GLY HIS LYS
401	MET VAL MET GLY HIS LYS
402	MET VAL PHE GLY HIS LYS
403	MET VAL PRO GLY HIS LYS
404	MET VAL TRP GLY HIS LYS
405	MET VAL VAL GLY HIS LYS
406	PHE ALA ALA GLY HIS LYS
407	PHE ALA GLY GLY HIS LYS
408	PHE ALA ILE GLY HIS LYS
409	PHE ALA LEU GLY HIS LYS

410	PHE ALA MET GLY HIS LYS
411	PHE ALA PHE GLY HIS LYS
412	PHE ALA PRO GLY HIS LYS
413	PHE ALA TRP GLY HIS LYS
414	PHE ALA VAL GLY HIS LYS
415	PHE GLY ALA GLY HIS LYS
416	PHE GLY GLY GLY HIS LYS
417	PHE GLY ILE GLY HIS LYS
418	PHE GLY LEU GLY HIS LYS
419	PHE GLY MET GLY HIS LYS
420	PHE GLY PHE GLY HIS LYS
421	PHE GLY PRO GLY HIS LYS
422	PHE GLY TRP GLY HIS LYS
423	PHE GLY VAL GLY HIS LYS
424	PHE ILE ALA GLY HIS LYS
425	PHE ILE GLY GLY HIS LYS
426	PHE ILE ILE GLY HIS LYS
427	PHE ILE LEU GLY HIS LYS
428	PHE ILE MET GLY HIS LYS
429	PHE ILE PHE GLY HIS LYS
430	PHE ILE PRO GLY HIS LYS
431	PHE ILE TRP GLY HIS LYS
432	PHE ILE VAL GLY HIS LYS
433	PHE LEU ALA GLY HIS LYS
434	PHE LEU GLY GLY HIS LYS
435	PHE LEU ILE GLY HIS LYS
436	PHE LEU LEU GLY HIS LYS
437	PHE LEU MET GLY HIS LYS
438	PHE LEU PHE GLY HIS LYS
439	PHE LEU PRO GLY HIS LYS
440	PHE LEU TRP GLY HIS LYS
441	PHE LEU VAL GLY HIS LYS
442	PHE MET ALA GLY HIS LYS
443	PHE MET GLY GLY HIS LYS
444	PHE MET ILE GLY HIS LYS
445	PHE MET LEU GLY HIS LYS
446	PHE MET MET GLY HIS LYS
447	PHE MET PHE GLY HIS LYS
448	PHE MET PRO GLY HIS LYS
449	PHE MET TRP GLY HIS LYS
450	PHE MET VAL GLY HIS LYS
451	PHE PHE ALA GLY HIS LYS
452	PHE PHE GLY GLY HIS LYS

453	PHE PHE ILE GLY HIS LYS
454	PHE PHE LEU GLY HIS LYS
455	PHE PHE MET GLY HIS LYS
456	PHE PHE PHE GLY HIS LYS
457	PHE PHE PRO GLY HIS LYS
458	PHE PHE TRP GLY HIS LYS
459	PHE PHE VAL GLY HIS LYS
460	PHE PRO ALA GLY HIS LYS
461	PHE PRO GLY GLY HIS LYS
462	PHE PRO ILE GLY HIS LYS
463	PHE PRO LEU GLY HIS LYS
464	PHE PRO MET GLY HIS LYS
465	PHE PRO PHE GLY HIS LYS
466	PHE PRO PRO GLY HIS LYS
467	PHE PRO TRP GLY HIS LYS
468	PHE PRO VAL GLY HIS LYS
469	PHE TRP ALA GLY HIS LYS
470	PHE TRP GLY GLY HIS LYS
471	PHE TRP ILE GLY HIS LYS
472	PHE TRP LEU GLY HIS LYS
473	PHE TRP MET GLY HIS LYS
474	PHE TRP PHE GLY HIS LYS
475	PHE TRP PRO GLY HIS LYS
476	PHE TRP TRP GLY HIS LYS
477	PHE TRP VAL GLY HIS LYS
478	PHE VAL ALA GLY HIS LYS
479	PHE VAL GLY GLY HIS LYS
480	PHE VAL ILE GLY HIS LYS
481	PHE VAL LEU GLY HIS LYS
482	PHE VAL MET GLY HIS LYS
483	PHE VAL PHE GLY HIS LYS
484	PHE VAL PRO GLY HIS LYS
485	PHE VAL TRP GLY HIS LYS
486	PHE VAL VAL GLY HIS LYS
487	PRO ALA ALA GLY HIS LYS
488	PRO ALA GLY GLY HIS LYS
489	PRO ALA ILE GLY HIS LYS
490	PRO ALA LEU GLY HIS LYS
491	PRO ALA MET GLY HIS LYS
492	PRO ALA PHE GLY HIS LYS
493	PRO ALA PRO GLY HIS LYS
494	PRO ALA TRP GLY HIS LYS
495	PRO ALA VAL GLY HIS LYS

496	PRO GLY ALA GLY HIS LYS
497	PRO GLY GLY GLY HIS LYS
498	PRO GLY ILE GLY HIS LYS
499	PRO GLY LEU GLY HIS LYS
500	PRO GLY MET GLY HIS LYS
501	PRO GLY PHE GLY HIS LYS
502	PRO GLY PRO GLY HIS LYS
503	PRO GLY TRP GLY HIS LYS
504	PRO GLY VAL GLY HIS LYS
505	PRO ILE ALA GLY HIS LYS
506	PRO ILE GLY GLY HIS LYS
507	PRO ILE ILE GLY HIS LYS
508	PRO ILE LEU GLY HIS LYS
509	PRO ILE MET GLY HIS LYS
510	PRO ILE PHE GLY HIS LYS
511	PRO ILE PRO GLY HIS LYS
512	PRO ILE TRP GLY HIS LYS
513	PRO ILE VAL GLY HIS LYS
514	PRO LEU ALA GLY HIS LYS
515	PRO LEU GLY GLY HIS LYS
516	PRO LEU ILE GLY HIS LYS
517	PRO LEU LEU GLY HIS LYS
518	PRO LEU MET GLY HIS LYS
519	PRO LEU PHE GLY HIS LYS
520	PRO LEU PRO GLY HIS LYS
521	PRO LEU TRP GLY HIS LYS
522	PRO LEU VAL GLY HIS LYS
523	PRO MET ALA GLY HIS LYS
524	PRO MET GLY GLY HIS LYS
525	PRO MET ILE GLY HIS LYS
526	PRO MET LEU GLY HIS LYS
527	PRO MET MET GLY HIS LYS
528	PRO MET PHE GLY HIS LYS
529	PRO MET PRO GLY HIS LYS
530	PRO MET TRP GLY HIS LYS
531	PRO MET VAL GLY HIS LYS
532	PRO PHE ALA GLY HIS LYS
533	PRO PHE GLY GLY HIS LYS
534	PRO PHE ILE GLY HIS LYS
535	PRO PHE LEU GLY HIS LYS
536	PRO PHE MET GLY HIS LYS
537	PRO PHE PHE GLY HIS LYS
538	PRO PHE PRO GLY HIS LYS

539	PRO PHE TRP GLY HIS LYS
540	PRO PHE VAL GLY HIS LYS
541	PRO PRO ALA GLY HIS LYS
542	PRO PRO GLY GLY HIS LYS
543	PRO PRO ILE GLY HIS LYS
544	PRO PRO LEU GLY HIS LYS
545	PRO PRO MET GLY HIS LYS
546	PRO PRO PHE GLY HIS LYS
547	PRO PRO PRO GLY HIS LYS
548	PRO PRO TRP GLY HIS LYS
549	PRO PRO VAL GLY HIS LYS
550	PRO TRP ALA GLY HIS LYS
551	PRO TRP GLY GLY HIS LYS
552	PRO TRP ILE GLY HIS LYS
553	PRO TRP LEU GLY HIS LYS
554	PRO TRP MET GLY HIS LYS
555	PRO TRP PHE GLY HIS LYS
556	PRO TRP PRO GLY HIS LYS
557	PRO TRP TRP GLY HIS LYS
558	PRO TRP VAL GLY HIS LYS
559	PRO VAL ALA GLY HIS LYS
560	PRO VAL GLY GLY HIS LYS
561	PRO VAL ILE GLY HIS LYS
562	PRO VAL LEU GLY HIS LYS
563	PRO VAL MET GLY HIS LYS
564	PRO VAL PHE GLY HIS LYS
565	PRO VAL PRO GLY HIS LYS
566	PRO VAL TRP GLY HIS LYS
567	PRO VAL VAL GLY HIS LYS
568	TRP ALA ALA GLY HIS LYS
569	TRP ALA GLY GLY HIS LYS
570	TRP ALA ILE GLY HIS LYS
571	TRP ALA LEU GLY HIS LYS
572	TRP ALA MET GLY HIS LYS
573	TRP ALA PHE GLY HIS LYS
574	TRP ALA PRO GLY HIS LYS
575	TRP ALA TRP GLY HIS LYS
576	TRP ALA VAL GLY HIS LYS
577	TRP GLY ALA GLY HIS LYS
578	TRP GLY GLY GLY HIS LYS
579	TRP GLY ILE GLY HIS LYS
580	TRP GLY LEU GLY HIS LYS
581	TRP GLY MET GLY HIS LYS

582	TRP GLY PHE GLY HIS LYS
583	TRP GLY PRO GLY HIS LYS
584	TRP GLY TRP GLY HIS LYS
585	TRP GLY VAL GLY HIS LYS
586	TRP ILE ALA GLY HIS LYS
587	TRP ILE GLY GLY HIS LYS
588	TRP ILE ILE GLY HIS LYS
589	TRP ILE LEU GLY HIS LYS
590	TRP ILE MET GLY HIS LYS
591	TRP ILE PHE GLY HIS LYS
592	TRP ILE PRO GLY HIS LYS
593	TRP ILE TRP GLY HIS LYS
594	TRP ILE VAL GLY HIS LYS
595	TRP LEU ALA GLY HIS LYS
596	TRP LEU GLY GLY HIS LYS
597	TRP LEU ILE GLY HIS LYS
598	TRP LEU LEU GLY HIS LYS
599	TRP LEU MET GLY HIS LYS
600	TRP LEU PHE GLY HIS LYS
601	TRP LEU PRO GLY HIS LYS
602	TRP LEU TRP GLY HIS LYS
603	TRP LEU VAL GLY HIS LYS
604	TRP MET ALA GLY HIS LYS
605	TRP MET GLY GLY HIS LYS
606	TRP MET ILE GLY HIS LYS
607	TRP MET LEU GLY HIS LYS
608	TRP MET MET GLY HIS LYS
609	TRP MET PHE GLY HIS LYS
610	TRP MET PRO GLY HIS LYS
611	TRP MET TRP GLY HIS LYS
612	TRP MET VAL GLY HIS LYS
613	TRP PHE ALA GLY HIS LYS
614	TRP PHE GLY GLY HIS LYS
615	TRP PHE ILE GLY HIS LYS
616	TRP PHE LEU GLY HIS LYS
617	TRP PHE MET GLY HIS LYS
618	TRP PHE PHE GLY HIS LYS
619	TRP PHE PRO GLY HIS LYS
620	TRP PHE TRP GLY HIS LYS
621	TRP PHE VAL GLY HIS LYS
622	TRP PRO ALA GLY HIS LYS
623	TRP PRO GLY GLY HIS LYS
624	TRP PRO ILE GLY HIS LYS

625	TRP PRO LEU GLY HIS LYS
626	TRP PRO MET GLY HIS LYS
627	TRP PRO PHE GLY HIS LYS
628	TRP PRO PRO GLY HIS LYS
629	TRP PRO TRP GLY HIS LYS
630	TRP PRO VAL GLY HIS LYS
631	TRP TRP ALA GLY HIS LYS
632	TRP TRP GLY GLY HIS LYS
633	TRP TRP ILE GLY HIS LYS
634	TRP TRP LEU GLY HIS LYS
635	TRP TRP MET GLY HIS LYS
636	TRP TRP PHE GLY HIS LYS
637	TRP TRP PRO GLY HIS LYS
638	TRP TRP TRP GLY HIS LYS
639	TRP TRP VAL GLY HIS LYS
640	TRP VAL ALA GLY HIS LYS
641	TRP VAL GLY GLY HIS LYS
642	TRP VAL ILE GLY HIS LYS
643	TRP VAL LEU GLY HIS LYS
644	TRP VAL MET GLY HIS LYS
645	TRP VAL PHE GLY HIS LYS
646	TRP VAL PRO GLY HIS LYS
647	TRP VAL TRP GLY HIS LYS
648	TRP VAL VAL GLY HIS LYS
649	VAL ALA ALA GLY HIS LYS
650	VAL ALA GLY GLY HIS LYS
651	VAL ALA ILE GLY HIS LYS
652	VAL ALA LEU GLY HIS LYS
653	VAL ALA MET GLY HIS LYS
654	VAL ALA PHE GLY HIS LYS
655	VAL ALA PRO GLY HIS LYS
656	VAL ALA TRP GLY HIS LYS
657	VAL ALA VAL GLY HIS LYS
658	VAL GLY ALA GLY HIS LYS
659	VAL GLY GLY GLY HIS LYS
660	VAL GLY ILE GLY HIS LYS
661	VAL GLY LEU GLY HIS LYS
662	VAL GLY MET GLY HIS LYS
663	VAL GLY PHE GLY HIS LYS
664	VAL GLY PRO GLY HIS LYS
665	VAL GLY TRP GLY HIS LYS
666	VAL GLY VAL GLY HIS LYS
667	VAL ILE ALA GLY HIS LYS

668	VAL ILE GLY GLY HIS LYS
669	VAL ILE ILE GLY HIS LYS
670	VAL ILE LEU GLY HIS LYS
671	VAL ILE MET GLY HIS LYS
672	VAL ILE PHE GLY HIS LYS
673	VAL ILE PRO GLY HIS LYS
674	VAL ILE TRP GLY HIS LYS
675	VAL ILE VAL GLY HIS LYS
676	VAL LEU ALA GLY HIS LYS
677	VAL LEU GLY GLY HIS LYS
678	VAL LEU ILE GLY HIS LYS
679	VAL LEU LEU GLY HIS LYS
680	VAL LEU MET GLY HIS LYS
681	VAL LEU PHE GLY HIS LYS
682	VAL LEU PRO GLY HIS LYS
683	VAL LEU TRP GLY HIS LYS
684	VAL LEU VAL GLY HIS LYS
685	VAL MET ALA GLY HIS LYS
686	VAL MET GLY GLY HIS LYS
687	VAL MET ILE GLY HIS LYS
688	VAL MET LEU GLY HIS LYS
689	VAL MET MET GLY HIS LYS
690	VAL MET PHE GLY HIS LYS
691	VAL MET PRO GLY HIS LYS
692	VAL MET TRP GLY HIS LYS
693	VAL MET VAL GLY HIS LYS
694	VAL PHE ALA GLY HIS LYS
695	VAL PHE GLY GLY HIS LYS
696	VAL PHE ILE GLY HIS LYS
697	VAL PHE LEU GLY HIS LYS
698	VAL PHE MET GLY HIS LYS
699	VAL PHE PHE GLY HIS LYS
700	VAL PHE PRO GLY HIS LYS
701	VAL PHE TRP GLY HIS LYS
702	VAL PHE VAL GLY HIS LYS
703	VAL PRO ALA GLY HIS LYS
704	VAL PRO GLY GLY HIS LYS
705	VAL PRO ILE GLY HIS LYS
706	VAL PRO LEU GLY HIS LYS
707	VAL PRO MET GLY HIS LYS
708	VAL PRO PHE GLY HIS LYS
709	VAL PRO PRO GLY HIS LYS
710	VAL PRO TRP GLY HIS LYS

711	VAL PRO VAL GLY HIS LYS
712	VAL TRP ALA GLY HIS LYS
713	VAL TRP GLY GLY HIS LYS
714	VAL TRP ILE GLY HIS LYS
715	VAL TRP LEU GLY HIS LYS
716	VAL TRP MET GLY HIS LYS
717	VAL TRP PHE GLY HIS LYS
718	VAL TRP PRO GLY HIS LYS
719	VAL TRP TRP GLY HIS LYS
720	VAL TRP VAL GLY HIS LYS
721	VAL VAL ALA GLY HIS LYS
722	VAL VAL GLY GLY HIS LYS
723	VAL VAL ILE GLY HIS LYS
724	VAL VAL LEU GLY HIS LYS
725	VAL VAL MET GLY HIS LYS
726	VAL VAL PHE GLY HIS LYS
727	VAL VAL PRO GLY HIS LYS
728	VAL VAL TRP GLY HIS LYS
729	VAL VAL VAL GLY HIS LYS

在一些实施方案中，所述环肽化合物的结构式如表 B 所示。
表 B：优选的环肽化合物结构式（所有氨基酸均为 L 型）

SEQ ID NO:	环肽化合物结构式
52	ALA PHE PRO GLY HIS LYS
214	ILE PHE PRO GLY HIS LYS
414	PHE ALA VAL GLY HIS LYS
250	LEU ALA PRO GLY HIS LYS
297	LEU PHE VAL GLY HIS LYS
205	ILE MET PRO GLY HIS LYS
289	LEU PHE ALA GLY HIS LYS
291	LEU PHE ILE GLY HIS LYS
196	ILE LEU PRO GLY HIS LYS
232	ILE TRP PRO GLY HIS LYS
268	LEU ILE PRO GLY HIS LYS
292	LEU PHE LEU GLY HIS LYS
707	VAL PRO MET GLY HIS LYS
340	MET GLY PRO GLY HIS LYS
710	VAL PRO TRP GLY HIS LYS
293	LEU PHE MET GLY HIS LYS
169	ILE ALA PRO GLY HIS LYS
79	ALA VAL PRO GLY HIS LYS
421	PHE GLY PRO GLY HIS LYS
296	LEU PHE TRP GLY HIS LYS

46	ALA PHE ALA GLY HIS LYS
295	LEU PHE PRO GLY HIS LYS
25	ALA ILE PRO GLY HIS LYS
246	LEU ALA ILE GLY HIS LYS
286	LEU MET PRO GLY HIS LYS
304	LEU PRO PRO GLY HIS LYS
252	LEU ALA VAL GLY HIS LYS
277	LEU LEU PRO GLY HIS LYS
380	MET PRO GLY GLY HIS LYS
461	PHE PRO GLY GLY HIS LYS
160	GLY VAL PRO GLY HIS LYS
367	MET MET PRO GLY HIS LYS
358	MET LEU PRO GLY HIS LYS
349	MET ILE PRO GLY HIS LYS
62	ALA PRO TRP GLY HIS LYS
3	ALA ALA ILE GLY HIS LYS
4	ALA ALA LEU GLY HIS LYS
9	ALA ALA VAL GLY HIS LYS
84	GLY ALA ILE GLY HIS LYS
85	GLY ALA LEU GLY HIS LYS
88	GLY ALA PRO GLY HIS LYS
90	GLY ALA VAL GLY HIS LYS
165	ILE ALA ILE GLY HIS LYS
166	ILE ALA LEU GLY HIS LYS
168	ILE ALA PHE GLY HIS LYS
171	ILE ALA VAL GLY HIS LYS
245	LEU ALA GLY GLY HIS LYS
247	LEU ALA LEU GLY HIS LYS
248	LEU ALA MET GLY HIS LYS
249	LEU ALA PHE GLY HIS LYS
251	LEU ALA TRP GLY HIS LYS
325	MET ALA ALA GLY HIS LYS
327	MET ALA ILE GLY HIS LYS
328	MET ALA LEU GLY HIS LYS
331	MET ALA PRO GLY HIS LYS
333	MET ALA VAL GLY HIS LYS
406	PHE ALA ALA GLY HIS LYS
407	PHE ALA GLY GLY HIS LYS
408	PHE ALA ILE GLY HIS LYS
409	PHE ALA LEU GLY HIS LYS
412	PHE ALA PRO GLY HIS LYS
568	TRP ALA ALA GLY HIS LYS
569	TRP ALA GLY GLY HIS LYS

570	TRP ALA ILE GLY HIS LYS
571	TRP ALA LEU GLY HIS LYS
574	TRP ALA PRO GLY HIS LYS
576	TRP ALA VAL GLY HIS LYS
649	VAL ALA ALA GLY HIS LYS
650	VAL ALA GLY GLY HIS LYS
651	VAL ALA ILE GLY HIS LYS
652	VAL ALA LEU GLY HIS LYS
655	VAL ALA PRO GLY HIS LYS
657	VAL ALA VAL GLY HIS LYS

在一些实施方案中，所述环肽化合物的结构式如表 C 所示。
表 C：更优选的环肽化合物结构式（所有氨基酸均为 L 型）

SEQ ID NO:	环肽化合物结构式
4	ALA ALA LEU GLY HIS LYS
9	ALA ALA VAL GLY HIS LYS
25	ALA ILE PRO GLY HIS LYS
46	ALA PHE ALA GLY HIS LYS
52	ALA PHE PRO GLY HIS LYS
79	ALA VAL PRO GLY HIS LYS
85	GLY ALA LEU GLY HIS LYS
88	GLY ALA PRO GLY HIS LYS
160	GLY VAL PRO GLY HIS LYS
166	ILE ALA LEU GLY HIS LYS
169	ILE ALA PRO GLY HIS LYS
171	ILE ALA VAL GLY HIS LYS
196	ILE LEU PRO GLY HIS LYS
205	ILE MET PRO GLY HIS LYS
214	ILE PHE PRO GLY HIS LYS
232	ILE TRP PRO GLY HIS LYS
245	LEU ALA GLY GLY HIS LYS
246	LEU ALA ILE GLY HIS LYS
247	LEU ALA LEU GLY HIS LYS
249	LEU ALA PHE GLY HIS LYS
250	LEU ALA PRO GLY HIS LYS
252	LEU ALA VAL GLY HIS LYS
268	LEU ILE PRO GLY HIS LYS
286	LEU MET PRO GLY HIS LYS
289	LEU PHE ALA GLY HIS LYS
291	LEU PHE ILE GLY HIS LYS
292	LEU PHE LEU GLY HIS LYS
293	LEU PHE MET GLY HIS LYS
295	LEU PHE PRO GLY HIS LYS

296	LEU PHE TRP GLY HIS LYS
297	LEU PHE VAL GLY HIS LYS
304	LEU PRO PRO GLY HIS LYS
340	MET GLY PRO GLY HIS LYS
380	MET PRO GLY GLY HIS LYS
406	PHE ALA ALA GLY HIS LYS
409	PHE ALA LEU GLY HIS LYS
412	PHE ALA PRO GLY HIS LYS
414	PHE ALA VAL GLY HIS LYS
421	PHE GLY PRO GLY HIS LYS
461	PHE PRO GLY GLY HIS LYS
568	TRP ALA ALA GLY HIS LYS
574	TRP ALA PRO GLY HIS LYS
576	TRP ALA VAL GLY HIS LYS
649	VAL ALA ALA GLY HIS LYS
650	VAL ALA GLY GLY HIS LYS
652	VAL ALA LEU GLY HIS LYS
655	VAL ALA PRO GLY HIS LYS
707	VAL PRO MET GLY HIS LYS
710	VAL PRO TRP GLY HIS LYS

在一些实施方案中，所述环肽化合物的结构式如表 D 所示。
表 D：最优选环肽化合物结构式（所有氨基酸均为 L 型）

SEQ ID NO:	环肽化合物结构式
414	PHE ALA VAL GLY HIS LYS
250	LEU ALA PRO GLY HIS LYS
205	ILE MET PRO GLY HIS LYS
292	LEU PHE LEU GLY HIS LYS
52	ALA PHE PRO GLY HIS LYS
214	ILE PHE PRO GLY HIS LYS
297	LEU PHE VAL GLY HIS LYS
289	LEU PHE ALA GLY HIS LYS
291	LEU PHE ILE GLY HIS LYS
196	ILE LEU PRO GLY HIS LYS
232	ILE TRP PRO GLY HIS LYS
268	LEU ILE PRO GLY HIS LYS
707	VAL PRO MET GLY HIS LYS
340	MET GLY PRO GLY HIS LYS
710	VAL PRO TRP GLY HIS LYS

表 A、表 B、表 C 和表 D 所示环肽化合物结构式中，其左侧氨基酸和与右侧氨基酸通过肽键形成环。
在本发明的第二方面，本发明提供了药物组合物，其包含前述的环肽化合物或其立体异构体。

在一些实施方案中，所述药物组合物还包含至少一种载体和/或赋形剂。

在本发明的第三方面，本发明提供了美容组合物（如护肤品、化妆品、生发液等），其包含前述的环肽化合物或其立体异构体。

在一些实施方案中，所述美容组合物还包含功能性物质。

5 在一些实施方案中，所述功能性物质选自皮肤调理剂、抗氧化剂、表面活性剂、保湿剂、防腐剂、螯合剂、香精中的一种或多种。

在本发明的第四方面，本发明提供了前述的环肽化合物或其立体异构体或者前述的药物组合物在制备药物中的用途，所述药物用于选自以下（1）-（7）中的一种或多种：

- 10 (1) 延缓皮肤老化；
(2) 减少皮肤损伤；
(3) 加速皮肤伤口愈合；
(4) 减少色素沉着过度；
(5) 刺激毛发生长；
15 (6) 提高毛发移植的成功率；
(7) 预防脱发。

在本发明的第五方面，本发明提供了前述的环肽化合物或其立体异构体或者前述的药物组合物，其用于选自以下（1）-（7）中的一种或多种的用途：

- 20 (1) 延缓皮肤老化；
(2) 减少皮肤损伤；
(3) 加速皮肤伤口愈合；
(4) 减少色素沉着过度；
(5) 刺激毛发生长；
(6) 提高毛发移植的成功率；
25 (7) 预防脱发。

在本发明的第六方面，本发明提供了选自以下（1）-（7）中的一种或多种的方法，其包括：给予有需要的受试者有效量的前述的环肽化合物或其立体异构体或者前述的药物组合物，

- 30 (1) 延缓皮肤老化的方法；
(2) 减少皮肤损伤的方法；
(3) 加速皮肤伤口愈合的方法；
(4) 减少色素沉着过度的方法；
(5) 刺激毛发生长的方法；
(6) 提高毛发移植的成功率的方法；
35 (7) 预防脱发的方法。

在本发明的第七方面，本发明提供了前述的环肽化合物或其立体异构体或者前述的美容组合物用于选自以下（1）-（17）中的一种或多种的用途，所述用途为非治疗性用途：

- 40 (1) 皮肤抗老化；
(2) 皮肤抗皱和减少细纹；
(3) 改善皮肤的机械特性：紧实度、肤色、弹性和/或柔韧性；
(4) 提高皮肤密度(重建效果)；
(5) 增加皮肤体积(丰盈效果)；
(6) 对抗牵拉痕外观；

- (7) 减少皮肤损伤;
(8) 加速皮肤伤口愈合;
(9) 抗斑;
(10) 改善皮肤同质性和/或光泽;
5 (11) 减少皮肤色素沉着;
(12) 保湿;
(13) 刺激毛发生长;
(14) 提高毛发移植的成功率;
(15) 预防脱发;
10 (16) 眼睫毛的局部美容;
(17) 增加头发宽度、密度和/或长度。
- 在本发明的第八方面, 本发明提供了选自以下(1) - (17)中的一种或多种的方法, 其包括: 给予有需要的受试者有效量的前述的环肽化合物或其立体异构体或者前述的美容组合物,
- 15 (1) 皮肤抗老化的方法;
(2) 皮肤抗皱和减少细纹的方法;
(3) 改善皮肤的机械特性: 紧实度、肤色、弹性和/或柔韧性的方法;
(4) 提高皮肤密度(重建效果)的方法;
(5) 增加皮肤体积(丰盈效果)的方法;
20 (6) 对抗牵拉痕外观的方法;
(7) 减少皮肤损伤的方法;
(8) 加速皮肤伤口愈合的方法;
(9) 抗斑方法;
(10) 改善皮肤同质性和/或光泽的方法;
25 (11) 减少皮肤色素沉着的方法;
(12) 保湿方法;
(13) 刺激毛发生长的方法;
(14) 提高毛发移植的成功率的方法;
(15) 预防脱发的方法;
30 (16) 眼睫毛的局部美容方法;
(17) 增加头发宽度、密度和/或长度的方法。
- 在本发明的第九方面, 本发明提供了前述的环肽化合物或其立体异构体或者前述的美容组合物用于选自以下(1) - (17)中的一种或多种的用途:
- 35 (1) 皮肤抗老化;
(2) 皮肤抗皱和减少细纹;
(3) 改善皮肤的机械特性: 紧实度、肤色、弹性和/或柔韧性;
(4) 提高皮肤密度(重建效果);
(5) 增加皮肤体积(丰盈效果);
40 (6) 对抗牵拉痕外观;
(7) 减少皮肤损伤;
(8) 加速皮肤伤口愈合;
(9) 抗斑;
(10) 改善皮肤同质性和/或光泽;
(11) 减少皮肤色素沉着;

- (12) 保湿;
- (13) 刺激毛发生长;
- (14) 提高毛发移植的成功率;
- (15) 预防脱发;
- 5 (16) 眼睫毛的局部美容;
- (17) 增加头发宽度、密度和/或长度。

有益效果

- 1、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
10 或其立体异构体可通过显著提升 Collagen I 含量达到抗皱功效。
- 2、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
或其立体异构体可显著提升透明质酸(HA)含量，从而达到紧致功效。
- 3、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
或其立体异构体可显著提升弹力蛋白(Elastin)含量，从而达到紧致功效。
- 15 4、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
或其立体异构体可显著提升 Collagen I 含量、透明质酸(HA)含量和弹力蛋白
(Elastin)含量，从而达到抗皱、紧致功效，医药、美容效果优异。
- 5、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
20 未表现出明显的细胞毒性（例如在 5 μ M 的浓度范围内），具有良好的药物和美
容方向应用前景。
- 6、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
或其立体异构体作为药用时，具有选自以下一种或多种有益效果：
 - (1) 延缓皮肤老化;
 - (2) 减少皮肤损伤;
 - 25 (3) 加速皮肤伤口愈合;
 - (4) 减少色素沉着过度;
 - (5) 刺激毛发生长;
 - (6) 提高毛发移植的成功率;
 - (7) 预防脱发。
- 30 7、本发明的环肽化合物（例如表 A、表 B、表 C 或表 D 中的环肽化合物）
或其立体异构体作为非治疗用途的美容时，具有选自以下一种或多种有益效果：
 - (1) 皮肤抗老化;
 - (2) 皮肤抗皱和减少细纹;
 - (3) 改善皮肤的机械特性：紧实度、肤色、弹性和/或柔韧性;
 - 35 (4) 提高皮肤密度(重建效果);
 - (5) 增加皮肤体积(丰盈效果);
 - (6) 对抗牵拉痕外观;
 - (7) 减少皮肤损伤;
 - (8) 加速皮肤伤口愈合;
 - 40 (9) 抗斑;
 - (10) 改善皮肤同质性和/或光泽;
 - (11) 减少皮肤色素沉着;
 - (12) 保湿;
 - (13) 刺激毛发生长;

- (14) 提高毛发移植的成功率;
 - (15) 预防脱发;
 - (16) 眼睫毛的局部美容;
 - (17) 增加头发宽度、密度和/或长度。
- 5 8、本发明的环肽化合物 (例如表 A、表 B、表 C 或表 D 中的环肽化合物) 或其立体异构体作为美容时, 具有选自以下一种或多种有益效果:
- (1) 皮肤抗老化;
 - (2) 皮肤抗皱和减少细纹;
 - (3) 改善皮肤的机械特性: 紧实度、肤色、弹性和/或柔韧性;
 - 10 (4) 提高皮肤密度(重建效果);
 - (5) 增加皮肤体积(丰盈效果);
 - (6) 对抗牵拉痕外观;
 - (7) 减少皮肤损伤;
 - (8) 加速皮肤伤口愈合;
 - 15 (9) 抗斑;
 - (10) 改善皮肤同质性和/或光泽;
 - (11) 减少皮肤色素沉着;
 - (12) 保湿;
 - (13) 刺激毛发生长;
 - 20 (14) 提高毛发移植的成功率;
 - (15) 预防脱发;
 - (16) 眼睫毛的局部美容;
 - (17) 增加头发宽度、密度和/或长度。
- 25 9、本发明的环肽化合物 (例如表 A、表 B、表 C 或表 D 中的环肽化合物) 或其立体异构体的以上 8 个方面的功效与 GHK 三肽相当甚至更优。

具体实施方式

下面将结合实施例对本发明的实施方案进行详细描述, 但是本领域技术人员将会理解, 下列实施例仅用于说明本发明, 而不应视为限定本发明的范围。实施

30 例中未注明具体条件者, 按照常规条件或制造商建议的条件进行。所用试剂或仪器未注明生产厂商者, 均为可以通过市购获得的常规产品。

在本发明中, 除非另有说明, 否则本文中使用的科学和技术名词具有本领域技术人员所通常理解的含义。并且, 本文中所用的蛋白质和核酸化学、分子生物学、细胞和组织培养、微生物学、免疫学相关术语和实验室操作步骤均为相应领

35 域内广泛使用的术语和常规步骤。同时, 为了更好地理解本发明, 下面提供相关术语的定义和解释。

术语“立体异构体”指在有相同分子式的化合物分子中, 原子或取代基互相连接的次序相同, 但在空间的排列方式不同, 属于有机化学范畴中的同分异构现象。

术语“不存在”表示其两侧的基团直接相连。例如, 式 I 所示的环肽化合物中,

40 AA4 不存在, 则式 I 所示的环肽化合物的结构式变为*AA1-AA2-GLY-HIS-LYS-AA3*。

术语“载体”指能改变药物进入人体的方式和在体内的分布、控制药物的释放速度并将药物输送到靶向器官的体系。药物载体释放和靶向系统能够减少药物降解及损失, 降低副作用, 提高生物利用度。如可作为载体的高分子表面活性剂由

于其独特的两亲性结构，可以进行自组装，形成各种形式的聚集体，优选的实例如胶束、微乳液、凝胶、液晶、囊泡等。这些聚集体具有包载药物分子的能力，同时又对膜有良好的渗透性，可以作为优良的药物载体。

5 术语“赋形剂”指在药物制剂中除主药以外的附加物，也可称为辅料，辅料包括但不限于：离子交换剂，氧化铝，硬脂酸铝，卵磷脂，血清蛋白如人血白蛋白，缓冲物质如磷酸盐，甘油，山梨酸，山梨酸钾，饱和植物脂肪酸的部分甘油酯混合物，水，盐或电解质，如硫酸鱼精蛋白，磷酸氢二钠，磷酸氢钾，氯化钠，锌盐，胶态氧化硅，三硅酸镁，聚乙烯吡咯烷酮，纤维素物质，聚乙二醇，羧甲基纤维素钠，聚丙烯酸酯，蜂蜡，羊毛脂等等。

10 术语“皮肤调理剂”包括但不限于氢醌、曲酸、熊果苷、鞣花酸、壬二酸、壬二酰二甘氨酸、L-抗坏血酸及其衍生物、甘草提取物、凹缘金虎尾果提取物、绣球提取物、烷氧基水杨酸、虎杖提取物、槐花提取物、姜黄提取物、桑树皮提取物、余甘子提取物、豌豆提取物、芦荟素等。

15 术语“抗氧化剂”包括但不限于丁羟甲苯、丁羟茴醚、倍酸丙酯、倍酸辛酯、十二醇倍酸酯、叔丁基氢醌、生育酚、抗坏血酸棕榈酸酯、柠檬酸异丙酯混合物、单酸甘油酯柠檬酸酯、阿诺克索默、亚硫酸钠、亚硫酸氢钠、焦亚硫酸钠、半胱氨酸、异抗坏血酸、硫脲、二月桂醇硫代丙二酸酯、去甲二氢愈创木酸、硫辛酸、 α -生育酚乙酸酯、类胡萝卜素、余甘子单宁、抗坏血酸、谷胱甘肽、辅酶 Q10 等。

20 术语“表面活性剂”可以为阴离子表面活性剂、阳离子表面活性剂、非离子表面活性剂、两性表面活性剂、天然表面活性剂、含氟表面活性剂等。

术语“保湿剂”包括但不限于甘油、丙二醇、丁二醇、山梨（糖）醇、山梨醇聚醚-20、酰胺类保湿剂、甘油聚醚类保湿剂、乳酸和乳酸钠、吡咯烷酮羧酸钠、羟乙基脲、赤藓醇、甘油聚醚-5 乳酸酯、透明质酸钠、糖类同分异构体、D-泛醇、聚乙二醇、双甘油、甲基丙烯酰氧乙基磷酸胆碱等。

25 术语“防腐剂”包括但不限于羟苯酯类及其盐类、甲醛和甲醛供体、异噻唑啉酮类、酚类防腐剂、酸类防腐剂、卤化物防腐剂、季铵化合物、醇类、常用的复配防腐剂和天然防腐剂等。

术语“螯合剂”可选自乙二胺四乙酸及其钠盐、甘氨酸、柠檬酸、琥珀酸等。

30 术语“香精”具体可以是檀香、茉莉、玫瑰、甜橙、香草味香精等。香精也可以包括精油，具体可以是酸橙果皮油、苦橙叶/嫩枝油、香叶天竺葵油、突厥蔷薇花油等。

35 术语“治疗”一般是指获得需要的药理和/或生理效应。该效应根据完全或部分地预防疾病或其症状，可以是预防性的；和/或根据部分或完全稳定或治愈疾病和/或由于疾病产生的副作用，可以是治疗性的。本文使用的“治疗”涵盖了对患者疾病的任何治疗，包括：(a)预防易感染疾病或症状但还没诊断出患病的患者所发生的疾病或症状；(b)抑制疾病的症状，即阻止其发展；或(c)缓解疾病的症状，即，导致疾病或症状退化。

40 术语“受试者”包括人或非人动物。本发明中术语“非人动物”包括所有脊椎动物，例如非哺乳动物(例如鸟类、两栖动物、爬行动物)和哺乳动物，例如非人灵长类、家畜和/或驯化动物(例如绵羊、犬、猫、奶牛、猪等)。

术语“有效量”指在必需的剂量和时间上有效实现期望的效果的量。本发明的“有效量”可根据诸如个体的皮肤/毛发状态、年龄、性别和体重等因素而变化。

本发明中，20 种常规氨基酸和其缩写遵从常规用法。参见 Immunology-A Synthesis (第 2 版, E.S. Golub 和 D.R. Gren, Eds., Sinauer Associates, Sunderland,

Mass. (1991))，其通过引用合并入本文。

本领域技术人员公知，术语“氨基酸残基”指的是氨基酸的氨基失去一个氢、羧基失去一个羟基后，剩余的不完整的氨基酸结构，具有氨基端（N 端）和羧基端（C 端）。

5 本发明的环肽化合物（包括但不限于表 A、表 B、表 C、表 D 中的环肽化合物）中，如无特殊说明，默认从左向右为 N 端至 C 端，且左侧 N 端与右侧 C 端连接形成 NC 环肽。

另外，实施例中的缩写具有本领域公知的常规含义，现列举说明如下：

- 10 AcOH, Acetic Acid, 乙酸
ACN, Acetonitrile, 乙腈
DCM, Dichloromethane (Methylene chloride), 二氯甲烷
DMF, N,N-Dimethylformamide, N,N-二甲基甲酰胺
DIEA, N,N-Diisopropylethylamine, N,N-二异丙基乙胺
Fmoc, 9-fluorenylmethyloxycarbonyl, 9-芴基甲氧基羰基
15 HOBT, 1-Hydroxybenzotriazole, 1-羟基苯并三唑
Piperidine, 哌啶
PyBOP, Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, 六氟磷酸苯并三唑-1-基-氧基三吡咯烷基磷
Resin, 树脂
20 TBTU, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-苯并三氮唑-N,N,N',N'-四甲基脲四氟硼酸酯
TFA, Trifluoroacetic acid, 三氟乙酸
TFE, 2,2,2-Trifluoroethanol, 2,2,2-三氟乙醇
TIS, Triisopropylsilane, 三异丙基硅烷

25 下面结合具体实施例对本发明进行进一步的解释说明，但无论如何不能理解为对本发明的限制。另外，如无特别说明，各原料或试剂均可以市购获得。

实施例 1：环肽化合物的合成和鉴定

1、环肽化合物的合成

30 以 SEQ ID NO:52 所示的环肽化合物为例，以赖氨酸为起始，从 C 端向 N 端（从右向左）依次缩合氨基酸。

第一步、固相合成

称取 Fmoc-Lys(Boc)-2-Cl Resin (S=0.32mmol/g)，放到玻璃反应柱加 DCM 溶胀 30min，减压抽掉 DCM。加入 20%哌啶/DMF 溶液反应 20min 除去保护基 Fmoc，
35 减压抽掉溶液，用 DMF 洗涤 5 遍。取样显色检测，得到连有 Lys 的固相树脂（通过 Lys 的 C 端连接）。

称取 Fmoc-His(Trt)-OH 加入到树脂，DMF 溶解并加入 DIEA、TBTU，搅拌 60min，减压抽掉溶液，DMF 洗涤 5 遍。取样显色检测，得到连有 Lys-His 的固相树脂（从 C 端到 N 端）。

40 重复上述类似过程，依次偶联 Gly、Pro、Phe、Ala，最终得到连有多肽 Lys-His-Gly-Pro-Phe-Ala 的固相树脂（从 C 端到 N 端），即肽树脂。

然后，依次用 DMF，DCM，甲醇洗涤树脂三遍，干燥至恒重。

第二步、肽树脂裂解

裂解试剂的配制：按 1g 肽树脂比体积为 10mL±2mL 的裂解试剂（AcOH：

TFE: DCM=1: 2: 7, 体积比) 来计算裂解试剂的用量。具体步骤为, 依次将所需裂解试剂 DCM, TFE, AcOH 加入裂解反应瓶, 裂解试剂温度控制在 0~10℃; 裂解试剂在搅拌下加入肽树脂中, 待体系温度稳定后; 再温控在 25~30℃搅拌反应 2 小时后, 将裂解液滤出。

5 第三步、处理反应

将第二步所得裂解液投入 TBTU/DIEA 搅拌反应, 反应结束后, 旋转蒸发仪旋蒸掉溶剂, 然后按 1g 肽树脂比体积为 10ml±2ml 的混合试剂 (TFA: H₂O: TIS=95: 2.5: 2.5, 体积比) 来计算混合试剂的用量, 之后依次将所需试剂 H₂O, TFA, TIS 加入反应瓶。搅拌反应 2 小时后, 采用 5 倍浓缩液体积量的冰乙醚将其沉淀, 滤出沉淀物并于室温减压干燥, 得粗品。

10 第四步、冻干纯化

将粗品研细, 准备纯化水, 在搅拌下缓慢加入研细粗品, 同时滴加乙腈水溶液, 待粗品加完并溶解完全后, 用 0.45μm 的微孔滤膜过滤; 粗品纯化采用 C-18 柱填料制备柱, 流动相 A: 0.1%的 TFA 水溶液, 流动相 B: 0.1%的 TFA 乙腈溶液, 在常温下用合适梯度进行分离纯化, 收集目标产物, 分析检测, 归类。纯度要求≥95%, 将不合格目标物收集, 用合适梯度再次进行分离纯化, 将合格主峰减压冷冻干燥, 得到粉末状精制多肽 (SEQ ID NO:52)。

本领域技术人员可参照以上合成步骤制备获得本申请的其他环肽化合物。

2、环肽化合物的鉴定

20 称取以上制备得到的精制多肽, 溶解在水和乙腈的混合溶液直至溶液澄清, 过滤后上样。高效液相色谱测定条件: C18 柱, 4.6μm×250mm; 流动相 A: 0.1%的 TFA 乙腈溶液, 流动相 B: 0.1%的 TFA 水溶液; 梯度条件: 0.01 min 25% A, 75% B → 25 min 50% A, 50% B → 25.01 min 100% A → 30 min stop; 检测波长: 220nm; 流速: 1.0 ml/min; 柱温: 25℃; 进样量: 10 μL。

25 质谱检测器为 Agilent-6125B, 采用电喷雾离子源(ESI), 正离子扫描; 质谱电压 +4.5kv; 检测器 1.5 kv; 喷雾器流速 1.5 L/min; CDL -20.0 v; CDL 温度 250 ℃; 加热模块温度 200 ℃; 流动相: 50%水/50%乙腈; 流动性流速 0.2 mL/min。

部分示例性环肽化合物的质谱数据如下表 1 所示。

表 1: 示例性环肽化合物的质谱数据

SEQ ID NO:	理论 MS 值 [M+H] ⁺	实测 MS 值 [M+H] ⁺
52	638.7	639.0
214	680.8	680.8
414	640.8	640.6
250	604.7	604.8
297	682.8	682.8
205	664.8	665.0
289	654.8	654.4
291	696.9	697.0
196	646.8	646.3
232	719.9	719.4
268	646.8	646.5
292	696.9	696.5
707	650.8	650.5
340	608.7	608.4

710	705.8	705.4
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如表 1 所示，本发明的制备方法可以成功获得预期的环肽化合物。

实施例 2：环肽化合物的生物活性测试

1、测试方法

A、成纤维细胞毒性测试

测试材料：人源成纤维细胞（广东博溪生物科技有限公司，批号 Fb20081902），DMEM 培养液（Gibco，23042301，有效期 230522）、PBS（索莱宝，P1010）、MTT（Sigma，M5655）、DMSO（Sigma，D4540-1L），CO₂ 培养箱（Thermo，150I）、超净工作台（苏净安泰，SW-CJ-1F）、倒置显微镜（Olympus，CKX53）。

测试方法：

1) 细胞接种：复苏细胞后，待铺板率达到 60%左右时，接种细胞至 96 孔板，培养箱（37℃、5%CO₂）中孵育过夜。

2) 试验分组：试验设置调零组、溶剂对照组、阳性对照组与样品组。样品组中，每个样品设置 7 个浓度梯度，每个浓度梯度下设置 3 个重复孔。

3) 配液：按测试浓度 0.0781、0.1563、0.3125、0.625、1.25、2.5、5 μM 配制不同浓度的样品工作液。

4) 给药：待 96 孔板中细胞铺板率达到 50%~60%时进行给药。溶剂对照组每孔加入 200μL 培养液；阳性对照组每孔加入 200μL 含 10%DMSO 的培养液；样品组每孔加入 200μL 含有相应浓度样品的培养液；调零组无细胞接种，仅加入 200μL 细胞培养液。给药完成后将 96 孔板放置在培养箱（37℃、5%CO₂）中培养 24h。

5) 检测：细胞孵育培养 24h 后，弃掉上清，加入 MTT 工作液(0.5 mg/mL)，37℃避光孵育 4h，孵育结束后，弃掉上清，每孔加 150μL DMSO，在 490nm 处读取 OD 值。

6) 细胞相对活力计算：根据下述公式计算

细胞相对活力 =
$$\frac{\text{样品孔 OD}-\text{调零孔 OD}}{\text{溶剂对照孔 OD}-\text{调零孔 OD}} \times 100\%。$$

部分示例性环肽化合物的检测结果数据如表 2 所示。

表 2：示例性环肽化合物的检测结果数据

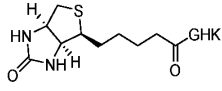
	SEQ ID NO:	浓度 (μM)							阳参
		0.0781	0.1563	0.3125	0.625	1.25	2.5	5	10% DMSO
环肽化合物	52	96.35%	96.02%	96.69%	96.69%	96.08%	94.03%	93.26%	0.61%
	214	99.39%	98.67%	98.40%	98.67%	97.51%	97.51%	95.36%	0.61%
	414	106.03%	105.69%	105.11%	104.20%	104.20%	102.07%	101.55%	2.07%
	250	118.62%	117.01%	116.72%	114.43%	114.02%	114.60%	114.89%	2.07%
	297	103.91%	102.94%	102.84%	102.78%	101.66%	100.59%	100.11%	0.54%
	205	104.12%	104.87%	102.41%	102.03%	99.95%	99.41%	99.14%	0.54%
	289	98.48%	96.48%	95.25%	95.39%	95.91%	95.01%	94.87%	0.43%
	291	97.96%	97.15%	97.48%	97.05%	96.58%	94.20%	94.49%	0.43%
	196	101.92%	101.21%	102.58%	101.26%	100.40%	101.47%	99.85%	0.30%
	232	100.44%	97.64%	93.46%	94.05%	93.90%	91.59%	91.10%	1.87%
	268	97.22%	93.85%	94.77%	91.67%	91.81%	90.66%	90.38%	1.62%
	292	107.68%	107.63%	105.05%	102.37%	102.07%	102.88%	102.88%	0.30%
	707	102.27%	98.38%	97.64%	97.83%	93.62%	92.78%	91.58%	1.62%
	340	98.04%	98.71%	97.29%	96.66%	94.99%	94.28%	91.65%	1.17%
	710	97.66%	97.91%	97.54%	96.66%	96.20%	95.37%	95.82%	0.61%

如表 2 所示，在成纤维细胞毒性测试试验中，所有环肽化合物在 5 μM 的浓度范围内均未表现出明显的细胞毒性，具有良好的药物和美容方向应用前景。

- 5
- B、成纤维细胞 Collagen I (I 型胶原蛋白) 提升效果、成纤维细胞 HA (透明质酸) 提升效果、成纤维细胞弹力蛋白 (ELN) 提升效果
- 测试材料:人源成纤维细胞(广东博溪生物科技有限公司,批号 Fb20081902),DMEM 培养液(Gibco, 23042301,有效期 230522)、PBS(索莱宝, P1010)、TGF-β1 (Peprotech, 230504)、Collagen I ELISA 试剂盒(Cusabio, B21025824)、Elastin ELISA 试剂盒(Abcam, GR3446070-2)、HA ELISA 试剂盒(RD, P325066)。
- 10
- CO2 培养箱 (Thermo, 150I)、超净工作台 (苏净安泰, SW-CJ-1F)、酶标仪 (BioTek, Epoch)。

测试方法:

1) 接种: 复苏细胞后, 待铺板率达到 60%左右时, 接种细胞至 6 孔板, 培养箱 (37℃、5%CO₂) 中孵育过夜。

- 15
- 2)配液:样品组环肽化合物,阳参组 PC2(Biotinoyl-GHK, ) 和 PC3 () , 浓度均为 1μM, 配置受试物工作液。空白对照组 (BC) 仅加入细胞培养液。

3) 给药: 待 6 孔板中细胞铺板率达到 40%~60%时, 进行给药, 每孔给药量为 2mL, 每组设 3 个复孔, 培养箱 (37℃、5%CO₂) 中孵育 24h。

- 20
- 4) ELISA 检测: 按照 ELISA 试剂盒说明书进行 ELISA 检测, 检测指标分别为成纤维细胞 Collagen I 提升效果、成纤维细胞 HA 提升效果和成纤维细胞弹力蛋白提升效果。

部分示例性环肽化合物的活性测试数据如下表 3A、3B、3C 所示。

表 3A: 部分示例性环肽化合物的成纤维细胞 Collagen I 提升效果数据

空白对照/SEQ ID NO:	成纤维细胞 Collagen I 提升效果
空白对照 BC	35.6
414	40.54
250	55.85
205	49.25
214	42.51
297	52.28
289	41
232	67.93
268	61.46
707	66.21
340	90.07
710	110.87

- 25
- 如表 3A 所示, 与 BC 相比, 本发明的示例性的环肽化合物如 SEQ ID NO:214、414、250、297、205、289、232、268、707、340、710 所示的环肽化合物的 I 型胶原(Collagen I)含量显著提升, 说明本发明的环肽化合物可通过提升 Collagen I 含量达到抗皱功效。

表 3B: 部分示例性环肽化合物的成纤维细胞 HA 提升效果数据

空白对照/SEQ ID NO:	成纤维细胞 HA 提升效果
空白对照 BC	1402.44
414	1926.61

250	2142.56
205	2641.21
292	2635.98
52	2900.83
214	1965.3
297	2212.6
289	1978.48
291	2477.91
196	2305.13

如表 3B 所示,与 BC 相比,本发明的示例性的环肽化合物如 SEQ ID NO:52、250、297、205、291、196、292、414、214、289 所示的环肽化合物的透明质酸(HA)含量显著提升,说明本发明的环肽化合物可通过提升 HA 含量达到紧致功效。

5 表 3C: 部分示例性环肽化合物的成纤维细胞弹力蛋白提升效果数据

空白对照/SEQ ID NO:	成纤维细胞弹力蛋白提升效果
空白对照 BC	756.52
414	1124.58
250	1051.64
205	1074.17
292	1278.99
52	1043.27
214	1050.82
297	923.52
289	1034.59
291	1177.19
196	1175.6
232	1001.84
340	1304.87
710	1207.29

如表 3C 所示,与 BC 相比,本发明的示例性的环肽化合物如 SEQ ID NO:52、250、297、205、291、196、292、414、214、289、232、340、710 所示的环肽化合物的弹力蛋白(Elastin)含量显著提升,说明本发明的环肽化合物可通过提升弹力蛋白含量达到紧致功效。

10 另外,如表 3A、表 3B、表 3C 所示,与 BC 相比,本发明的示例性的环肽化合物如 SEQ ID NO:414、250、205、292 等所示的环肽化合物的 I 型胶原(Collagen I)含量、透明质酸(HA)含量、弹力蛋白(Elastin)含量显著提升,说明本发明的环肽化合物可通过提升 Collagen I 含量、HA 含量和弹力蛋白含量达到紧致、抗皱功效,医药、美容效果优异。

权 利 要 求

1、式 I 所示的环肽化合物或其立体异构体，
AA1-AA2-GLY-HIS-LYS-AA4-AA3

式 I

其中：

AA1 为氨基酸残基；

AA2 不存在或为氨基酸残基；

AA3 为氨基酸残基；

AA4 不存在或为氨基酸残基；

*表示式 I 的 N 端与 C 端相连形成环肽；

所述氨基酸为天然氨基酸或非天然氨基酸；

所述氨基酸为 D 型或 L 型，优选为 L 型。

2、权利要求 1 所述的环肽化合物或其立体异构体，其中，所述氨基酸为天然氨基酸；

优选地，所述氨基酸为疏水性天然氨基酸；

更优选地，所述氨基酸选自丙氨酸、甘氨酸、异亮氨酸、亮氨酸、甲硫氨酸、苯丙氨酸、脯氨酸、色氨酸、缬氨酸。

3、权利要求 1-2 任一项所述的环肽化合物或其立体异构体，其中，AA1 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA1 选自丙氨酸残基、甲硫氨酸残基、苯丙氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基；

更优选地，AA1 选自甲硫氨酸残基、丙氨酸残基、苯丙氨酸残基、甘氨酸残基、脯氨酸残基。

4、权利要求 1-3 任一项所述的环肽化合物或其立体异构体，其中，AA2 为氨基酸残基；

优选地，AA2 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA2 选自缬氨酸残基、脯氨酸残基、亮氨酸残基、丙氨酸残基、异亮氨酸残基、甲硫氨酸残基、色氨酸残基；

更优选地，AA2 选自脯氨酸残基、亮氨酸残基、缬氨酸残基、异亮氨酸残基、色氨酸残基。

5、权利要求 1-4 任一项所述的环肽化合物或其立体异构体，其中，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、异亮氨酸残基、缬氨酸残基；

更优选地，AA3 选自异亮氨酸残基、亮氨酸残基、苯丙氨酸残基、甲硫氨酸

酸残基、缬氨酸残基。

6、权利要求 1-5 任一项所述的环肽化合物或其立体异构体，其中，AA4 不存在。

7、权利要求 1-6 任一项所述的环肽化合物或其立体异构体，其中，所述环肽化合物具有式 I-1 所示的结构，

AA3-AA1-AA2-GLY-HIS-LYS

式 I-1

其中：

AA1 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA1 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基；

和/或

AA2 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA2 选自丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、缬氨酸残基；

和/或

AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、脯氨酸残基、甘氨酸残基、缬氨酸残基；

优选地，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、色氨酸残基、异亮氨酸残基、甘氨酸残基、缬氨酸残基；

更优选地，AA3 选自苯丙氨酸残基、丙氨酸残基、甲硫氨酸残基、亮氨酸残基、异亮氨酸残基、缬氨酸残基；

*表示式 I-1 的 N 端与 C 端相连形成环肽；

所述氨基酸为 D 型或 L 型，优选为 L 型。

8、权利要求 7 所述的环肽化合物或其立体异构体，其中，优选 AA1 选自甲硫氨酸残基、丙氨酸残基、苯丙氨酸残基、甘氨酸残基、脯氨酸残基；和/或

优选 AA2 选自脯氨酸残基、亮氨酸残基、缬氨酸残基、异亮氨酸残基、色氨酸残基；和/或

优选 AA3 选自异亮氨酸残基、亮氨酸残基、苯丙氨酸残基、甲硫氨酸残基、缬氨酸残基。

9、权利要求 1-8 任一项所述的环肽化合物或其立体异构体，其中，所述环肽化合物的结构式如表 A 所示；

优选地，所述环肽化合物的结构式如表 B 所示；

更优选地，所述环肽化合物的结构式如表 C 所示；

最优选地，所述环肽化合物的结构式如表 D 所示。

10、药物组合物，其包含权利要求 1-9 任一项所述的环肽化合物或其立体异构体；

任选地，还包含至少一种载体和/或赋形剂。

11、美容组合物，其包含权利要求 1-9 任一项所述的环肽化合物或其立体异构体；

任选地，还包含功能性物质；

优选地，所述功能性物质选自皮肤调理剂、抗氧化剂、表面活性剂、保湿剂、防腐剂、螯合剂、香精中的一种或多种。

12、权利要求 1-9 任一项所述的环肽化合物或其立体异构体或者权利要求 10 所述的药物组合物在制备药物中的用途，所述药物用于选自以下 (1) - (7) 中的一种或多种：

- (1) 延缓皮肤老化；
- (2) 减少皮肤损伤；
- (3) 加速皮肤伤口愈合；
- (4) 减少色素沉着过度；
- (5) 刺激毛发生长；
- (6) 提高毛发移植的成功率；
- (7) 预防脱发。

13、权利要求 1-9 任一项所述的环肽化合物或其立体异构体或者权利要求 11 所述的美容组合物用于选自以下 (1) - (17) 中的一种或多种的用途：

- (1) 皮肤抗老化；
- (2) 皮肤抗皱和减少细纹；
- (3) 改善皮肤的机械特性：紧实度、肤色、弹性和/或柔韧性；
- (4) 提高皮肤密度；
- (5) 增加皮肤体积；
- (6) 对抗牵拉痕外观；
- (7) 减少皮肤损伤；
- (8) 加速皮肤伤口愈合；
- (9) 抗斑；
- (10) 改善皮肤同质性和/或光泽；
- (11) 减少皮肤色素沉着；
- (12) 保湿；
- (13) 刺激毛发生长；
- (14) 提高毛发移植的成功率；
- (15) 预防脱发；
- (16) 眼睫毛的局部美容；
- (17) 增加头发宽度、密度和/或长度。