

多肽及其应用

本申请要求 2023 年 04 月 26 日提交中国专利局、申请号为 202310461975.3、发明名称为“多肽及其应用”的中国专利申请的优先权，其全部内容通过引用结合在本申请中。

- 5 本申请要求 2023 年 12 月 27 日提交中国专利局、申请号为 202311825930.6、发明名称为“多肽及其应用”的中国专利申请的优先权，其全部内容通过引用结合在本申请中。

技术领域

- 10 本发明涉及生物技术领域，具体涉及多肽及其应用。

背景技术

- 15 目前脑卒中的主要治疗措施及药物包括血管介入、溶栓、抗血小板、抗凝、降纤及神经保护剂治疗，血管介入、溶栓一般要求在卒中发生后极早期进行，血管介入需要在具有一定能力的医院完成，抗血小板、抗凝药物一般需要配合溶栓药物后期使用，效果有限且存在一定的出血风险，神经保护剂具有较好的潜力，一般针对急性期的治疗用药。然而还没有针对促进卒中病人亚急性期及恢复期康复的治疗药物上市，先前研究显示内皮素受体 B 激动剂在促进脑卒中病人长期恢复及后期康复中体现了巨大的潜力。

- 20 内皮素 (Endothelin, ET) 是一种含有 21 个氨基酸的多肽，可以分为 ET-1、ET-2、ET-3 三种亚型，它们与蛇毒 sarafotoxin b 和 c (S6b, S6c) 具有结构同源性。内皮素是目前已知的作用最强和效应最持久的血管活性肽，有强烈的血管收缩和促平滑肌细胞迁移、增殖作用，广泛作用于体内多种系统，与高血压、充血性心力衰竭、糖尿病、癌症及纤维化等疾病有着密切联系。

- 25 内皮素主要通过与其靶细胞膜上的内皮素受体 (Endothelin receptor, ETR) 结合后发挥其生物学效应，并在心脑血管疾病、肾脏疾病、糖尿病、自身免疫性疾病和肿瘤等众多疾病的发生发展中扮演了重要的角色。人的 ETR 分为 ETA 和 ETB 两种亚型，均为 G 蛋白偶联受体 (G-protein-coupled receptor, GPCR)，但两者功能存在差异。ETA 被认为是基本的缩血管和促生长受体，ETB 在血管系统中抑制细胞生长和血管收缩，因其参与 ET-1 的清除被称为“清除受体”。内皮素及其受体多样性地广泛分布于各组织，通过不同的亚型和信号传递系统介导复杂的生物学效应，与多种疾病有密切联系，其中 ETA 和 ETB 受体发挥了重要的作用。

- 30 研究显示 ETBR 激动剂在促进脑卒中病人长期恢复及后期康复中体现了巨大的潜力，目前发现的 ETBR 激动剂化合物中，sovateltide (IRL-1620, Suc-DEEAVYFAHLDIW) 是目前唯一一个推进到临床研究阶段的 ETBR 的激动剂，但 IRL-1620 由于半衰期很短，不到 2 分钟，暴露量很低，在临床前研究及临床研究中需要反复多次给药，大大降低了其药效持续性和患者依从性。

发明内容

- 40 有鉴于此，本发明提供了多肽及其应用。

本发明提供了多肽及其应用。本专利发现的多肽是建立在对于 ETBR 激动剂的机理研究之上，属于 ETBR 的高选择性激动剂。本专利开发的多肽通过构效关系研究和

结构修饰延长了药物的半衰期和体内暴露量,减少了给药次数,在动物实验中的副作用比 IRL-1620 更低,药物的安全窗口更大。本发明中的化合物可以用于与 ETBR 受体相关的疾病治疗,比如缺血性脑卒病人恢复期的康复问题,促进卒中病人更好的恢复。

5 为了实现上述发明目的,本发明提供以下技术方案:

本发明提供了多肽,其特征在于,包括:

(I)、具有如式I所示的结构;或

X1-X2-X3- (A5) -X4-X5- (A1) -X6 (A2) -X7-X8-X9- (A3) -X10-X11- (A4) -X12-X13-X14-X15-X16

10 式 I

(II)、在如(I)所示的结构的基础上经取代、缺失、添加和/或替换1个或多个氨基酸的序列;或

(III)、与(I)所示的结构相似性90%以上的序列;或

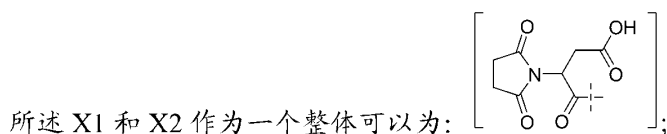
15 (IV)、具有如式I所示的结构所成的可药用的盐、溶剂化物、螯合物或非共价复合物;和/或

(V)、基于具有如式I所示的结构基础上的药物前体;和/或

(VI)、包括(IV)和/或(V)的任意混合物;

优选地,所述X1选自Suc、Fum、MeO-Fum、Ac、SA、MA、FA、A1-D或A1-NH-C₂H₄-NH-Suc;

20 优选地,所述X2选自D、E或K(A1);



优选地,所述X3选自E、D或K(A1);

优选地,所述X4选自E、E(C16)或D;

优选地,所述X5选自A、K、R、H、E或D;

25 优选地,所述X6选自V、I、K、Dab、Orn、L、F、W或C;

优选地,所述X7选自Y、F或W;

优选地,所述X8选自F、Y或W;

优选地,所述X9选自A、K、R、H、D、E、Dab或Orn;

优选地,所述X10选自H、K或R;

30 优选地,所述X11选自K、L、L(N-Me)、I、V、Cit、H、R、L-2-氨基-4-哌基丁酸或Orn;

优选地,所述X12选自D或E;

优选地,所述X13选自I、I(N-Me)、2-Abu、L、P或V;

优选地,所述X14选自I、2-Abu、L或V;



优选地,所述X16选自OH或NH₂;

优选地，所述 X12 为 D；
优选地，所述 X13 选自 I、I (N-Me)、2-Abu、P 或 V；
优选地，所述 X14 为 I；



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- 优选地，所述 A1 选自 -γE-AEEA-AEEA-ODDA、ODDA-γE-AEEA-AEEA-、Biotin、-AEEA-AEEA-γE-ODDA 或不存在；
优选地，所述 A2 选自 -γE-AEEA-AEEA-ODDA 或不存在；
优选地，所述 A3 选自 -γE-AEEA-AEEA-ODDA 或不存在；
优选地，所述 A4 选自 -AEEA-AEEA-γE -ODDA、-γE-AEEA-AEEA-C18、
10 -γE-AEEA-AEEA-C16、-γE-AEEA-AEEA-C12、-γE-AEEA-AEEA-B、-γE-AEEA-AEEA-ODDA、CPAK-MPA-、-AEEA-γE-C18、-AEEA-γE-C16、-AEEA-γE-C12、-AEEA-E-C12 或不存在。

在本发明的一些具体实施方案中，所述式I所示的结构通过如下任意项环化：

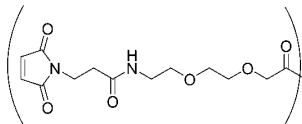
- 15
- (I)、引入 C 生成二硫键；和/或
(II)、D 或 E 侧链的羧基与 K 或 Dab 侧链的氨基生成酰胺键。

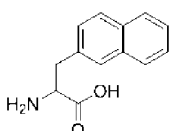
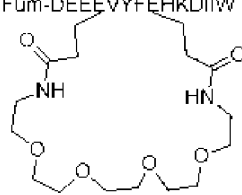
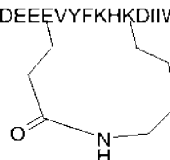
在本发明的一些具体实施方案中，所述环化包括如下任意项：

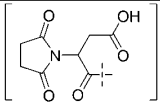
- 20
- (I)、在 X3 与 X4 之间插入 C，同时将 X6 替换为 C，通过两个 C 生成二硫键环化；和/或
(II)、X3 的 E 与 X6 的 K 或 Dab 生成酰胺键环化；和/或
(III)、X5 的 E 与 X11 的 K 生成酰胺键环化。

在本发明的一些具体实施方案中，所述多肽序列如下：

序号 SEQ ID No.	编号	序列	MW
2	BX-5	Suc-DEEAVYFAHKDIIW	1836
3	F-BX-5	Fum-DEEAVYFAHKDIIW	1834
4	BX-7	Suc-DEEAVYFAHLDVIW	1806
5	BX-8	Suc-DEEAVYFAHLD(2-Abu)IW	1792
6	BX-34	Fum-DEEAVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	2549
7	BX-43	Suc-DEEAKYFAHLDIIW	1850
8	BX-45	Suc-DEEEVYFAHKDIIW	1893
9	BX-48	Suc-D环(EEAK)YFAHLDIIW	1832
10	BX-49	Suc-D环(EEADab)YFAHLDIIW	1804
11	BX-50	Suc-DEE环(EVYFAHK)DIIW	1876
12	BX-51	Fum-DEEAVYFAHOrn(-AEEA-AEEA-γE-ODDA)DIIW	2535
13	BX-52	Fum-DEEEVYFAHKDIIW	1891
14	BX-53	Suc-DEEEVYFAHOrnDIIW	1880

15	BX-54	Suc-DEEEVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	2610
16	BX-57	Suc-DE环(CEEC)YFAHKDIIW	1999
17	BX-58	MeO-Fum-DEEEVYFAHKDIIW	1906
18	BX-59	Fum-DEEEVYFAHOrnDIIW	1878
19	BX-60	Fum-DEEEVYFAHK(-AEEA-AEEA-γE -ODDA)DIIW	2608
20	BX-61	Suc-DEEAVYFAHOrn(-AEEA-AEEA-γE -ODDA)DIIW	2538
21	BX-62	Fum-DEE环(EVYFK)HKD(2-Abu)IW	1903
22	BX-63	Suc-D环(EEAK)YFAHLD(2-Abu)IW	1804
23	BX-64	Fum-D环(EEAK)YFAHLD(2-Abu)IW	1802
24	BX-65	MeO-Fum-D环(EEAK)YFAHLD(2-Abu)IW	1814
25	BX-66	Fum-DEEK(-γE-AEEA-AEEA-ODDA)VYFAHLDIIW	2592
26	BX-67	Fum-DEEAK(-γE-AEEA-AEEA-ODDA)YFAHLDIIW	2564
27	BX-68	Fum-DEEAVYFK(-γE-AEEA-AEEA-ODDA)HLDIIW	2592
28	BX-69	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C18)DIIW	2520
29	BX-70	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C16)DIIW	2492
30	BX-71	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C12)DIIW	2436
31	BX-72	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-B)DIIW	2433
32	BX-74	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	2552
33	BX-75	MeO-Fum-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	2564
34	BX-76	Suc-D环(EEAK)YFAHLDVIW	1818
35	BX-77	Suc-D环(EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)DIIW	2563
36	BX-78	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DVIW	2538
37	BX-79	Suc-D环(EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)DVIW	2550
38	BX-86	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW-NH2	2549
39	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW  MPA	2661
40	BX-99	Fum-D环(EEAK)YFAHLDVIW	1916
41	BX-100	Fum-D环(EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)DVIW	2547
42	BX-101	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DVIW	2536
43	BX-102	Fum-D环(EEAK)YFAHLDIIW	1829
44	BX-103	Fum-D环(EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)DIIW	2561
45	BX-104	Fum-D环 (EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)D(2-Abu)IW	2534
46	BX-105	Fum-DEEAKYFAHLDIIW	1847
47	BX-106	Fum-DEEAKYFAHLDVIW	1836
48	BX-107	Fum-DEEAKYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	2579
49	BX-108	Fum-DEEAKYFAHK(-γE-AEEA-AEEA-ODDA)DVIW	2567
50	BX-109	Fum-DEEAK(-γE-AEEA-AEEA-ODDA)YFAHLDIIW	2566

51	BX-110	Fum-DEEAK(-γE-AEEA-AEEA-ODDA)YFAHLDVIW	2549
52	BX-111	SA-DEEAVYFAHLDIIW	1844
53	BX-112	MA-DEEAVYFAHLDIIW	1844
54	BX-13-2	Fum-DEEAVYFAHKDIIW I  W1:	1843.8
55	BX-9	suc-DEEAVYFAHR1DIIW (R1=L-2氨基-4胍基丁酸)	1849.98
56	BX-31	Fum-DEEAVYFAHOrnDIIW	1819
57	BX-32	Fum-DEEAVYFAHCitDIIW	1862
58	BX-38	Suc-DE环(CEAC)YFAHLDIIW	1927
59	BX-23	Fum-DEEAVYFAHKDVIW	1704.9
60	BX-24	Fum-DEEAVYFAHKD(2-Abu)IW	1805.9
61	BX-25	Suc-DEEAVYFAHLDI(N-Me)IW	1833.85
62	BX-26	Suc-DEEAVYFAHL(N-Me)DIIW	1833.85
63	BX-27	Suc-DEEAVYFAHL(N-Me)DI(N-Me)IW	1847.86
64	BX-28	Fum-DEEAVYFAHL(N-Me)DIIW	1845.85
65	BX-29	Fum-DEEAVYFAHL(N-Me)DI(N-Me)IW	1847.86
66	FBX-7	Fum-DEEAVYFAHLDVIW	1805.9
67	FBX-8	Fum-DEEAVYFAHLD(2-Abu)IW	1790.9
68	QP-1	Fum-DEEEVYFEHKDIIW  QP1	1848
69	QP-3	Fum-DEEEVYFKHKDIIW 	1931
70	BX-15	FA-DEEAVYFAHKDIIW	1912.87

71	BX-16	Fum-DEEE(Biotin)VYFAHKDIIW	2160.4
72	BX-10	suc-DEEAVYFAHLDPIW	1804.96
73	BX14-1	Fum-DEE(C16)AVYFAHLDIIW	2044.1
74	BX-6	Suc-DEEAVYFAHRDIIW	1864.03
75	BX-21	Fum-DEEALYFAHKDIIW	1848
76	BX-22	Fum-DEEAFYFAHKDIIW	1882
77	BX-223	Fum-DEEAVYFAHK(-AEEA-γE-C18)DIIW	2374
78	BX-224	Fum-DEEAVYFAHK(-AEEA-γE-C16)DIIW	2346
79	BX-225	Fum-DEEAVYFAHK(-AEEA-γE-C12)DIIW	2290
80	BX-253	Fum-K(-AEEA-AEEA-γE-ODDA)EEAVYFAHLDIIW	2547
81	BX-254	Fum-DK(-AEEA-AEEA-γE-ODDA)EAVYFAHLDIIW	2533
82	BX-255	(ODDA-γE-AEEA-AEEA-)DDEEAVYFAHLDIIW	2550
83	BX-256	(ODDA-γE-AEEA-AEEA-)NH-C ₂ H ₄ -NH-Suc-DEEAVYFAHL DIIW	2594
84	BX-221	 EEAVYFAHK(ODDA-γE-AEEA-AEEA-)DIIW	2533
86	BX-229	Fum-DEEAVYFAHK(-AEEA-γE-C12)DVIW	2276
87	BX-238	Fum-DEEAVYFAHK(-AEEA-E-C12)DVIW	2276
88	BX-56	Suc-DE环(CEEC)YFAHLDIIW	1984

本发明还提供所述多肽的制备方法，包括如下步骤：

步骤 1：经固相多肽合成获得所述多肽的肽树脂；

步骤 2：裂解、纯化制得所述多肽。

具体地，本发明提供了多肽 BX-34 的制备方法，包括如下步骤：

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- 10
- 15
- 步骤 1：称取 0.50g（0.25mmol）的 Fmoc-Trp(Boc)-Wang Resin 于反应器中，DCM 10mL 溶胀 10min，抽滤，DMF 洗 2 次，加 25%的 4-甲基哌啶/DMF（体积比）反应 30min，去除 Fmoc 基团。抽滤，用 DMF 洗涤树脂 4 遍，DCM 洗涤 2 遍，茚三酮检测，树脂溶液蓝色；称取 Fmoc-Ile-OH（1mmol，4 eq.）和 HBTU（1mmol，4 eq.），DMF 溶解，加入 DIEA（2mmol，8 eq.），混合均匀，加入树脂中，室温（25℃±5℃）磁力搅拌反应 1h，抽滤，DMF、MeOH 和 DCM 依次洗涤 3 遍，茚三酮检测，树脂无色透明，溶液浅黄色，反应完全。加入 25%的 4-甲基哌啶/DMF（体积比）去除 Fmoc 基团。依次循环，完成 Ile、Asp(OtBu)、Lys(Dde)、His(Trt)、Ala、Phe、Tyr(tBu)、Val、Ala、Glu(OtBu)、Glu(OtBu)、Asp(OtBu)和 OtBu-Fum 的偶合。随后，向肽树脂中加入 2%水合肼/DMF 反应，10min×3 次，以脱除 Lys 侧链的 Dde，然后依次缩合 AEEA、AEEA、Glu-α-OtBu 以及 OtBu-ODDA；

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- 步骤 2：树脂抽干，加入预冷裂解液（TFA: TIS: H₂O=95:2.5:2.5）15mL，室温（25℃±5℃）搅拌反应 3h，抽出反应液，树脂用少量 TFA 洗涤 2 次，抽出。合并反应液，加入预冷的甲基叔丁基醚约 200mL，析出白色沉淀，离心（5000rpm×5min），倒去上清液，沉淀复加入甲基叔丁基醚，涡旋，离心，弃去上清。沉淀放入真空干燥器中干燥 12h，得到粗品。

步骤3: 将粗肽用约1%氨水溶解, 过滤, 滤液用制备液相纯化, 梯度洗脱以得到目标化合物纯品, 将纯度>95%的目标化合物组分合并, 用水泵及旋转蒸发仪在40°C左右减压旋出乙腈, 所得浓缩液用液氮冷冻成固体, 然后使用冻干机冷冻干燥48h, 得到目标化合物, 经质谱鉴定分子量。

5 在本发明的一些具体实施方案中, 所述纯化采用的制备柱包括C18-10-100, 30×250mm, 采用的流速为25mL/min; 所述制备液相包括A相: 0.1%TFA/水, B相: 0.1%TFA/90%乙腈/水。

在本发明的一些具体实施方案中, 所述多肽BX-34的制备方法还可以制备BX-5、F-BX-5、BX-7、BX-8、BX-43、BX-45、BX-51、BX-52、BX-53、BX-54、BX-58、
10 BX-59、BX-60、BX-61、BX-66、BX-67、BX-68、BX-69、BX-70、BX-71、BX-72、BX-73、BX-74、BX-75、BX-78、BX-86、BX-101、BX-105、BX-106、BX-107、BX-108、BX-109、BX-110、BX-111、BX-112、BX-229和BX-238。

具体地, 本发明还提供了多肽BX-76的制备方法, 包括如下步骤:

步骤1: 参照BX-34的合成方法, 完成主链的合成;

15 步骤2: 氮气保护下, 向肽树脂中加入0.3当量的四三苯基膦钨和12当量的苯硅烷的DCM溶液, 室温(25°C±5°C)反应2h, 以脱除Glu侧链的烯丙酯和Lys侧链的烯丙氧羰基; 抽滤, 用DCM溶剂洗5遍, DMF洗3遍, 加入2当量的PYBOP、2当量的HOBt以及4当量的DIEA, DMF溶解, 室温(25°C±5°C)反应5h; 抽滤, DMF洗3遍, DCM洗3遍, 茚三酮检测, 如果反应不完全, 重复缩合一次;

20 步骤3: 之后参照BX-34的方法, 进行裂解和纯化, 得到目标化合物纯品, 经质谱鉴定分子量。

在本发明的一些具体实施方案中, 所述多肽BX-76的制备方法还可以制备BX-48、BX-49、BX-50、BX-62、BX-63、BX-64、BX-65、BX-77、BX-79、BX-100、BX-103、BX-104、BX-99、BX-102。

25 具体地, 本发明还提供了多肽BX-56的制备方法, 包括如下步骤:

步骤1: 参照BX-34的合成方法, 完成主链的合成;

步骤2: 向肽树脂中加入5当量的碘的DMF溶液, 室温(25°C±5°C)反应6h, 以脱除Cys侧链的保护基Trt, 同时进行氧化。抽滤, DMF洗6遍, DCM洗3遍, 干燥;

30 步骤3: 参照BX-34的合成方法, 裂解, 纯化, 得到目标化合物纯品, 经质谱鉴定分子量。

在本发明的一些具体实施方案中, 所述多肽BX-56的制备方法还可以制备BX-57。

具体地, 本发明还提供了多肽BX-95的制备方法, 包括如下步骤:

35 步骤1: 参照BX-34的合成方法, 得到主链纯肽, 参照BX-34的合成方法, 得到CPAK纯肽;

步骤2: 将所述主链纯肽与所述CPAK纯肽等当量溶于50%的乙腈水溶液中, 三乙胺调pH值至8-9, 室温(25°C±5°C)反应至完全;

步骤3: 参照BX-34的方法, 纯化, 得到目标化合物纯品, 经质谱鉴定分子量。

40 在上述研究的基础上, 本发明还提供了所述制备方法制得的多肽。

本发明还提供了所述多肽在制备治疗与ETBR受体相关疾病的药物中的应用。

在本发明的一些具体实施方案中, 所述与ETBR受体相关疾病包括脑卒中、阿尔

茨海默氏病、脊髓损伤、主动脉瓣狭窄或新生儿缺氧缺血性脑病中的一种或多种；

所述脑卒中包括缺血性脑卒中和/或出血性脑卒中。

本发明还提供了药物，包括所述多肽以及药学上可接受的辅料或助剂。

本发明还提供了药物组合物，包括所述药物以及其他任意有效成分。

5 本发明还提供了治疗与 ETBR 受体相关疾病的方法，其包含向受试者施用以下任意项：

(I)、所述多肽；和/或

(II)、所述药物；和/或

(III)、所述药物组合物。

10 在本发明的一些具体实施方案中，所述与 ETBR 受体相关疾病包括脑卒中、阿尔茨海默氏病、脊髓损伤、主动脉瓣狭窄或新生儿缺氧缺血性脑病中的一种或多种；

所述脑卒中包括缺血性脑卒中和/或出血性脑卒中。

本专利发现的多肽是建立在对于 ETBR 激动剂的机理研究之上，属于 ETBR 的高选择性激动剂。本专利开发的多肽通过构效关系研究和结构修饰延长了药物的半衰期和体内暴露量，减少了给药次数，在动物实验中的副作用比 IRL-1620 更低，药物的安全窗口更大。本发明中的化合物可以用于与 ETBR 受体相关的疾病治疗，比如缺血性脑卒中病人恢复期的康复治疗，促进卒中病人更好的恢复。

附图说明

20 为了更清楚地说明本发明实施例或现有技术中的技术方案，下面将对实施例或现有技术描述中所需要使用的附图作简单地介绍。

图 1 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-15 的 EC50；B 示 BX-6 的 EC50；C 示 BX-10 的 EC50；D 示 BX-21 的 EC50；E 示 BX-22 的 EC50；F 示 BX-5 的 EC50；

25 图 2 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-9 的 EC50；B 示 BX-8 的 EC50；C 示 BX-7 的 EC50；D 示 F-BX-5 的 EC50；E 示 BX-13-2 的 EC50；F 示 BX-31 的 EC50；

图 3 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-32 的 EC50；B 示 BX-38 的 EC50；C 示 BX-43 的 EC50；D 示 BX-45 的 EC50；E 示 QP-1 的 EC50；F 示 QP-3 的 EC50；

30 图 4 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-24 的 EC50；B 示 BX-53 的 EC50；C 示 BX-54 的 EC50；D 示 BX-58 的 EC50；E 示 FBX-8 的 EC50；F 示 BX-34 的 EC50；

35 图 5 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-48 的 EC50；B 示 BX-49 的 EC50；C 示 BX-50 的 EC50；

图 6 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-69 的 EC50 及其测定数据；B 示 BX-70 的 EC50 及其测定数据；C 示 BX-71 的 EC50 及其测定数据；

40 图 7 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定；其中，A 示 BX-76 的 EC50 及其测定数据；B 示 BX-95 的 EC50 及其测定数据；C 示 BX-99 的 EC50 及其测定数据；

图 8 示实施例 6 中多肽对犬 ETB 受体活性 EC50 测定；其中，A 示 Dog-BX-34

的 EC50 及其测定数据; B 示 Dog-BX-76 的 EC50 及其测定数据; C 示 Dog-BX-74 的 EC50 及其测定数据;

图 9 示实施例 6 中多肽对犬 ETB 受体活性 EC50 测定; 其中, A 示 Dog-BX-99 的 EC50 及其测定数据; B 示 Dog-BX-86 的 EC50 及其测定数据; C 示 Dog-BX-69 的 EC50 及其测定数据;

图 10 示实施例 6 中多肽对犬 ETB 受体活性 EC50 测定; 其中, A 示 Dog-BX-70 的 EC50 及其测定数据; B 示 Dog-BX-71 的 EC50 及其测定数据; C 示 Dog-BX-95 的 EC50 及其测定数据;

图 11 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 其中, A 示 Rat-BX-34 的 EC50 及其测定数据; B 示 Rat-F-BX-5 的 EC50 及其测定数据; C 示 Rat-BX-69 的 EC50 及其测定数据;

图 12 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 其中, A 示 Rat-BX-99 的 EC50 及其测定数据; B 示 Rat-BX-71 的 EC50 及其测定数据; C 示 Rat-BX-95 的 EC50 及其测定数据;

图 13 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 其中, A 示 Rat-BX-74 的 EC50 及其测定数据; B 示 Rat-BX-76 的 EC50 及其测定数据;

图 14 示实施例 5 中多肽对小鼠 ETB 受体活性 EC50 测定; 其中, A 示 Mouse-BX-34 的 EC50 及其测定数据; B 示 Mouse-BX-69 的 EC50 及其测定数据; C 示 Mouse-BX-70 的 EC50 及其测定数据;

图 15 示实施例 5 中多肽对小鼠 ETB 受体活性 EC50 测定; 其中, A 示 Mouse-BX-71 的 EC50 及其测定数据; B 示 Mouse-BX-95 的 EC50 及其测定数据; C 示 Mouse-F-BX-5 的 EC50 及其测定数据;

图 16 示实施例 7 中多肽 BX34 对 dMACO 模型小鼠脑部血流灌注量的影响;

图 17 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定; 其中, A 示 BX-223 的 EC50; B 示 BX-224 的 EC50; C 示 BX-225-Na 的 EC50;

图 18 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定; 其中, A 示 BX-253 的 EC50; B 示 BX-254 的 EC50; C 示 BX-256 的 EC50;

图 19 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定; 其中, A 示 BX-221 的 EC50; B 示 BX-56 的 EC50; C 示 BX-238 的 EC50;

图 20 示实施例 3 中多肽对人 ETB 受体活性 EC50 测定; 其中, A 示 BX-229 的 EC50; B 示 BX-255 的 EC50;

图 21 示实施例 6 中多肽对犬 ETB 受体活性 EC50 测定; 其中, A 示 Dog-BX-224 的 EC50 及其测定数据; B 示 Dog-BX-225 的 EC50 及其测定数据; C 示 Dog-BX-253 的 EC50 及其测定数据;

图 22 示实施例 6 中多肽对犬 ETB 受体活性 EC50 测定; 其中, A 示 Dog-BX-254 的 EC50 及其测定数据; B 示 Dog-BX-255 的 EC50 及其测定数据; C 示 Dog-BX-256 的 EC50 及其测定数据;

图 23 示实施例 6 中多肽对犬 ETB 受体活性 EC50 测定; 其中, A 示 Dog-BX-56 的 EC50 及其测定数据; B 示 Dog-BX-229-Na 的 EC50 及其测定数据; C 示 Dog-BX-238 的 EC50 及其测定数据;

图 24 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 其中, A 示 Rat-BX-223 的 EC50 及其测定数据; B 示 Rat-BX-224 的 EC50 及其测定数据; C 示 Rat-BX-225

的 EC50 及其测定数据;

图 25 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 其中, A 示 Rat-BX-255 的 EC50 及其测定数据; B 示 Rat-BX-254 的 EC50 及其测定数据; C 示 Rat-BX-253 的 EC50 及其测定数据;

图 26 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 其中, A 示 Rat-BX-56 的 EC50 及其测定数据; B 示 Rat-BX-238 的 EC50 及其测定数据; C 示 Rat-BX-229 的 EC50 及其测定数据;

图 27 示实施例 4 中多肽对大鼠 ETB 受体活性 EC50 测定; 具体示 Rat-BX-256 的 EC50 及其测定数据;

图 28 示实施例 5 中多肽对小鼠 ETB 受体活性 EC50 测定; 其中, A 示 Mouse-BX-223 的 EC50 及其测定数据; B 示 Mouse-BX-224 的 EC50 及其测定数据; C 示 Mouse-BX-225 的 EC50 及其测定数据;

图 29 示实施例 5 中多肽对小鼠 ETB 受体活性 EC50 测定; 其中, A 示 Mouse-BX-253 的 EC50 及其测定数据; B 示 Mouse-BX-254 的 EC50 及其测定数据; C 示 Mouse-BX-255 的 EC50 及其测定数据;

图 30 示实施例 5 中多肽对小鼠 ETB 受体活性 EC50 测定; 其中, A 示 Mouse-BX-256 的 EC50 及其测定数据; B 示 Mouse-BX-238 的 EC50 及其测定数据; C 示 Mouse-BX-56 的 EC50 及其测定数据;

图 31 示实施例 5 中多肽对小鼠 ETB 受体活性 EC50 测定; 其中, A 示 Mouse-BX-229 的 EC50 及其测定数据;

图 32 示实施例 13 中建模给药后第 7 天 Garcia JH 评分;

图 33 示实施例 13 中建模给药后第 14 天 Garcia JH 评分;

图 34 示实施例 13 中 VEGF-A 蛋白表达量的变化;

图 35 示实施例 13 中 BDNF 蛋白表达量的变化。

具体实施方式

本发明公开了多肽及其应用, 本领域技术人员可以借鉴本文内容, 适当改进工艺参数实现。特别需要指出的是, 所有类似的替换和改动对本领域技术人员来说是显而易见的, 它们都被视为包括在本发明。本发明的方法及应用已经通过较佳实施例进行了描述, 相关人员明显能在不脱离本发明内容、精神和范围内对本文所述的方法和应用进行改动或适当变更与组合, 来实现和应用本发明技术。

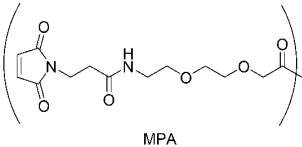
本发明部分多肽结构及生物实验结果如下:

表 1 多肽结构及对人 ETB 受体的活性

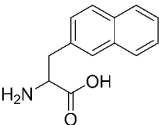
序列 编号 SE Q ID No :	编号	序列	hETBR激动 活性EC50 /nM	MW
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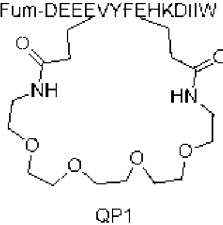
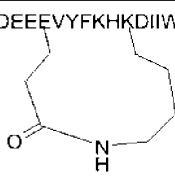
1	对照化合物 (IRL1620)	Suc-DEEAVYFAHLDIIW	EC50=1.333nM	1820
2	BX-5	Suc-DEEAVYFAHKDIIW	EC50=25.16nM	1836
3	F-BX-5	Fum-DEEAVYFAHKDIIW	EC50=7.608nM	1834
4	BX-7	Suc-DEEAVYFAHLDVIW	EC50=0.8973nM	1806
5	BX-8	Suc-DEEAVYFAHLD(2-Abu)IW	EC50=1.356nM	1792
6	BX-34	Fum-DEEAVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	EC50=18.31nM	2549
7	BX-43	Suc-DEEAKYFAHLDIIW	EC50=4.774nM	1850
8	BX-45	Suc-DEEEVYFAHKDIIW	EC50=28.97nM	1893
9	BX-48	Suc-D环(EEAK)YFAHLDIIW	EC50=1.769nM	1832
10	BX-49	Suc-D环(EEADab)YFAHLDIIW	EC50=4.439nM	1804
11	BX-50	Suc-DEE环(EVYFAHK)DIIW	EC50=30.52nM	1876
12	BX-51	Fum-DEEAVYFAHOrn(-AEEA-AEEA-γE-ODDA)DIIW	37.60%@100nM 47.83%@10nM	2535
13	BX-52	Fum-DEEEVYFAHKDIIW	121.00%@100nM 145.60%@10nM	1891
14	BX-53	Suc-DEEEVYFAHOrnDIIW	EC50=10.74nM	1880
15	BX-54	Suc-DEEEVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	EC50=34.05nM	2610
16	BX-57	Suc-DE环(CEEC)YFAHKDIIW	121.58%@100nM 86.20%@10nM	1999
17	BX-58	MeO-Fum-DEEEVYFAHKDIIW	EC50=4.477nM	1906
18	BX-59	Fum-DEEEVYFAHOrnDIIW	93.46%@100	1878

			nM 125.64% @ 10 nM	
19	BX-60	Fum-DEEEVYFAHK(-AEEA-AEEA- γ E-ODD A)DIW	4.84% @ 100n M -15.72% @ 10n M	2608
20	BX-61	Suc-DEEAVYFAHOrn(-AEEA-AEEA- γ E -ODDA)DIW	40.94% @ 100 nM 13.97% @ 10n M	2538
21	BX-62	Fum-DEE环(EVYFK)HKD(2-Abu)IW	129.39% @ 10 0nM 99.31% @ 10n M	1903
22	BX-63	Suc-D环(EEAK)YFAHLD(2-Abu)IW	122.93% @ 10 0nM 90.08% @ 10n M	1804
23	BX-64	Fum-D环(EEAK)YFAHLD(2-Abu)IW	132.16% @ 10 0nM 79.92% @ 10n M	1802
24	BX-65	MeO-Fum-D环(EEAK)YFAHLD(2-Abu)IW	99.24% @ 100 nM 59.02% @ 10n M	1814
25	BX-66	Fum-DEEK(- γ E-AEEA-AEEA-ODDA)VYFAH LDIW	60.51% @ 100 nM 7.67% @ 10n M	2592
26	BX-67	Fum-DEEAK(- γ E-AEEA-AEEA-ODDA)YFAH LDIW	46.98% @ 100 nM 2.68% @ 10n M	2564
27	BX-68	Fum-DEEAVYFK(- γ E-AEEA-AEEA-ODDA)H LDIW	-18.64% @ 100 nM -39.42% @ 10n M	2592
28	BX-69	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-C18) DIW	T1/2=30min; EC50=1153n M	2520
29	BX-70	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-C16)	T1/2=41min;	2492

		DIIW	EC50=19.11nM	
30	BX-71	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C12)DIIW	T1/2=23min; EC50=74.7nM	2436
31	BX-72	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-B)DIW	18.34%@100nM, 23.56%@10nM	2433
32	BX-74	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	1.82%@100nM -14.10%@10nM	2552
33	BX-75	MeO-Fum-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	-10.59%@100nM 14.68%@10nM	2564
34	BX-76	Suc-D环(EEAK)YFAHLDVIW	EC50=20.00nM	1818
35	BX-77	Suc-D环(EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)DIW	4.69%@100nM -16.59%@10nM	2563
36	BX-78	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DVIW	23.41%@100nM -14.2%@10nM	2538
37	BX-79	Suc-D环(EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)DVW	19.85%@100nM 2.13%@10nM	2550
38	BX-86	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW-NH2	70.55%@100nM 105.53%@10nM	2548
39	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW  MPA	EC50=45.6nM	2661
40	BX-99	Fum-D环(EEAK)YFAHLDVIW	EC50=33.12nM	1916

41	BX-100	Fum-D环 (EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)DV IW	15.03%@100 nM 18.79%@10n M	2547
42	BX-101	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-ODD A)DVIW	30.96%@100 nM, -5.97%@10n M	2536
43	BX-102	Fum-D环(EEAK)YFAHLDIIW	155.47%@10 0nM, 113.81%@10 nM	1829
44	BX-103	Fum-D环 (EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)DII W	14.93%@100 nM 45.51%@10n M	2561
45	BX-104	Fum-D环 (EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)D(2-Abu)IW	-21.93%@100 nM -1299.77%@1 0nM	2534
46	BX-105	Fum-DEEAKYFAHLDIIW	253.05%@10 0nM 64.66%@10n M	1847
47	BX-106	Fum-DEEAKYFAHLDVIW	117.63%@10 0nM 117.57%@10 nM	1836
48	BX-107	Fum-DEEAKYFAHK(- γ E-AEEA-AEEA-ODD A)DIIW	100.37%@10 0nM 50.48%@10n M	2579
49	BX-108	Fum-DEEAKYFAHK(- γ E-AEEA-AEEA-ODD A)DVIW	9.56%@100n M -1185.11%@1 0nM	2567
50	BX-109	Fum-DEEAK(- γ E-AEEA-AEEA-ODDA)YFAH LDIIW	74.1%@100n M -1095.4%@10 nM	2566
51	BX-110	Fum-DEEAK(- γ E-AEEA-AEEA-ODDA)YFAH LDVIW	132.61%@10 0nM 138.99%@10	2549

			nM	
52	BX-111	SA-DEEAVYFAHLDIIW	64.98%@100 nM -11.84%@10n M	1844
53	BX-112	MA-DEEAVYFAHLDIIW	114.05%@10 0nM 466.59%@10 nM	1844
54	BX-13-2	Fum-DEEAVYFAHKDIIW1  W1: W1命名为 2-amino-3-(naphthalen-2-yl)propanoic acid, 2- 氨基-3-(萘-2-基)丙酸	EC50=11.76n M	1843. 8
55	BX-9	suc-DEEAVYFAHR1DIIW (R1=L-2氨基-4胍基丁酸)	EC50=23.18n M	1849. 98
56	BX-31	Fum-DEEAVYFAHOrnDIIW	EC50=56.67n M	1819
57	BX-32	Fum-DEEAVYFAHCitDIIW	EC50=118.3n M	1862
58	BX-38	Suc-DE环(CEAC)YFAHLDIIW	EC50=45.71n M	1927
59	BX-23	Fum-DEEAVYFAHKDVIW	89.28%@100 nM 26.12%@10n M	1704. 9
60	BX-24	Fum-DEEAVYFAHKD(2-Abu)IW	EC50=8.515n M	1805. 9
61	BX-25	Suc-DEEAVYFAHLDI(N-Me)IW	28.86%@100 nM 19.19%@1 0nM	1833. 85
62	BX-26	Suc-DEEAVYFAHL(N-Me)DIIW	30.58%@100 nM 11.94%@10n M	1833. 85
63	BX-27	Suc-DEEAVYFAHL(N-Me)DI(N-Me)IW	0.42%@100n M 1.72%@10n M	1847. 86

64	BX-28	Fum-DEEAVYFAHL(N-Me)DIIW	-10.73%@100 nM 8.27%@10n M	1845. 85
65	BX-29	Fum-DEEAVYFAHL(N-Me)DI(N-Me)IW	6.51%@100n M 15.61%@10n M	1847. 86
66	FBX-7	Fum-DEEAVYFAHLDVIW	99.81%@100 nM 91.89%@10n M	1805. 9
67	FBX-8	Fum-DEEAVYFAHLD(2-Abu)IW	EC50=1.766n M	1790. 9
68	QP-1	Fum-DEEEVYFEHKDIIW  QP1	EC50=9.653n M	1848
69	QP-3	Fum-DEEEVYFKHKDIIW 	EC50=3.852n M	1931
70	BX-15	FA-DEEAVYFAHKDIIW	EC50=41.14	1912. 87
71	BX-16	Fum-DEEE(Biotin)VYFAHKDIIW	22.24%@1μ M 14.10%@10μ M	2160. 4
72	BX-10	suc-DEEAVYFAHLDPIW	EC50=30.85n M	1804. 96
73	BX14-1	Fum-DEE(C16)AVYFAHLDIIW	15.80 %@1μ M 18.63%@10μ M	2044. 1
74	BX-6	Suc-DEEAVYFAHRDIIW	EC50=25.13n M	1864. 03
75	BX-21	Fum-DEEALYFAHKDIIW	EC50=11.96n M	1848

4	BX-48	Suc-D环(EEAK)YFAHLDIIW	9.37%@100μM 4.45%@10μM	1832
5	BX-49	Suc-D环(EEADab)YFAHLDIIW	-15.45%@100nM -20.86%@10nM	1804
6	BX-50	Suc-DEE环(EVYFAHK)DIIW	-6.92%@100nM 10.07%@10nM	1876
7	BX-52	Fum-DEEEVYFAHKDIIW	-11.24%@100nM -2.49%@10nM	1891
8	BX-53	Suc-DEEEVYFAHOrnDIIW	-17.02%@100nM -17.65%@10nM	1880
9	BX-54	Suc-DEEEVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	-8.66%@100μM -18.46%@10μM	2610
10	BX-57	Suc-DE环(CEEC)YFAHKDIIW	-10.53%@100μM -29.04%@10μM	1999
11	BX-58	MeO-Fum-DEEEVYFAHKDIIW	-2.01%@100μM -5.95%@10μM	1906
12	BX-59	Fum-DEEEVYFAHOrnDIIW	-7.67%@100μM -10.61%@10μM	1878
13	BX-62	Fum-DEE环(EVYFK)HKD(2-Abu)IW	-19.09%@100nM -17.37%@10nM	1903
14	BX-63	Suc-D环(EEAK)YFAHLD(2-Abu)IW	4.43%@100μM -15.24%@10μM	1804
15	BX-64	Fum-D环(EEAK)YFAHLD(2-Abu)IW	6.41%@100μM -13.52%@10μM	1802
16	BX-66	Fum-DEEK(-γE-AEEA-AEEA-ODDA)VYFAHLDIIW	-0.94%@100μM 13.13%@10μM	2592
17	BX-69	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C18)DIIW	11.53%@100μM 13.06%@10μM	2520
18	BX-70	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C16)DIIW	13.53%@100μM -15.81%@10μM	2492
19	BX-71	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C12)DIIW	-9.49%@100μM -9.66%@10μM	2436
20	BX-74	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	-13.51%@100μM -2.64%@10μM	2552

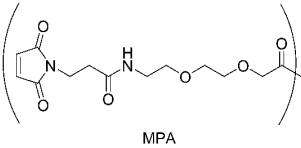
21	BX-76	Suc-D环(EEAK)YFAHLDVIW	-20.87%@10μM -7.56%@100μM	1818
22	BX-77	Suc-D环 (EEAK)YFAHK(-γE-AEEA-AEEA-ODDA) DIIW	-6.32%@100μM -29.53%@10μM	2563
23	BX-78	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-OD DA)DVIW	-23.02%@100μ M -6.06%@10μM	2538
24	BX-79	Suc-D环 (EEAK)YFAHK(-γE-AEEA-AEEA-ODDA) DVIW	-46.08%@10μM -12.17%@100μ M	2550
25	BX-86	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-O DDA)DIIW-NH2	10.42%@100μ M 18.26%@10μM	2549
26	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW 	-7.46%@100μM -9.81%@10μM	2661
27	BX-100	Fum-D环 (EEAK)YFAHK(-γE-AEEA-AEEA-ODDA) DVIW	9.52%@100μM -39.09%@10μM	2547
28	BX-229 -Na	Fum-DEEAVYFAHK(-AEEA-γE-C12)DVI W	0.68%@100μM	2276
29	BX-238	Fum-DEEAVYFAHK(-AEEA-E-C12)DVIW	-5.07%@100μM -4.74%@10μM	2276
30	BX-225	Fum-DEEAVYFAHK(-AEEA-γE-C12)DII W	3.59%@100μM 0.52%@10μM	2290
31	BX-253	Fum-K(-AEEA-AEEA-γE-ODDA)EEAVYF AHL DIIW	-9.03%@100μM -12.86%@10μM	2547

表 7 部分多肽结构及对犬 ETB 受体的活性

序号	编号	序列	DETAR激动 活性	MW
1	BX-34	Fum-DEEAVYFAHK(-AEEA-AEEA-γE-ODD A)DIIW	EC50=312.7n M	2549
3	BX-52	Fum-DEEEVYFAHKDIIW	104.49%@100 nM 76.82%@10n M	1891
4	BX-57	Suc-DE环(CEEC)YFAHKDIIW	49.81%@100n M	1999

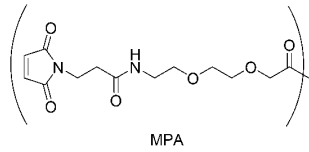
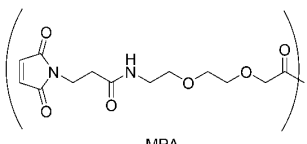
			-20.49%@10nM	
5	BX-59	Fum-DEEEVYFAHOrnDIIW	117.46%@100nM 14.7%@10nM	1878
6	BX-69	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C18)DIIW	EC50=30.66nM	2520
7	BX-70	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C16)DIIW	EC50=64.44nM	2492
8	BX-71	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C12)DIIW	EC50=63.33nM	2436
9	BX-74	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	EC50=519.2nM	2552
10	BX-76	Suc-D环(EEAK)YFAHLDVIW	EC50=30.55nM	1818
11	BX-86	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW-NH ₂	EC50=411.4nM	2548
12	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW 	EC50=69.1nM	2661
13	BX-99	Fum-D环(EEAK)YFAHLDVIW	EC50=17.22nM	2547
14	BX-56	Suc-DE环(CEEC)YFAHLDIIW	EC50=8.04nM	1984
15	BX238	Fum-DEEAVYFAHK(-AEEA-E-C12)DVIW	EC50=11.9nM	2276
16	BX229-Na	Fum-DEEAVYFAHK(-AEEA-γE-C12)DVIW	EC50=17.9nM	2276
17	BX-224	Fum-DEEAVYFAHK(-AEEA-γE-C16)DIIW	EC50=58.2nM	2346
18	BX-225	Fum-DEEAVYFAHK(-AEEA-γE-C12)DIIW	EC50=17.7nM	2290
19	BX-253	Fum-K(-AEEA-AEEA-γE-ODDA)EEAVYFAHLDIIW	EC50=252.4nM	2547
20	BX-254	Fum-DK(-AEEA-AEEA-γE-ODDA)EAVYFAHLDIIW	EC50=95.53nM	2533
21	BX-255	(ODDA-γE-AEEA-AEEA-)DDEEAVYFAHLDIIW	EC50=223.2nM	2550
22	BX-256	(ODDA-γE-AEEA-AEEA-)NH-C ₂ H ₄ -NH-Suc-DEEAVYFAHLDIIW	EC50=139.6nM	2594

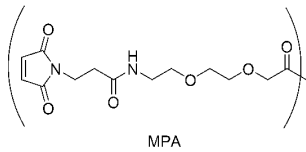
表 8 部分多肽结构及对大鼠 ETB 受体的活性

序号	编号	序列	DETAR激动活性	MW
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1	BX-34	Fum-DEEAVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	EC50=10.2nM	2549
2	F-BX-5	Fum-DEEAVYFAHKDIIW	EC50=924.3nM	1834
3	BX-52	Fum-DEEEVYFAHKDIIW	389.09% @ 100nM 22.36% @ 10nM	1891
4	BX-57	Suc-DE环(CEEC)YFAHKDIIW	218.34% @ 100nM -67.42% @ 10nM	1999
5	BX-59	Fum-DEEEVYFAHOrnDIIW	46.94% @ 100nM 314.15% @ 10nM	1878
6	BX-69	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C18)DIIW	EC50=33.23nM	2520
7	BX-70	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C16)DIIW	101.29% @ 100nM 55.75% @ 10nM	2492
8	BX-71	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C12)DIIW	EC50=22.2nM	2436
9	BX-74	Suc-DEEAVYFAHK(-γE-AEEA-AEEA-ODDA)DIIW	EC50=129.5nM	2552
10	BX-76	Suc-D环(EEAK)YFAHLDVIW	EC50=505.7nM	1818
12	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW  MPA	EC50=23.98nM	2661
13	BX-99	Fum-D环(EEAK)YFAHLDVIW	19.00nM	2547
14	BX-56	Suc-DE环(CEEC)YFAHLDIIW	12nM	1984
15	BX238	Fum-DEEAVYFAHK(-AEEA-E-C12)DVIW	EC50=9.88nM	2276
16	BX229-Na	Fum-DEEAVYFAHK(-AEEA-γE-C12)DVIW	EC50=7.22nM	2276
17	BX-223	Fum-DEEAVYFAHK(-AEEA-γE-C18)DIIW	EC50=16.08nM	2374
18	BX-224	Fum-DEEAVYFAHK(-AEEA-γE-C16)DIIW	EC50=48.3nM	2346
19	BX-225	Fum-DEEAVYFAHK(-AEEA-γE-C12)DIIW	EC50=21nM	2290
20	BX-253	Fum-K(-AEEA-AEEA-γE-ODDA)JEEAVYFAHLDIIW	EC50=187.2nM	2547
21	BX-254	Fum-DK(-AEEA-AEEA-γE-ODDA)EAVYFAHLDIIW	EC50=134.9nM	2533

22	BX-255	(ODDA-γE-AEEA-AEEA-)DDEEAVYFAHLDIIW	EC50=53nM	2550
23	BX-256	(ODDA-γE-AEEA-AEEA-)NH-C ₂ H ₄ -NH-Suc-DEEAVYFAHLDIIW	EC50=116.4nM	2594

表 9 部分多肽结构及对小鼠 ETB 受体的活性

序号	编号	序列	DETR激动活性	MW
1	BX-34	Fum-DEEAVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	EC50=71.7nM	2549
2	F-BX-5	Fum-DEEAVYFAHKDIIW	EC50=12.88nM	1834
3	BX-69	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C18)DIIW	EC50=71.48nM	2520
4	BX-70	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C16)DIIW	EC50=31.21nM	2492
5	BX-71	Fum-DEEAVYFAHK(-γE-AEEA-AEEA-C12)DIIW	EC50=4.175nM	2436
6	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW 	EC50=22.13nM	2661
7	BX56	Suc-DE环(CEEC)YFAHLDIIW	EC50=8.51nM	1984
8	BX238	Fum-DEEAVYFAHK(-AEEA-E-C12)DVIW	EC50=46.5nM	2276
9	BX229-Na	Fum-DEEAVYFAHK(-AEEA-γE-C12)DVIW	EC50=9.05nM	2276
10	BX-223	Fum-DEEAVYFAHK(-AEEA-γE-C18)DIIW	EC50=79.8nM	2374
11	BX-224	Fum-DEEAVYFAHK(-AEEA-γE-C16)DIIW	EC50=120nM	2346
12	BX-225	Fum-DEEAVYFAHK(-AEEA-γE-C12)DIIW	EC50=64.8nM	2290
13	BX-253	Fum-K(-AEEA-AEEA-γE-ODDA)EEAVYFAHLDIIW	EC50=60.2nM	2547
14	BX-254	Fum-DK(-AEEA-AEEA-γE-ODDA)EAVYFAHLDIIW	EC50=69.5nM	2533
15	BX-255	(ODDA-γE-AEEA-AEEA-)DDEEAVYFAHLDIIW	EC50=27.57nM	2550
16	BX-25	(ODDA-γE-AEEA-AEEA-)NH-C ₂ H ₄ -NH-Suc-DEE	EC50=45.5nM	259

	6	AVYFAHLDIIW	M	4
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表 10 缩写或英文全称的中文解释

缩写或英文	含义
Boc	叔丁氧羰基
DCM	二氯甲烷
DIEA	二异丙基乙胺
DMF	N,N-二甲基甲酰胺
MeOH	甲醇
ACN	乙腈
DIC	二异丙基碳二亚胺
HOBt	苯并三氮唑
Fmoc	芴甲氧羰基
HBTU	O-苯并三氮唑-四甲基脒六氟磷酸酯
PYBOP	六氟磷酸苯并三唑-1-基-氧基三吡咯烷基磷
OtBu	-O-C(CH ₃) ₃
Dde	1-(4, 4-二甲基-2, 6-二氧代环己亚基)乙基
Alloc	烯丙氧羰基
Oall	烯丙酯
Resin	树脂
Trt	三苯甲基
TFA	三氟醋酸
TIS	三异丙基硅烷
Suc	丁二酰基
Fum	富马酰基
AEEA	氨基乙氧基乙氧基乙酸
ODDA	十八烷二酸
Orn	鸟氨酸
Dab	二氨基丁酸
C12	月桂酰基
C16	棕榈酰基
C18	硬脂酰基
B	苧醇甲酰基
SA	山梨酸 Sorbic acid,
MA	反,反-粘康酸 trans,trans-Muconic Acid
2-Abu	2-氨基丁酸
FA	阿魏酸, Ferulic Acid
D	天, D1代表第一天、D2代表第2天
h	小时
min	分钟
saline	生理盐水组
sham	假手术组

BX-229-Na或 BX229Na或 BX229-Na	BX-229的钠盐形式
BX34、BX48、 BX225、BX229、 BX238、BX253、 BX254、BX255、 BX256等	分别等同于BX-34、BX-48、BX-225、BX-229、BX-238、BX-253、 BX-254、BX-255、BX-256等；化合物编号中间的横杠“-”可以省略

一般说明：化合物编号中间的横杠“-”可以省略，部分实验中编号省略了横杠，例如 BX229 等同于 BX-229；如无特殊说明，多肽默认是三氟乙酸盐形式；有些化合物会在编号后面标出特殊盐型如 BX-229-Na，BX229Na 都代表 BX-229 的钠盐形式。

表 11 主要试剂和溶剂

编号	原料名称	厂家
1	Fmoc-Trp(Boc)-Wang Resin	吉尔生化（上海）有限公司
2	Fmoc-Ile-OH	
3	Fmoc-Asp(OtBu)-OH	
4	Fmoc-Leu-OH	
5	Fmoc-His(Trt)-OH	
6	Fmoc-Ala-OH	
7	Fmoc-Phe-OH	
8	Fmoc-Tyr(tBu)-OH	
9	Fmoc-Val-OH	
10	Fmoc-Glu(OtBu)-OH	
11	Fmoc-Glu-OtBu	
12	Fmoc-Glu(OAll)-OH	
13	Fmoc-Dab(Boc)-OH	
14	Fmoc-Orn(Boc)-OH	
15	Fmoc-Lys(Boc)-OH	
16	Fmoc-Lys(Dde)-OH	
17	Fmoc-Lys(Alloc)-OH	
18	Fmoc-Cys(Trt)-OH	
19	OtBu-Suc	
20	OtBu-Fum	
21	Fmoc-AEEA-OH	
22	OtBu-ODDA	
23	PCDNA3.1	生工生物工程（上海）股份有限公司

5 本发明提供的多肽及其应用中所用原料及试剂如无特别说明均可由市场购得。
下面结合实施例，进一步阐述本发明：

制备例：BX-34系列化合物的合成

1、BX-34 的合成

10 称取 0.50g(0.25mmol)的 Fmoc-Trp(Boc)-Wang Resin 于反应器中，加入 DCM 10mL

- 溶胀 10min, 抽滤, DMF 洗 2 次, 加 25% 的 4-甲基哌啶/DMF (体积比) 反应 30min, 去除 Fmoc 基团。抽滤, 用 DMF 洗涤树脂 4 遍, DCM 洗涤 2 遍, 茚三酮检测, 树脂溶液蓝色; 称取 Fmoc-Ile-OH (1mmol, 4 eq.) 和 HBTU (1mmol, 4 eq.), DMF 溶解, 加入 DIEA (2mmol, 8 eq.), 混合均匀, 加入树脂中, 室温 (25°C±5°C) 磁力搅拌反应 1h, 抽滤, DMF、MeOH 和 DCM 依次洗涤 3 遍, 茚三酮检测, 树脂无色透明, 溶液浅黄色, 反应完全。加入 25% 的 4-甲基哌啶/DMF (体积比) 去除 Fmoc 基团。依次循环, 完成 Ile、Asp(OtBu)、Lys(Dde)、His(Trt)、Ala、Phe、Tyr(tBu)、Val、Ala、Glu(OtBu)、Glu(OtBu)、Asp(OtBu) 和 OtBu-Fum 的偶合。随后, 向肽树脂中加入 2% 水合肼/DMF 反应, 10min×3 次, 以脱除 Lys 侧链的 Dde, 然后依次缩合 AEEA、AEEA、Glu-α-OtBu 以及 OtBu-ODDA。肽树脂抽干, 加入预冷裂解液 (TFA: TIS: H₂O=95:2.5:2.5) 15mL, 室温 (25°C±5°C) 搅拌反应 3h, 抽出反应液, 树脂用少量 TFA 洗涤 2 次, 抽出。合并反应液, 加入预冷的甲基叔丁基醚约 200mL, 析出白色沉淀, 离心 (5000rpm×5min), 倒去上清液, 沉淀复加入甲基叔丁基醚, 涡旋, 离心, 弃去上清。沉淀放入真空干燥器中干燥 12h, 得到粗品。将粗肽用约 1% 氨水溶解, 过滤, 滤液用制备液相纯化。制备柱: C18-10-100, 30×250mm。流速: 25mL/min。A 相: 0.1%TFA/水, B 相: 0.1%TFA/90%乙腈/水。梯度洗脱以得到目标化合物纯品。将纯度>95%的目标化合物组分合并, 用水泵及旋转蒸发仪在 40°C 左右减压旋出乙腈, 所得浓缩液用液氮冷冻成固体, 然后使用冻干机冷冻干燥 48h, 得到目标化合物。经质谱鉴定, 分子量正确 ($[M+3]^3=850.8$)。
- 20 2、BX-5 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+1]^+=1837.3$)。
- 25 3、F-BX-5 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=918$)。
- 4、BX-7 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+1]^+=1807.4$)。
- 30 5、BX-8 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+1]^+=1792.1$)。
- 6、BX-43 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+1]^+=1851.4$)。
- 35 7、BX-45 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+1]^+=1893.2$)。
- 8、BX-51 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=1268.5$)。
- 40 9、BX-52 的合成
参照 BX-34 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确

($[M+2]^{2+}=946.9$)。

10、BX-53 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+1]^+=1881.5$)。

5 11、BX-54 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+2]^{2+}=1306.2$)。

12、BX-58 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
10 ($[M+1]^+=1907.3$)。

13、BX-59 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+2]^{2+}=939.9$)。

14、BX-60 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
15 ($[M+2]^{2+}=1305.6$)。

15、BX-61 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+2]^{2+}=1270.4$)。

20 16、BX-66 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+2]^{2+}=1297.2$)。

17、BX-67 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
25 ($[M+2]^{2+}=1283.3$)。

18、BX-68 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+2]^{2+}=1297.6$)。

19、BX-69 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
30 ($[M+3]^{3+}=841.1$)。

20、BX-70 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=831.7$)。

35 21、BX-71 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=825.8$)。

22、BX-72 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
40 ($[M+3]^{3+}=1653.4$)。

23、BX-73 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确

($[M+2]^{2+}=1066$)。

24、BX-74 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=851.6$)。

5 25、BX-75 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=855.7$)。

26、BX-78 的合成

10 参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=847.1$)。

27、BX-86 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=850.8$)。

28、BX-101 的合成

15 参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=846.3$)。

29、BX-105 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+1]^+=1848.2$)。

20 30、BX-106 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+1]^+=1837.3$)。

31、BX-107 的合成

25 参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=860.7$)。

32、BX-108 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=856.7$)。

33、BX-109 的合成

30 参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=856.3$)。

34、BX-110 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+3]^{3+}=850.7$)。

35 35、BX-111 的合成

参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+1]^+=1845.5$)。

36、BX-112 的合成

40 参照 BX-34 的合成方法，得到目标化合物纯品，经质谱鉴定，分子量正确
($[M+1]^+=1845.3$)。

37、BX-229 的合成

称取 0.50g(0.25mmol)的 Fmoc-Trp(Boc)-Wang Resin 于反应器中，加入 DCM 10mL

溶胀 10min, 抽滤, DMF 洗 2 次, 加 25% 的 4-甲基哌啶/DMF (体积比) 反应 30min, 去除 Fmoc 基团。抽滤, 用 DMF 洗涤树脂 4 遍, DCM 洗涤 2 遍, 茚三酮检测, 树脂溶液蓝色; 称取 Fmoc-Ile-OH (1mmol, 4 eq.) 和 HBTU (1mmol, 4 eq.), DMF 溶解, 加入 DIEA (2mmol, 8 eq.), 混合均匀, 加入树脂中, 室温 (25°C±5°C) 磁力搅拌反应 1h, 抽滤, DMF、MeOH 和 DCM 依次洗涤 3 遍, 茚三酮检测, 树脂无色透明, 溶液浅黄色, 反应完全。加入 25% 的 4-甲基哌啶/DMF (体积比) 去除 Fmoc 基团。依次循环, 完成 Val、Asp(OtBu)、Lys(Dde)、His(Trt)、Ala、Phe、Tyr(tBu)、Val、Ala、Glu(OtBu)、Glu(OtBu)、Asp(OtBu) 和 OtBu-Fum 的偶合。随后, 向肽树脂中加入 2% 水合肼/DMF 反应, 10min×3 次, 以脱除 Lys 侧链的 Dde, 然后依次缩合 AEEA、Glu- α -OtBu 以及 C12-OH。肽树脂抽干, 加入预冷裂解液 (TFA: TIS: H₂O=95:2.5:2.5) 15mL, 室温 (25°C±5°C) 搅拌反应 3h, 抽出反应液, 树脂用少量 TFA 洗涤 2 次, 抽出。合并反应液, 加入预冷的甲基叔丁基醚约 200mL, 析出白色沉淀, 离心 (5000rpm×5min), 倒去上清液, 沉淀复加入甲基叔丁基醚, 涡旋, 离心, 弃去上清。沉淀放入真空干燥器中干燥 12h, 得到粗品。将粗肽用约 1% 氨水溶解, 过滤, 滤液用制备液相纯化。制备柱: C18-10-100, 30×250mm。流速: 25mL/min。A 相: 0.1% TFA/水, B 相: 0.1% TFA/90% 乙腈/水。梯度洗脱以得到目标化合物纯品。将纯度>95% 的目标化合物组分合并, 用水泵及旋转蒸发仪在 40°C 左右减压旋出乙腈, 所得浓缩液用液氮冷冻成固体, 然后使用冻干机冷冻干燥 48h, 得到目标化合物。经质谱鉴定, 分子量正确 ($[M-2]^2=1137.3$)。

20 38、BX-229 钠盐的制备

将上步得到的 BX-229 固体溶于 0.1N 的氢氧化钠水溶液 (含 10 当量的氢氧化钠) 中, 用制备液相转盐。制备柱: C18-10-100, 30×250mm。流速: 25mL/min。A 相: 水, B 相: 乙腈。上样后水冲洗 15min, 然后梯度洗脱将产物从制备柱上洗脱下来。将纯度>95% 的目标化合物组分合并, 用水泵及旋转蒸发仪在 40°C 左右减压旋出乙腈, 所得浓缩液用液氮冷冻成固体, 然后使用冻干机冷冻干燥 48h, 得到目标化合物。

25 39、BX-238 的合成

称取 0.50g (0.25mmol) 的 Fmoc-Trp(Boc)-Wang Resin 于反应器中, 加入 DCM 10mL 溶胀 10min, 抽滤, DMF 洗 2 次, 加 25% 的 4-甲基哌啶/DMF (体积比) 反应 30min, 去除 Fmoc 基团。抽滤, 用 DMF 洗涤树脂 4 遍, DCM 洗涤 2 遍, 茚三酮检测, 树脂溶液蓝色; 称取 Fmoc-Ile-OH (1mmol, 4 eq.) 和 HBTU (1mmol, 4 eq.), DMF 溶解, 加入 DIEA (2mmol, 8 eq.), 混合均匀, 加入树脂中, 室温 (25°C±5°C) 磁力搅拌反应 1h, 抽滤, DMF、MeOH 和 DCM 依次洗涤 3 遍, 茚三酮检测, 树脂无色透明, 溶液浅黄色, 反应完全。加入 25% 的 4-甲基哌啶/DMF (体积比) 去除 Fmoc 基团。依次循环, 完成 Val、Asp(OtBu)、Lys(Dde)、His(Trt)、Ala、Phe、Tyr(tBu)、Val、Ala、Glu(OtBu)、Glu(OtBu)、Asp(OtBu) 和 OtBu-Fum 的偶合。随后, 向肽树脂中加入 2% 水合肼/DMF 反应, 10min×3 次, 以脱除 Lys 侧链的 Dde, 然后依次缩合 AEEA、Glu(OtBu) 以及 C12-OH。肽树脂抽干, 加入预冷裂解液 (TFA: TIS: H₂O=95:2.5:2.5) 15mL, 室温 (25°C±5°C) 搅拌反应 3h, 抽出反应液, 树脂用少量 TFA 洗涤 2 次, 抽出。合并反应液, 加入预冷的甲基叔丁基醚约 200mL, 析出白色沉淀, 离心 (5000rpm×5min), 倒去上清液, 沉淀复加入甲基叔丁基醚, 涡旋, 离心, 弃去上清。沉淀放入真空干燥器中干燥 12h, 得到粗品。将粗肽用约 1% 氨水溶解, 过滤, 滤液用制备液相纯化。制备柱: C18-10-100, 30×250mm。流速: 25mL/min。A 相: 0.1% TFA/

水, B相: 0.1%TFA/90%乙腈/水。梯度洗脱以得到目标化合物纯品。将纯度>95%的目标化合物组分合并, 用水泵及旋转蒸发仪在 40°C左右减压旋出乙腈, 所得浓缩液用液氮冷冻成固体, 然后使用冻干机冷冻干燥 48h, 得到目标化合物。经质谱鉴定, 分子量正确 ($[M-2]^2=1136.8$)。

5 40、BX-76 的合成

参照 BX-34 的合成方法, 完成主链的合成。氮气保护下, 向肽树脂中加入 0.3 当量的四三苯基膦钨和 12 当量的苯硅烷的 DCM 溶液, 室温 (25°C±5°C) 反应 2h, 以脱除 Glu 侧链的烯丙酯和 Lys 侧链的烯丙氧羰基。抽滤, 用 DCM 溶剂洗 5 遍, DMF 洗 3 遍, 加入 2 当量的 PYBOP、2 当量的 HOBt 以及 4 当量的 DIEA, DMF 溶解, 室
10 温 (25°C±5°C) 反应 5h。抽滤, DMF 洗 3 遍, DCM 洗 3 遍, 茚三酮检测, 如果反应不完全, 重复缩合一次。之后参照 BX-34 的方法, 进行裂解和纯化, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^2=910$)。

41、BX-48 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
15 ($[M+2]^2=917.5$)。

42、BX-49 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=903.2$)。

43、BX-50 的合成

20 参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=939$)。

44、BX-62 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=952.9$)。

25 45、BX-63 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=902.9$)。

46、BX-64 的合成

30 参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=901.9$)。

47、BX-65 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=908.2$)。

48、BX-77 的合成

35 参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=1282.8$)。

49、BX-79 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=1276.4$)。

40 50、BX-100 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确
($[M+2]^2=1274.7$)。

51、BX-103 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=1281.6$)。

52、BX-104 的合成

5 参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=1268.4$)。

53、BX-99 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=959.3$)。

10 54、BX-102 的合成

参照 BX-76 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=915.5$)。

55、BX-56 的合成

15 参照 BX-34 的合成方法, 完成主链的合成。向肽树脂中加入 5 当量的碘的 DMF 溶液, 室温 ($25^{\circ}\text{C}\pm 5^{\circ}\text{C}$) 反应 6h, 以脱除 Cys 侧链的保护基 Trt, 同时进行氧化。抽滤, DMF 洗 6 遍, DCM 洗 3 遍, 干燥。参照 BX-34 的合成方法, 裂解, 纯化, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=993.2$)。

56、BX-57 的合成

20 参照 BX-56 的合成方法, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+2]^{2+}=1000.4$)。

57、BX-95 的合成

25 参照 BX-34 的合成方法, 得到主链纯肽。同样, 参照 BX-34 的合成方法, 得到 CPAK 纯肽。将二者等当量溶于 50% 的乙腈水溶液中, 三乙胺调 pH 值至 8-9, 室温 ($25^{\circ}\text{C}\pm 5^{\circ}\text{C}$) 反应至完全。参照 BX-34 的方法, 纯化, 得到目标化合物纯品, 经质谱鉴定, 分子量正确 ($[M+3]^{3+}=850.5$)。

实施例1: 多肽对人ETB受体活性筛选

293T-17 细胞按照每孔 65 万铺于 6 孔板, 37°C , 5% CO_2 培养箱中培养过夜后, 转染含人 ETB 受体基因的表达载体 PCDNA3.1-hETB, 每孔转染 2.5 μg 质粒, 继续培养 48h, 在荧光显微镜下观察细胞表达绿色荧光后, 用胰酶消化并计数。化合物对人 ETB 受体的活性测定采用 Cisbio Bioassays 的 IP-One Gq 试剂盒, 用试剂盒中的 Stim Buffer 悬浮细胞, 将细胞悬液加入 96 孔检测板, 每个孔加入 7 μL 细胞悬液 (含 3 万细胞), 待活性筛选的多肽 (本发明制备例制得的多肽) 及阳性对照多肽 IRL1620 用 Stim B 溶解为 2 $\times$ 的浓度, 加 7 μL 于上述待测细胞中, 阴性对照孔加 7 μL 入 PBS 溶液于上述细胞中。IRL1620 作为阳性对照多肽。封板于 37°C 细胞培养箱中孵育 1h。检测孔、阳性对照孔、PBS 对照孔各添加 3 μL IP1 d2 工作液和 3 μL IP1 Tb cryptotat Antibody 工作液。封板避光室温 ($25^{\circ}\text{C}\pm 5^{\circ}\text{C}$) 作用 1h。拆下板密封, 在 ID5 酶标仪上测定吸光度为 665nm 和 620nm 数值。计算每个孔受体和供体发射信号的比率, 即 (665nm 信号/ 620nm 信号) $\times 10^4$ 数值。特定浓度下待测样本测定的 665nm 信号/ 620nm 信号数值的平均值为 F1、同等浓度阳性对照品 IRL1620 测定的 665nm 信号/ 620nm 信号数值平均值为 F2, PBS 阴性对照测定的 665nm 信号/ 620nm 信号数值平均值为 T1。待测多肽样品相对于阳性对照样品 IRL1620 的活性百分比 = $(F1-T1) \times 100 / (F2-T1)$ 。

hETB 序列 (NCBI 登录号: NM_000115.5)。

实施例2: 多肽对人ETA受体的选择性

293T-17 细胞按照每孔 65 万铺于 6 孔板, 37°C, 5% CO₂ 培养箱中培养过夜后,
5 转染含人 ETA 受体基因的表达式载体 PCDNA3.1-hETA, 每孔转染 2.5μg 质粒, 继续培养 48h, 在荧光显微镜下观察细胞表达绿色荧光后, 用胰酶消化并计数。化合物对人 ETA 受体的活性测定采用 Cisbio Bioassays 的 IP-One Gq 试剂盒, 用试剂盒中的 Stim Buffer 悬浮细胞, 将细胞悬液加入 96 孔检测板, 每个孔加入 7μL 细胞悬液 (含 3 万细胞), 待活性筛选的多肽 (本发明制备例制得的多肽) 及阳性对照多肽人内皮素
10 ET1 用 Stim B 溶解为 2× 的浓度, 加 7μL 于上述待测细胞中, 阴性对照孔加 7μL 入 PBS 溶液于上述细胞中。人内皮素 ET1 (ET1:CSCSSLMDKECVYFCHLDIIW (C1-C15,C3-C11)) SEQ ID No.85 作为阳性对照多肽。封板于 37°C 的细胞培养箱中孵育 1h。检测孔、阳性对照孔、PBS 对照孔各添加 3μL IP1 d2 工作液添和 3μL IP1 Tb cryptotote Antibody 工作液。封板避光室温 (25°C±5°C) 作用 1h。拆下板密封, 在 ID5 酶标仪上测定吸光度为 665nm 和 620nm 数值。计算每个孔受体和供体发射信号的比率, 即 (665nm 信号/620nm 信号) × 10⁴ 数值。特定浓度下待测样本测定的 665nm 信号/620nm 信号数值的平均值为 F3、同等浓度阳性对照品人内皮素 ET1 测定的 665nm 信号/620nm 信号数值平均值为 F5, PBS 阴性对照测定的 665nm 信号/620nm 信号数值平均值为 T3。待测多肽样品相对于阳性对照样品 ET1 的活性百分比 = (F3-T3) × 100 / (F5-T3) (见表 6)。hETA 序列 (NCBI 登录号: L06622.1)

实施例3: 多肽对人ETB受体活性EC50测定 (见表1, 图1~7)

293T-17 细胞按照每孔 65 万铺于 6 孔板, 37°C, 5% CO₂ 培养箱中培养过夜后,
25 转染含人 ETB 受体基因的表达式载体 PCDNA3.1-hETB, 每孔转染 2.5μg 质粒, 继续培养 48h, 在荧光显微镜下观察细胞表达绿色荧光后, 用胰酶消化并计数。化合物对人 ETB 受体的活性测定采用 Cisbio Bioassays 的 IP-One Gq 试剂盒, 用试剂盒中的 Stim Buffer 悬浮细胞, 将细胞悬液加入 96 孔检测板, 每个孔加入 7μL 细胞悬液 (含 3 万细胞), 待测定的多肽 (本发明制备例制得的多肽) 分别用 Stim B 稀释为 11 个浓度梯度, 待测定多肽每个浓度梯度用 Stim B 溶解为 2× 的浓度, 加 7μL 于上述待测细胞
30 中, 阴性对照孔加 7μL PBS 溶液于上述细胞中。封板于 37°C 的细胞培养箱中孵育 1h。检测孔、阳性对照孔人内皮素 ET1 (ET1:CSCSSLMDKECVYFCHLDIIW (C1-C15,C3-C11))、PBS 对照孔各添加 3μL IP1 d2 工作液添和 3μL IP1 Tb cryptotote Antibody 工作液。封板避光室温 (25°C±5°C) 作用 1h。拆下板密封, 在 ID5 酶标仪上测定吸光度为 665nm 和 620nm 数值。计算每个孔受体和供体发射信号的比率, 即
35 (665nm 信号/620nm 信号) × 10⁴ 数值。不同浓度下待测样本测定的 665nm 信号/620nm 信号数值的平均值为 F, 以 F 值为纵坐标, 以多肽浓度的对数值为横坐标, 绘制点图, 采用合适的方法拟合生成曲线, 计算多肽对人 ETB 受体的 EC50 值。另一种拟合曲线的方法, 采用实施例 1 中的方法先计算待测多肽各个浓度相对于阳性对照样品人内皮素 ET1 的激活率, 以此激活率为纵坐标, 以多肽浓度的对数值为横坐标, 绘制点图,
40 采用合适的方法拟合生成曲线, 计算多肽对人 ETB 受体的 EC50 值。

实施例4: 多肽对大鼠ETB受体活性EC50测定 (见表8)

方法同实施例3, 仅转染质粒为含大鼠 ETB 受体基因的表达式载体 PCDNA3.1-RETb。计算得到多肽对大鼠 ETB 受体的 EC50 值 (图 11~13)。大鼠 ETB 受体序列 (NCBI 登录号: X57764.1)

实施例5: 多肽对小鼠ETB受体活性EC50测定 (见表9)

方法同实施例3, 仅转染质粒为含小鼠 ETB 受体基因的表达式载体 PCDNA3.1-mETB。计算得到多肽对小鼠 ETB 受体的 EC50 值 (图 14、15)。小鼠 ETB 序列 (NCBI 登录号: NM_001276296)

实施例6: 多肽对犬ETB受体活性EC50测定 (见表7)

方法同实施例3, 仅转染质粒为含犬 ETB 受体基因的表达式载体 PCDNA3.1-DETB。计算得到多肽对犬 ETB 受体的 EC50 值 (图 8~10)。犬内皮素受体 B 序列: (NCBI 登录号: NM_001010943.2)

实施例7: 多肽BX-34对dMACO模型小鼠脑部血流灌注量的影响

受试药物: 本发明制备例制得的 BX-34。

采用 C57 BL/6 雄性 8 周龄小鼠, 适应性饲养至少 3D。实验当日异氟烷麻醉下将小鼠大脑皮层正中开口, 长约 2cm, 置于激光散斑血流仪下拍摄小鼠左右两侧脑血流视频, 作为缺血前血流灌注影像。之后用颅骨钻在矢状缝与冠状缝交点右后方将颅骨开口 (3mm×1.5mm); 镜下找到右侧大脑中动脉远端, 用 11 号缝合线将中动脉结扎; 同时分离并结扎右侧颈总动脉; 再次采集小鼠左右两侧脑血流视频, 作为缺血后血流灌注影像; 缝合头皮, 于复温箱中给动物复温。将建模成功的 dMACO 小鼠随机分配到 7、14、42μg/Kg 的 BX-34 单次给药组, 5、10μg/Kg IRL1620 单次给药组及 10μg/Kg IRL1620 三次给药组及生理盐水对照组。单次给药组于建模后 1h 尾静脉给药, 三次给药组分别于建模后 1h、3h、5h 尾静脉给药。于给药后 24h、48h、7D 分别再次采集每只动物左右脑血流视频。分析数据时导入 ROI 或选定需要计算血流的区域; 双击血流图片计算选定区域的平均血流值。以建模后、给药后 24h、48h、7D 的右脑血流灌注量的平均值与建模前右脑血流的平均值的比值进行各组统计分析。结果见图 16。

结果可见, 在 dMCAO 模型小鼠单次给予 42μg/kg 的 BX-34 后 24h、48h 和 7D, 脑部血流灌注量与生理盐水组相比均有显著增加, 而 IRL1620 无论 5μg/kg 单次给药、10μg/kg 单次给药, 或 10μg/kg 三次给药与生理盐水组相比均没有显著差异。单次给予 42μg/kg 的 BX-34 (此给药量与 10μg/Kg IRL1620 三次给药的总药量为同摩尔剂量) 显著增加了 dMCAO 小鼠脑部血液灌注量, 且此效应有剂量依赖性。

实施例8: 多肽的半衰期测定

本实施例中的多肽 (F-BX-5、BX-34、BX-48、BX-76、BX-86、BX-69、BX-70、BX-71、BX-56、BX-225、BX-238、BX-229、BX-253) 由本发明制备例制得。

血浆样本给药及处理方法: 表 12 中化合物 (以 BX-34 为例) 注射 3 只 C57 BL/6 小鼠, 60μg/mL, 每只鼠注射 200μL, 注射药物后 1min, 5min, 15min, 30min 采血, 采血后立即加入蛋白酶抑制剂, 3200rpm, 4 度离心 10min。取血浆后加入 2 倍体积的乙腈沉淀蛋白后 10000rpm 离心 5min, 0.22μm 滤器过滤后, 上液质联用仪器检测, 根

据对照药品和检测药品的积分面积计算血药浓度，不同药物各个时间点的 3 个检测值计算平均值。同时准备空白鼠血浆沉淀蛋白后样本作为对照。

表 12 多肽的半衰期数据

化合物编号	静脉给药剂量	半衰期(min)	AUC _{last 0-30 min} (ng.h/mL)
IRL1620	0.48 mpk	<2.6	130
F-BX-5	0.96 mpk	<3	127
BX-34	0.48 mpk	63	7736
BX-48	0.48 mpk	3.9	757
BX-76	0.96 mpk	3.6	250
BX-86	0.96 mpk	63	1146
BX-69	0.96 mpk	30	1611
BX-70	0.96 mpk	41	1701
BX-71	0.96 mpk	23	2049
BX-56	1 mpk	8.9	1376
BX-225	1 mpk	37	4981
BX-238	1 mpk	53	2302
BX-229	1 mpk	77	3393
BX-253	1 mpk	63	3989

- 5液质联用检测条件：
仪器型号：Agilent InfinityLab LC/MSD 1260-G6125C
色谱柱：Poroshell 120 SB-C18 4.6*100mm, 2.7μm
流动相 A: 0.1%甲酸-超纯水 流动相 B: 0.1%甲酸-乙腈
梯度设置：

时间（min）	A 相	B 相	流速
0	90%	10%	0.4mL/min
18	0	100%	0.4mL/min
20	0	100%	0.4mL/min
- 10柱温：45℃；进样量：20μl；
离子源：ESI；干燥器温度：350℃；干燥器流量：12L/min；雾化压力：45psi；
毛细管电压：4000v。
扫描类型：SIM；碎裂电压：135v；扫描/驻留时间：200ms。
- 15**实施例9：多肽BX34、BX48对pMACO模型大鼠体内药效**
受试药物：本发明制备例制得的 BX-34、BX-48（因分子量不同，采用相同摩尔剂量给药）。
采用雄性 SD 大鼠，280-300g，适应性饲养至少 3D。于异氟烷麻醉下采用线栓法进行大脑中动脉闭塞诱发局灶性脑缺血。将动物置于安全的仰卧位，进行中线切口，并暴露右颈总动脉，颈外动脉和颈内动脉。从颈外动脉向颈内动脉腔推进 4.0 单丝尼龙线，直至感觉到阻力（~20mm），表明大脑中动脉闭塞。允许尼龙细丝保留在原
- 20

位，以创建局灶性脑缺血的永久模型。将造模成功的大鼠随机分为4组：溶剂（生理盐水）组10只，7μg/Kg的BX-34 10只，5μg/Kg的BX-48 10只，5μg/Kg的IRL1620 组10只，分别于建模后2h、4h、6h各给药1次，共三次给药。在给药前以及给药后24h、3D、7D测定各组抓力。在给药前及给药后24h和7D进行转棒测试和足部错误测试，转棒测试记录时间、和路程，以24h和7D测定数值比前测数值作为分析指标；足部错误具体测定方法如下：将大鼠放在高架的网格地板上（29×29cm，网格开口3cm²）2min，记录每个前肢从网格掉落的足部错误次数及总步数。%足部错误=（前肢错误步数/总前肢步数）×100。行为学测试结果见表13、表14和表15。

结果显示，各给药组，3D和7D转棒测试、抓力测试结果好于生理盐水组，较生理盐水组有明显改善。给药7D后给药组足部错误百分比较生理盐水降低，BX-34和BX-48的足部错误百分比较低，低于生理盐水和IRL1620给药组。

表 13 抓力测定结果

抓力测试	24h/pre	3D/pre	7D/pre
1-IRL1620-5μg/Kg-3Time	47%±27%	57%±11%	61%+13%
2-BX34-7μg/Kg-3Time	40%±24%	63%±14%	67%±19%
4-saline-3Time	38%±22%	54%±17%	56%±23%
5-BX48-5μg/Kg-3Time	47%±23%	60%±7%	66%±22%

表 14 转棒测定结果

实验分组	24h/前测（%）			7D/前测（%）			
	转棒测试	时间/s	速度	路程/m	时间/s	速度	路程/m
1-IRL1620-5μg/Kg-3Time		59.43%±71.65%	57.24%±70.27%	55.14%+76.29%	64.06%±27.89%	60.63%±34.62%	45.93%±43.82%
2-BX34-7μg/Kg-3Time		38.34%±38.08%	39.09%±35.03%	28.25%±44.00%	65.5%±29.94%	62.27%±34.12%	49.60%±49.48%
4-saline-3Time		17.06%±22.65%	23.76%±14.01%	6.99%±10.61%	43.52%±25.05%	47.64%±10.12%	21.42%±16.99%
5-BX48-5μg/Kg-3Time		23.79%±27.04%	47.16%±30.98%	16.15%±22.62%	81.64%±10.87%	76.52%±13.55%	64.97%±19.43%

表 15 足部错误测定结果

足部错误分析	前测平均值	24h平均值	7D平均值
1-IRL1620-5μg/Kg-3Time	1%±2%	14.2%±17.61%	4.3%+3.14%
2-BX34-7μg/Kg-3Time	1%±1%	10.64%±15.53%	3.46%±2.92%
4-saline-3Time	0.78%±0.72%	13.88%±17.10%	5.18%±5.74%
5-BX48-5μg/Kg-3Time	1.11%±0.95%	10.89%±10.53%	2.24%±3.1%

20 实施例10：IRL1620、BX225、BX229、BX238、BX253、BX254、BX255、BX256多肽静脉给药急性毒性初步研究

静脉给药急性毒性实验中，雄性SD大鼠，体重200-230g，给药量范围为480μg/Kg至30μg/Kg之间，从高剂量到低剂量给药，尾静脉注射给药，给药后观察24h，如果某一给药剂量出现大鼠死亡，降低给药剂量注射观察。初步观察大鼠的毒性反应和死亡情况，统计大鼠死亡时间和不出现死亡的剂量。通过大鼠不出现死亡的剂量，初步判定多肽急性毒性的大小。急性毒性研究显示，大鼠能耐受IRL1620、BX225、BX229、BX238、BX253、BX254、BX255的最大耐受剂量分别为30μg/Kg、30μg/Kg、60μg/Kg、30μg/Kg、480μg/Kg、120μg/Kg、120μg/kg，BX225、BX229、BX238、BX253、BX254、BX255多肽注射SD大鼠的最大耐受剂量好于IRL1620，BX253静脉注射的急性毒性最小（表16）。

表 16: IRL1620、BX225、BX229、BX238、BX253、BX254、BX255、BX256 静脉给药急毒

动物编号	药物	静脉给药剂量	动物状态观察记录
1	IRL1620	120μg/Kg	5分钟呼吸急促身体发紫，9分钟死亡
2	IRL1620	60μg/Kg	3分钟呼吸急促，8分钟死亡
3	IRL1620	30μg/Kg	13分钟呼吸急促，30分钟不喜动，1.5小时恢复
4	IRL1620	30μg/Kg	15分钟呼吸急促，25分钟不喜动，1.5小时恢复
5	IRL1620	30μg/Kg	25分钟趴卧不动，1.5小时不喜动，第二天早晨观察死亡（估计在夜间死亡）
1	BX238	240μg/Kg	5-6分钟腹式呼吸，9分钟呼吸急促瘫软，11分钟死亡
2	BX238	120μg/Kg	5分钟呼吸急促，14分钟眼球变淡发紫，16分钟死亡
3	BX238	60μg/Kg	40-45分钟呼吸急促，1小时死亡
4	BX238	30μg/Kg	50分钟呼吸加快，1.2小时不喜动，第二天早晨观察已经死亡（估计在夜间死亡）
5	BX238	30μg/Kg	53分钟呼吸加快，1.2小时不喜动，第二天早晨观察已经死亡（估计在夜间死亡）
1	BX255	480μg/Kg	给药后23分钟身体发紫，给药后29分钟死亡
2	BX255	360μg/Kg	给药后12分钟身体发紫，给药后22分钟死亡
3	BX255	240μg/Kg	给药后前27分钟没有明显反应，27分钟呼吸加快，给药后49分钟死亡
4	BX255	240μg/Kg	给药后前24分钟没有明显反应，27分钟呼吸加快，给药后43分钟死亡
5	BX255	120μg/Kg	1小时前没有明显不良反应，近2小时呼吸略有加快，第二天观察状态良好恢复
6	BX255	120μg/Kg	9分钟不喜动，1小时10分钟恢复
7	BX255	120μg/Kg	9分钟不喜动，1小时10分钟恢复
8	BX255	120μg/Kg	12分钟静卧，不喜动，17分钟恢复活跃状态，通过瞳孔观察动物有痛苦，28分钟无痛苦
9	BX255	120μg/Kg	17分钟出现呼吸困难，10秒左右恢复正常，通过瞳孔观察动物有痛苦，28分钟无痛苦
1	BX225	240μg/Kg	4分钟呼吸急促，5分钟瘫软，7分钟眼球暗淡，12分钟死亡
2	BX225	120μg/Kg	2分钟呼吸略急促，25分钟动物不喜动，反应迟钝，呼吸加快，1.5小时基本缓解
3	BX225	120μg/Kg	10分钟动物不喜动，反应迟钝，呼吸略急促，时间持续近1小时，1小时10分钟基本缓解
4	BX225	120μg/Kg	27分钟出现腹式呼吸，卧地不动，40分钟呼吸困难死亡
5	BX225	120μg/Kg	25分钟出现腹式呼吸，卧地不动，32分钟呼吸困难死亡
6	BX225	60μg/Kg	7分钟静卧，不喜动，10分钟恢复活跃，通过瞳孔观察动物有痛苦，23分钟无痛苦
7	BX225	60μg/Kg	7分钟静卧，不喜动，10分钟恢复活跃，通过瞳孔观察动物有痛苦，35分钟呼吸急促，70分钟死亡
8	BX225	30μg/Kg	观察24小时无明显异常
9	BX225	30μg/Kg	观察24小时无明显异常
10	BX225	30μg/Kg	观察24小时无明显异常
11	BX225	30μg/Kg	观察24小时无明显异常
12	BX225	30μg/Kg	观察24小时无明显异常
13	BX225	30μg/Kg	观察24小时无明显异常
1	BX253	240μg/Kg	无异常
2	BX253	480μg/Kg	无异常
3	BX253	480μg/Kg	无异常
4	BX253	480μg/Kg	无异常
5	BX253	480μg/Kg	无异常
6	BX253	480μg/Kg	无异常
1	BX254	240μg/Kg	无明显异常
2	BX254	240μg/Kg	给药后15分钟呼吸急促，四肢发紫，呼吸抑制，四肢游泳姿势后死亡，给药后20分钟死亡
3	BX254	240μg/Kg	给药后14分钟呼吸急促，四肢发紫，四肢无力，给药后21分钟呼吸抑制后死亡
4	BX254	480μg/Kg	给药后22分钟身体发紫，给药后25分钟死亡
5	BX254	360μg/Kg	给药后16分钟身体发紫，给药后26分钟死亡
1	BX256	240μg/Kg	给药后16分钟呼吸急促，四肢浅紫色，抽搐，给药后27分钟死亡
2	BX256	240μg/Kg	给药后15分钟呼吸急促，四肢和面部发紫，四肢无力，给药后21分钟死亡
1	BX229	60μg/Kg	1小时内无明显反应，1小时呼吸急促，10分钟后恢复正常
2	BX229	60μg/Kg	1小时内无明显反应，1小时呼吸急促，10分钟后恢复正常
3	BX229	120μg/Kg	给药后26分钟死亡，鼻腔有白色分泌物，腹泻
4	BX229	120μg/Kg	给药后26分钟死亡，鼻腔有白色分泌物，腹泻
5	BX229	90μg/Kg	给药后1小时死亡
6	BX229	90μg/Kg	给药25分钟后呼吸急促，25分钟恢复，不喜动
7	BX229	90μg/Kg	给药1小时后呼吸急促，皮肤发紫，30分钟后有所恢复
8	BX229	90μg/Kg	给药45分钟后呼吸急促，腹泻，25分钟后恢复
9	BX229	90μg/Kg	给药44分钟后呼吸急促，给药52分钟后抽搐死亡
10	BX229	90μg/Kg	给药43分钟后呼吸急促，30分钟后恢复

5 实施例11: IRL1620、BX229、BX238多肽皮下给药急性毒性初步研究

皮下给药急性毒性实验中，雄性 SD 大鼠，体重 200-230g，给药量范围为 60μg/Kg 至 960μg/Kg 之间，皮下给药后观察 48h。初步观察大鼠的毒性反应和死亡情况，统计大鼠死亡时间和不出现死亡的剂量。通过大鼠不出现死亡的剂量，初步判定多肽急性毒性的大小。实验结果见下表 17，由表中结果可见，BX229 多肽皮下给药的急性毒性远远小于 IRL1620。

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表 17: IRL1620、BX229、BX238 多肽皮下给药急性毒性初步研究

动物编号	药物	皮下给药剂量	动物状态观察记录
1	IRL1620	60μg/Kg	给药后25分钟呼吸急促, 15分钟后恢复
2	IRL1620	60μg/Kg	给药后26分钟呼吸急促, 16分钟后恢复
3	IRL1620	60μg/Kg	给药后25分钟呼吸急促, 15分钟后恢复
4	IRL1620	60μg/Kg	给药后30分钟呼吸急促, 17分钟后恢复
5	IRL1620	60μg/Kg	给药后25分钟呼吸急促, 16分钟后恢复
6	IRL1620	120μg/Kg	给药后26分钟呼吸急促, 持续23分钟后死亡
7	IRL1620	120μg/Kg	给药后26分钟呼吸急促, 50分钟后逐渐恢复
8	IRL1620	120μg/Kg	给药后26分钟呼吸急促, 持续26分钟后死亡
9	IRL1620	120μg/Kg	给药后28分钟呼吸急促, 50分钟后逐渐恢复
10	IRL1620	120μg/Kg	给药后27分钟呼吸急促, 50分钟后逐渐恢复
1	BX229- Na	120μg/Kg	观察24小时无明显反应
2	BX229- Na	120μg/Kg	观察24小时无明显反应
3	BX229- Na	240μg/Kg	观察48小时无明显异常反应
4	BX229- Na	240μg/Kg	观察48小时无明显异常反应
5	BX229- Na	480μg/Kg	观察48小时无明显异常反应
6	BX229- Na	480μg/Kg	观察48小时无明显异常反应
7	BX229- Na	960μg/Kg	2小时内无显著反应, 2小时10分钟死亡
8	BX229- Na	960μg/Kg	观察48小时无明显异常反应
9	BX229- Na	960μg/Kg	观察48小时无明显异常反应
10	BX229- Na	960μg/Kg	观察48小时无明显异常反应
11	BX229- Na	960μg/Kg	观察48小时无明显异常反应
1	BX238- Na	240μg/Kg	观察48小时无明显异常反应。
2	BX238- Na	240μg/Kg	观察48小时无明显异常反应。
3	BX238- Na	360μg/Kg	观察48小时无明显异常反应。
4	BX238- Na	360μg/Kg	观察48小时无明显异常反应。
5	BX238- Na	480μg/Kg	给药后50分钟呼吸急促, 不喜动, 给药后2小时恢复。
6	BX238- Na	480μg/Kg	给药后21分钟呼吸急促, 给药后26分钟死亡。
7	BX238- Na	480μg/Kg	给药后10分钟呼吸急促, 给药后47分钟死亡。
8	BX238- Na	480μg/Kg	给药后45分钟呼吸急促, 不喜动, 给药后2小时恢复。
9	BX238- Na	480μg/Kg	给药后20分钟呼吸急促, 给药后55分钟死亡。

实施例12: IRL1620、BX225、BX229多肽静脉给药对SD大鼠血压的影响

- 5受试药物: 本发明制备例制得的 IRL1620、BX225、BX229
- SD 雄性大鼠通过异氟烷麻醉后, 颈部备毛, 沿颈部正中开口, 暴露气管; 打开小动物呼吸机和麻醉机, 麻醉机气麻浓度设置为 1.2; 出口通道连接呼吸机进气口; 呼吸机潮气量设置为 2mL, 呼吸频率为 90 次/min, 呼吸比为 1: 2; 呼吸机出气端连接塑料软管, 将塑料软管插进大鼠气道中。
- 10打开生物信号数据采集和分析系统机器和软件, 数据采集板一端与塑料软管连接, 另一端与连接有 1mL 注射器的联通器阀门连接, 将注射器中注满带有肝素的生理盐水; 将肝素生理盐水注入数据采集板, 排出整个空间内的空气, 直到肝素生理盐水从另一端塑料软管口流出; 游离出大鼠右颈总动脉, 颈总动脉远心端打死结, 近心端打活结, 用显微剪在结点中间的动脉上剪开 1/2 大小的口子, 将有肝素生理盐水的
- 15塑料软管插入剪开的口子并固定, 使软管不能随意前后挪动; 用生物信号数据采集和分析系统的调零阀将初始值血压归零; 打开颈总动脉近心端活结, 可见软件出现动物实时血压数据, 等待动物血压趋于稳定后, 尾静脉给药实时观察记录动物血压变化。IRL1620 给药剂量 5μg/Kg, BX34 给药剂量 42μg/kg, BX229 给药剂量 6.6μg/Kg。
- 结果显示, 5μg/Kg IRL620、42μg/Kg BX34、6.6μg/Kg BX229 多肽对大鼠血压有一定影响, 能引起血压的降低, 5μg/Kg IRL620 给药后能引起大鼠血压瞬时较快的变化, 2min 内就降到最低血压, 血压最大降低幅度为基线血压的 16.1%±2.4%, 42μg/Kg BX34、6.6μg/Kg BX229 对大鼠血压的影响较为平缓, 血压缓慢降低, 20-35 钟内缓慢降低到最低血压, 血压最大降低幅度分别为基线血压的 9.5%±1.7%和 17.0%±2.0%。
- (表 18)

表 18 IRL1620、BX34、BX229 多肽静脉给药对 SD 大鼠血压的影响

药物（给药浓度）	IRL1620(5μg/Kg)	BX34(42μg/Kg)	BX229(6.6μg/Kg)
血压降低基线血压百分比的最大值（n=3）	16.1%±2.4%	9.5%±1.7%	17.0%±2.0%
从基线血压降到最低血压的时间	小于 2 分钟	20-35 分钟	20-30 分钟

实施例13：BX229-Na一周三次给药对小鼠tMCAO 模型的药效

受试药物：本发明制备例制得的 BX-229

5 雄性 C57 /6J 小鼠 51 只， 10-12 周龄，体重 25-30g，实验前，饲养至少 2D 以适应环境（斯贝福）。建立 tMCAO 小鼠模型，小鼠采用异氟烷麻醉。体温由恒温毯控制，监测小鼠体温并维持体温在 37±0.5℃。在小鼠颅骨上的皮肤上做正中切口，并向外侧牵拉皮肤，将可弯曲的微针尖固定在小鼠颅骨左侧顶骨表面。颈部正中切口分离右侧 颈总动脉(CCA)、颈外动脉(ECA)和颈内动脉(ICA)。根据 Longa 的方法(Longa et al., 1989)，通过颈外动脉切开术引入硅橡胶涂层的线栓（瑞沃德，线头直径 10 0.22mm-0.23mm，MSMC23B120PK50），并通过颈内动脉缓慢地向大脑中动脉的起始部推进。为了确保大脑中动脉的持续成功阻断，我们使用激光散斑血流仪监测所有卒中动物的局部脑血流（通常稳定后，血流能降低 40-60%），建模插栓后 45min 拔栓，缝合切口后，皮下注射 1mL 37℃温生理盐水，小鼠置于加热垫上直至恢复。为了减轻疼痛，麻醉苏醒后给小鼠皮下注射痛立定。

15 将建模成功的 C57 tMCAO 小鼠随机分为 3 组,生理盐水组、30μg/Kg 的 BX229-Na 给药组、100μg/Kg 的 BX229-Na 给药组，各组分别于栓塞后 4.5h 颈部皮下给药 1 次（D1），D3 和 D6 相同时间点相同部位再各给药一次。本次实验分组给药见表 19。假手术组 6 只。按 2mL/kg 颈部皮下注射给药。给药后 7D 和 14D 完成 Garcia JH 评分。20 14D 评分结束后，小鼠安乐死，取梗死侧脑组织，提取总蛋白，ELISA 的方法检测各实验组 VEGF-A 和 BDNF 蛋白标志物的变化。

表 19: 实验分组及给药方案

分组	数量	t-MCAO 建立	CPD	剂量 (μg/kg)	体积 (mL/kg)	给药频率
4	6	假手术	生理盐水	-	2	D1: tMCAO 栓塞后 4.5 h
1	15	tMCAO	生理盐水	-	2	颈部皮下 2 点注射，D3
2	15	tMCAO	BX229	30	2	和 D6: 按照 D1 相同时
3	15	tMCAO	BX229	100	2	间点和部位各给药 1 次

实验结果显示，从 7D Garcia JH-15 分评分结果分析，假手术组和生理盐水溶剂对照组 7D 评分有显著差异，BX229-30μg/Kg 和 BX229-100μg/Kg 给药组的评分结果好

于生理盐水组，有一定的剂量依赖趋势，BX229-100μg/Kg 给药组 Garcia JH-15 分评分总分比生理盐水组高 1 分。从 14D Garcia JH-15 分评分结果分析，假手术组和生理盐水溶剂对照组 14D 评分有显著差异，BX229-30μg/Kg 和 BX229-100μg/Kg 给药组的评分结果好于生理盐水组，有剂量依赖关系，BX229-100μg/Kg 给药组 Garcia JH-15 分评分和生理盐水组相比有显著差异 (P<0.05)。图 32 和图 33

结果显示，BX229Na-30μg/Kg 三次给药组，BX229Na-100μg/Kg 三次给药组 VEGF-A 和 BDNF 蛋白的表达量较生理盐水组相比有一定提高，BX229Na-100μg/Kg 三次给药组 VEGF-A 蛋白的表达量高于假手术组，和生理盐水组相比有显著差异 (图 34、图 35、表 20、表 21)。BX229Na-100μg/Kg 三次给药组 BDNF 蛋白的表达量高于假手术组。

表 20: VEGF-A 蛋白表达量的变化

分组	VEGF-A pg/ml
Saline	426±115
BX229Na-30μg/Kg-3time	441±102
BX229Na-100μg/Kg-3time	562±56
Sham	505±122

表 21: BDNF 蛋白表达量的变化

分组	BDNF pg/ml
Saline	977±459
BX229Na-30μg/Kg-3time	1103±582
BX229Na-100μg/Kg-3time	1334±665
Sham	1093±151

15 实施例14: 多肽BX225和IRL1620对pMACO模型大鼠体内药效

受试药物: 本发明制备例制得的 BX-225、IRL1620

采用雄性 SD 大鼠，280-300g，适应性饲养至少 3D。于异氟烷麻醉下采用线栓法进行大脑中动脉闭塞诱发局灶性脑缺血。将动物置于安全的仰卧位，进行中线切口，并暴露右颈总动脉，颈外动脉和颈内动脉。从颈外动脉向颈内动脉腔推进 4.0 单丝尼龙线，直至感觉到阻力 (≈20mm)，表明大脑中动脉闭塞。允许尼龙细丝保留在原位，以创建局灶性脑缺血的永久模型。造模当天定义为 D1，第二天为 D2，依次类推。因实验无法同一批完成以及防止偶然误差的产生，本实验所有操作需遵循平行操作的原则，即每天的实验需要纳入每个组别的动物。手术造模顺序号为实验前根据动物体重大小进行排列所得。手术后将建模成功的 pMCAO 大鼠随机分为模型组和不同处理组。实验详细分组如下: (1) 5μg/Kg 的 IRL1620 三天 9 次给药组 15 只 (2) 6.6μg/Kg 的 BX225 三天 9 次给药组 15 只 (3) 19.8μg/Kg 的 BX225 三天 3 次给药组 15 只 (4)

模型（生理盐水）组 15 只（5）假手术组 6 只（假手术组使用同样的方式不结扎血管不插入线栓）。给药方式为尾静脉注射（iv），给药体积为 2mL/kg，首次给药时间为手术后 2h，给药频率根据试验设计分为一天内单次给予和多次给予，分别于 D1，D3 和 D6 给药，详细见表 22。模型组和假手术组给予相同体积的溶媒生理盐水。

5 mRS-6 分评分结果显示，BX225-6.6μg/Kg 三次给药组第 7D、14D、21D、30D mRS-6 分评分结果不断趋好(表 23)，14D 评测结果和生理盐水组及 IRL1620 三次给药组相比接近显著差异、7D、21D、30D 评测结果和生理盐水及 IRL1620 三次给药组相比有显著差异（P<0.05，表 23）。GarciaJH 评分结果显示， BX225-6.6μg/Kg 三次给药组第 7D、14D、21D、30D 的 GarciaJH 评分呈现不断改善的趋势，21D 和 30D 评测结果和生理盐水组相比有统计学差异（表 24、表 25）。

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表 22 IRL620 和 BX225 实验分组及给药方案

分组	数量	pMCAO 建立	CPD	剂量 (μg/kg)	体积 (mL/kg)	给药频率
5	6	假手术	溶媒	-	2	D1: pMCAO 后 2h, 4h, 6h; D3 和 D6: 按照 D0 相同时间点各给药 3 次
4	15	pMCAO	溶媒	-	2	
1	15	pMCAO	IRL1620	5	2	
1	15	pMCAO	BX225	6.6	2	
3	15	pMCAO	BX225	19.8	2	D1: pMCAO 后 2h; D3 和 D6: 按照 D1 相同时间点各给药 1 次

表 23 各实验组动物 4 周 mRS-6 分评分（*P<0.05&saline）

分组	mRS-7D	mRS-14D	mRS-21D	mRS-30D
IRL1620-5μg/Kg-3Time	2.54±2.03	2.77±2.66	2.72±2.71	2.52±2.87
BX225-6.6μg/Kg-3Time	1.67±0.50*	1.17±0.50	0.75±0.41*	0.50±0.31*
BX225-19.8μg/Kg-1Time	3.14±2.14	3.90±2.61	3.73±2.81	3.65±2.91
saline	3.33±2.22	2.89±2.57	2.70±2.72	2.59±2.81
sham	0.00±0.00	0.00±0.00	0.06±0.15	0.04±0.10

表 24 各实验组 21 天 Garcia JH 评分（*P<0.05&saline）

分组-21D	5min 自发活动	体态对称性	前肢伸展运动	笼网攀爬	两侧身体触觉反应	两侧胡须触碰反应	总分
4-saline	1.77±1.48	0.86±0.76	1.04±0.89	1.96±0.83	1.85±0.73	1.90±0.76	9.38±5.32
1-IRL1620-5μg/Kg-3Time	1.77±1.48	0.90±0.80	1.26±1.05	2.03±0.8	1.79±0.70	1.95±0.82	9.70±5.58

2-BX225-6.6μg/Kg-3Time	2.89±0.33	1.74±0.48	1.87±0.52	6 2.30±0.71	2.50±0.23	2.70±0.25	13.99±1.49*
3-BX225-19.8μg/Kg-1Time	1.17±1.47	0.63±0.80	0.80±1.01	1.69±0.85	1.60±0.77	1.63±0.80	7.51±5.58
sham	3.00±0.00	2.98±0.05	3.00±0.00	2.98±0.05	2.98±0.05	2.98±0.05	17.92±0.15

表 25 各实验组 30 天 Garcia JH 评分 (*P<0.05&saline)

分组-30D	5min 自发活动	体态对称性	前肢伸展运动	笼网攀爬	两侧身体触觉反应	两侧胡须触碰反应	总分
4-saline	1.69±1.44	1.21±1.00	1.38±1.15	2.09±0.91	1.70±0.59	1.81±0.68	9.88±5.66
1-IRL1620-5μg/Kg-3Time	1.77±1.48	0.90±0.80	1.26±1.05	2.03±0.86	1.79±0.70	1.95±0.82	9.70±5.58
2-BX225-6.6μg/Kg-3Time	3.00±0.00	2.07±0.29	2.25±0.23	2.81±0.15	2.29±0.18	2.39±0.13	14.81±0.56*
3-BX225-19.8μg/Kg-1Time	1.25±1.54	0.78±0.98	0.93±1.15	1.79±0.98	1.46±0.59	1.50±0.65	7.71±5.82
sham	2.83±0.41	2.98±0.05	3.00±0.00	2.96±0.10	2.69±0.37	2.75±0.18	17.21±1.04

5 以上对本发明所提供的多肽及其应用进行了详细介绍。本文应用了具体个例对本发明的原理及实施方式进行了阐述，以上实施例的说明只是用于帮助理解本发明的方法及其核心思想。应当指出，对于本技术领域技术人员来说，在不脱离本发明原理的前提下，还可以对本发明进行若干改进和修饰，这些改进和修饰也落入本发明权利要求的保护范围内。

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权 利 要 求

1、多肽，其特征在于，包括：

(I)、具有如式I所示的结构；或

5 X1-X2-X3- (A5) -X4-X5- (A1) -X6- (A2) -X7-X8-X9- (A3) -X10-X11- (A4) -X12-X13-X14-X15-X16

式 I

(II)、在如 (I) 所示的结构的基础上经取代、缺失、添加和/或替换 1 个或多个氨基酸的序列；或

10 (III)、与 (I) 所示的结构相似性 90%以上的序列；或

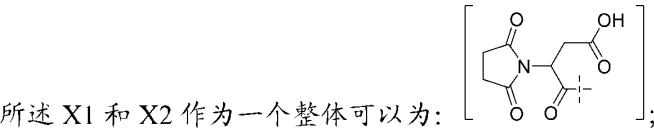
(IV)、具有如式I所示的结构所成的可药用的盐、溶剂化物、螯合物或非共价复合物；和/或

(V)、基于具有如式I所示的结构基础上的药物前体；和/或

(VI)、包括 (IV) 和/或 (V) 的任意混合物；

15 所述 X1 选自 Suc、Fum、MeO-Fum、Ac、SA、MA、FA、A1-D 或 A1-NH-C₂H₄-NH-Suc；

所述 X2 选自 D、E 或 K(A1)；



所述 X3 选自 E、D 或 K(A1)；

20 所述 X4 选自 E、E (C16) 或 D；

所述 X5 选自 A、K、R、H、E 或 D；

所述 X6 选自 V、I、K、Dab、Orn、L、F、W 或 C；

所述 X7 选自 Y、F 或 W；

所述 X8 选自 F、Y 或 W；

25 所述 X9 选自 A、K、R、H、D、E、Dab 或 Orn；

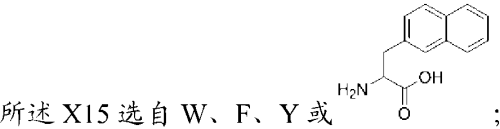
所述 X10 选自 H、K 或 R；

所述 X11 选自 K、L、L (N-Me)、I、V、Cit、H、R、L-2-氨基-4-胍基丁酸或 Orn；

所述 X12 选自 D 或 E；

30 所述 X13 选自 I、I (N-Me)、2-Abu、L、P 或 V；

所述 X14 选自 I、2-Abu、L 或 V；



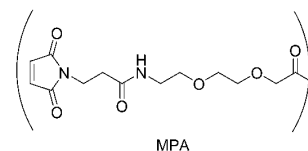
所述 X16 选自 OH 或 NH₂；

所述 A5 选自 C 或不存在；

35 所述 A1、A2、A3 或 A4 独立包括(Y1-Y2-Y3-Y4)；

所述 Y1 选自 -NH-(CH₂-CH₂-O)_{m1}-(CH₂)_{m2}-CO-、L/D-Glu、-CPAK-或不存在，

其中, L/D-Glu 通过 α -或 γ -羧基与多肽主链氨基酸的侧链氨基相连, 通过氨基与 Y2 羧基相连;



所述 Y2 选自 -NH-(CH₂-CH₂-O)_{m3}-(CH₂)_{m4}-CO-

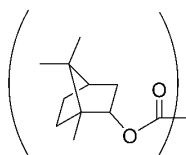
MPA

或不

存在;

- 5 所述 Y3 选自 -NH-(CH₂-CH₂-O)_{m5}-(CH₂)_{m6}-CO-、L/D-Glu 或不存在, 其中, L/D-Glu 通过 α -或 γ -羧基与 Y2 氨基相连, 通过氨基与 Y4 羧基相连; ;

所述 Y4 选自 D-Biotin、如式 2 所示结构、HOOC-(CH₂)_n-CO、CH₃-(CH₂)_n-CO 或不



式 2

10

其中, m₁、m₂、m₃、m₄、m₅ 或 m₆ 为 1-10 的整数;

其中, n 选自 10 至 25 的整数;

所述 A1、A2、A3 或 A4 只能单独存在或均不存在; 并且

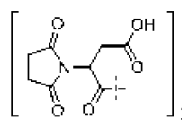
式 I 结构的多肽不包括 Suc-DEEAVYFAHLDIW。

15

2、如权利要求 1 所述的多肽, 其特征在于,

所述 X1 选自 Suc、Fum、MeO-Fum、Ac、SA、MA、FA、(ODDA - γ E-AEEA-AEEA-)D 或(ODDA - γ E-AEEA-AEEA-)NH-C₂H₄-NH-Suc;

所述 X2 为 D 或 K(A1);



20

所述 X1 和 X2 作为一个整体可以为:

所述 X3 为 E 或 K(A1);

所述 X4 选自 E 或 E (C16) ;

所述 X5 选自 A、K 或 E;

所述 X6 选自 V、K、Dab、L、F 或 C;

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所述 X7 为 Y;

所述 X8 为 F;

所述 X9 选自 A、K 或 E;

所述 X10 为 H;

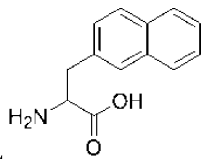
所述 X11 选自 K、L、L (N-Me)、R、Cit、L-2-氨基-4-胍基丁酸或 Orn;

30

所述 X12 为 D;

所述 X13 选自 I、I (N-Me)、2-Abu、P 或 V;

所述 X14 为 I;



所述 X15 选自 W 或 ;

所述 A1 选自 -γE-AEEA-AEEA-ODDA、ODDA-γE-AEEA-AEEA-、Biotin、-AEEA-AEEA-γE-ODDA 或不存在;

5 所述 A2 选自 -γE-AEEA-AEEA-ODDA 或不存在;

所述 A3 选自 -γE-AEEA-AEEA-ODDA 或不存在;

所述 A4 选自 -AEEA-AEEA-γE -ODDA、-γE-AEEA-AEEA-C18、-γE-AEEA-AEEA-C16、-γE-AEEA-AEEA-C12、-γE-AEEA-AEEA-B、-γE-AEEA-AEEA-ODDA、CPAK-MPA-、-AEEA-γE-C18、-AEEA-γE-C16、-AEEA-γE-C12、-AEEA-E-C12 或不存在。

3、如权利要求 1 或 2 所述的多肽，其特征在于，所述式I所示的结构通过如下任意项环化:

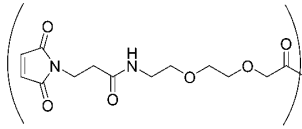
- (I)、引入 C 生成二硫键; 和/或
- (II)、D 或 E 侧链的羧基与 K 或 Dab 侧链的氨基生成酰胺键。

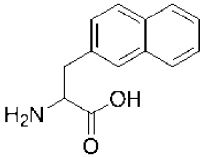
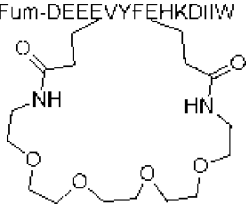
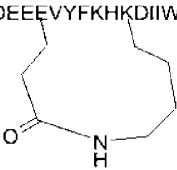
4、如权利要求 3 所述的多肽，其特征在于，所述环化包括如下任意项:

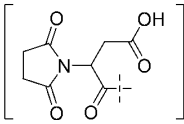
- (I)、在 X3 与 X4 之间插入 C，同时将 X6 替换为 C，通过两个 C 生成二硫键环化; 和/或
- (II)、X3 的 E 与 X6 的 K 或 Dab 生成酰胺键环化; 和/或
- (III)、X5 的 E 与 X11 的 K 生成酰胺键环化。

5、如权利要求 1 所述的多肽，其特征在于，所述多肽序列如下:

序号 SE Q ID No.	编号	序列	MW
2	BX-5	Suc-DEEAVYFAHKDIIW	1836
3	F-BX-5	Fum-DEEAVYFAHKDIIW	1834
4	BX-7	Suc-DEEAVYFAHLDVIW	1806
5	BX-8	Suc-DEEAVYFAHLD(2-Abu)IW	1792
6	BX-34	Fum-DEEAVYFAHK(-AEEA-AEEA-γE-ODDA)DIIW	2549
7	BX-43	Suc-DEEAKYFAHLDIIW	1850
8	BX-45	Suc-DEEEVYFAHKDIIW	1893
9	BX-48	Suc-D环(EEAK)YFAHLDIIW	1832
10	BX-49	Suc-D环(EEADab)YFAHLDIIW	1804
11	BX-50	Suc-DEE环(EVYFAHK)DIIW	1876
12	BX-51	Fum-DEEAVYFAHOrn(-AEEA-AEEA-γE-ODDA)DIIW	2535
13	BX-52	Fum-DEEEVYFAHKDIIW	1891

14	BX-53	Suc-DEEEVYFAHOrnDIIW	1880
15	BX-54	Suc-DEEEVYFAHK(-AEEA-AEEA- γ E-ODDA)DIIW	2610
16	BX-57	Suc-DE环(CEEC)YFAHKDIIW	1999
17	BX-58	MeO-Fum-DEEEVYFAHKDIIW	1906
18	BX-59	Fum-DEEEVYFAHOrnDIIW	1878
19	BX-60	Fum-DEEEVYFAHK(-AEEA-AEEA- γ E-ODDA)DIIW	2608
20	BX-61	Suc-DEEAVYFAHOrn(-AEEA-AEEA- γ E-ODDA)DIIW	2538
21	BX-62	Fum-DEE环(EVYFK)HKD(2-Abu)IW	1903
22	BX-63	Suc-D环(EEAK)YFAHLD(2-Abu)IW	1804
23	BX-64	Fum-D环(EEAK)YFAHLD(2-Abu)IW	1802
24	BX-65	MeO-Fum-D环(EEAK)YFAHLD(2-Abu)IW	1814
25	BX-66	Fum-DEEK(- γ E-AEEA-AEEA-ODDA)VYFAHLDIIW	2592
26	BX-67	Fum-DEEAK(- γ E-AEEA-AEEA-ODDA)YFAHLDIIW	2564
27	BX-68	Fum-DEEAVYFK(- γ E-AEEA-AEEA-ODDA)HLDIIW	2592
28	BX-69	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-C18)DIIW	2520
29	BX-70	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-C16)DIIW	2492
30	BX-71	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-C12)DIIW	2436
31	BX-72	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-B)DIIW	2433
32	BX-74	Suc-DEEAVYFAHK(- γ E-AEEA-AEEA-ODDA)DIIW	2552
33	BX-75	MeO-Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-ODDA)DIIW	2564
34	BX-76	Suc-D环(EEAK)YFAHLDVIW	1818
35	BX-77	Suc-D环(EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)DIIW	2563
36	BX-78	Suc-DEEAVYFAHK(- γ E-AEEA-AEEA-ODDA)DVIW	2538
37	BX-79	Suc-D环(EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)DVIW	2550
38	BX-86	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-ODDA)DIIW-NH2	2549
39	BX-95	Fum-DEEAVYFAHK(CPAK-MPA-)DIIW  MPA	2661
40	BX-99	Fum-D环(EEAK)YFAHLDVIW	1916
41	BX-100	Fum-D环(EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)DVIW	2547
42	BX-101	Fum-DEEAVYFAHK(- γ E-AEEA-AEEA-ODDA)DVIW	2536
43	BX-102	Fum-D环(EEAK)YFAHLDIIW	1829
44	BX-103	Fum-D环(EEAK)YFAHK(- γ E-AEEA-AEEA-ODDA)DIIW	2561
45	BX-104	Fum-D环 (EEAK)YFAHK(-γE-AEEA-AEEA-ODDA)D(2-Abu)IW	2534
46	BX-105	Fum-DEEAKYFAHLDIIW	1847
47	BX-106	Fum-DEEAKYFAHLDVIW	1836
48	BX-107	Fum-DEEAKYFAHK(- γ E-AEEA-AEEA-ODDA)DIIW	2579
49	BX-108	Fum-DEEAKYFAHK(- γ E-AEEA-AEEA-ODDA)DVIW	2567

50	BX-109	Fum-DEEAK(-γE-AEEA-AEEA-ODDA)YFAHLDIIW	2566
51	BX-110	Fum-DEEAK(-γE-AEEA-AEEA-ODDA)YFAHLDVIW	2549
52	BX-111	SA-DEEAVYFAHLDIIW	1844
53	BX-112	MA-DEEAVYFAHLDIIW	1844
54	BX-13-2	Fum-DEEAVYFAHKDIIW1  W1:	1843.8
55	BX-9	suc-DEEAVYFAHR1DIIW (R1=L-2氨基-4胍基丁酸)	1849.9 8
56	BX-31	Fum-DEEAVYFAHOrnDIIW	1819
57	BX-32	Fum-DEEAVYFAHCitDIIW	1862
58	BX-38	Suc-DE环(CEAC)YFAHLDIIW	1927
59	BX-23	Fum-DEEAVYFAHKDVIW	1704.9
60	BX-24	Fum-DEEAVYFAHKD(2-Abu)IW	1805.9
61	BX-25	Suc-DEEAVYFAHLDI(N-Me)IW	1833.8 5
62	BX-26	Suc-DEEAVYFAHL(N-Me)DIIW	1833.8 5
63	BX-27	Suc-DEEAVYFAHL(N-Me)DI(N-Me)IW	1847.8 6
64	BX-28	Fum-DEEAVYFAHL(N-Me)DIIW	1845.8 5
65	BX-29	Fum-DEEAVYFAHL(N-Me)DI(N-Me)IW	1847.8 6
66	FBX-7	Fum-DEEAVYFAHLDVIW	1805.9
67	FBX-8	Fum-DEEAVYFAHLD(2-Abu)IW	1790.9
68	QP-1	Fum-DEEEVYFEHKDIIW  QP1	1848
69	QP-3	Fum-DEEEVYFKHKDIIW 	1931

70	BX-15	FA-DEEAVYFAHKDIIW	1912.8 7
71	BX-16	Fum-DEEE(Biotin)VYFAHKDIIW	2160.4
72	BX-10	suc-DEEAVYFAHLDPIW	1804.9 6
73	BX14-1	Fum-DEE(C16)AVYFAHLDIIW	2044.1
74	BX-6	Suc-DEEAVYFAHRDIIW	1864.0 3
75	BX21	Fum-DEEALYFAHKDIIW	1848
76	BX22	Fum-DEEAFYFAHKDIIW	1882
77	BX-223	Fum-DEEAVYFAHK(-AEEA-γE-C18)DIIW	2374
78	BX-224	Fum-DEEAVYFAHK(-AEEA-γE-C16)DIIW	2346
79	BX-225	Fum-DEEAVYFAHK(-AEEA-γE-C12)DIIW	2290
80	BX-253	Fum-K(-AEEA-AEEA-γE-ODDA)EEAVYFAHLDIIW	2547
81	BX-254	Fum-DK(-AEEA-AEEA-γE-ODDA)EAVYFAHLDIIW	2533
82	BX-255	(ODDA-γE-AEEA-AEEA-)DDEEAVYFAHLDIIW	2550
83	BX-256	(ODDA-γE-AEEA-AEEA-)NH-C ₂ H ₄ -NH-Suc-DEEAVYFAHL DIIW	2594
84	BX-221	 EEAVYFAHK(ODDA-γE-AEEA-AEEA-)DII W	2533
86	BX-229	Fum-DEEAVYFAHK(-AEEA-γE-C12)DVIW	2276
87	BX-238	Fum-DEEAVYFAHK(-AEEA-E-C12)DVIW	2276
88	BX-56	Suc-DE环(CEEC)YFAHLDIIW	1984。

- 6、如权利要求 1 至 5 任一项所述多肽的制备方法，其特征在于，包括如下步骤：
步骤 1：经固相多肽合成获得所述多肽的肽树脂；
步骤 2：裂解、纯化制得所述多肽。
- 7、如权利要求 6 所述制备方法制得的多肽。
- 5 8、如下任意项在制备治疗与 ETBR 受体相关疾病的药物中的应用：
(I)、如权利要求 1 至 5 任一项所述的多肽；和/或
(II)、如权利要求 7 所述的多肽。
- 9、如权利要求 8 所述的应用，其特征在于，所述与 ETBR 受体相关疾病包括脑卒中、阿尔茨海默氏病、脊髓损伤、主动脉瓣狭窄或新生儿缺氧缺血性脑病中的一种
- 10 或多种；
所述脑卒中包括缺血性脑卒中和/或出血性脑卒中。
- 10、药物，其特征在于，包括如下任意项以及药学上可接受的辅料或助剂：
(I)、如权利要求 1 至 5 任一项所述的多肽；和/或
(II)、如权利要求 7 所述的多肽。
- 15 11、药物组合物，其特征在于，包括如权利要求 10 所述的药物以及其他任意有效成分。

12、治疗与 ETBR 受体相关疾病的方法，其特征在于，其包含向受试者施用以下任意项：

- 5 (I)、如权利要求 1 至 5 任一项所述的多肽；和/或
(II)、如权利要求 7 所述的多肽；和/或
(III)、如权利要求 10 所述的药物；和/或
(IV)、如权利要求 11 所述的药物组合物。

13、如权利要求 12 所述的方法，其特征在于，所述与 ETBR 受体相关疾病包括脑卒中、阿尔茨海默氏病、脊髓损伤、主动脉瓣狭窄或新生儿缺氧缺血性脑病中的一种或多种；

- 10 所述脑卒中包括缺血性脑卒中和/或出血性脑卒中。