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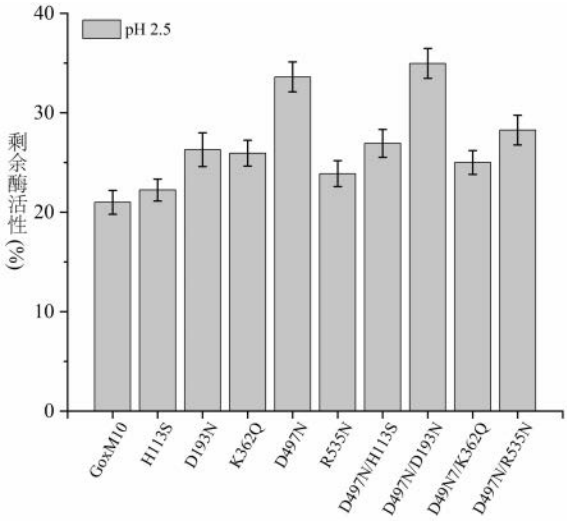
(54)发明名称

酸稳定性提高葡萄糖氧化酶GoxM10的突变体D497N及其衍生突变体和应用

(57)摘要

本发明属于饲料生物技术领域,具体涉及酸稳定性提高葡萄糖氧化酶GoxM10的突变体D497N及其衍生突变体和应用。本发明以高热稳定性葡萄糖氧化酶GoxM10为研究材料,采用蛋白质工程改造技术对其进行酸稳定性的改良研究。最后获得酸稳定性提升的突变体,从而促进了Gox在饲料工业中的应用。



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1. 酸稳定性提高的葡萄糖氧化酶GoxM10突变体,其特征在于,所述突变体具有将氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行D497N突变的氨基酸序列。

2.根据权利要求1所述的酸稳定性提高的葡萄糖氧化酶GoxM10突变体,其特征在于,所述突变体具有将氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行H113S/D497N或D193N/D497N或K362Q/D497N或D497N/R535N突变的氨基酸序列。

3.一种葡萄糖氧化酶基因,其特征在于,所述基因编码权利要求1或2所述的酸稳定性提高的葡萄糖氧化酶GoxM10突变体。

4.根据权利要求3所述的葡萄糖氧化酶基因,其特征在于,所述基因的核苷酸序列如SEQ ID NO:9或SEQ ID NO:13或SEQ ID NO:15或SEQ ID NO:17或SEQ ID NO:19所示。

5.包含权利要求3所述葡萄糖氧化酶基因的重组载体。

6.包含权利要求3所述葡萄糖氧化酶基因的重组菌株。

7.一种制备酸稳定性提高的葡萄糖氧化酶的方法,其特征在于,所述方法包括以下步骤:

构建包含编码权利要求1或2所述酸稳定性提高的葡萄糖氧化酶GoxM10突变体的基因的重组载体;

将所述重组载体导入宿主细胞;

诱导表达、并分离葡萄糖氧化酶。

8.一种改善葡萄糖氧化酶的酸稳定性的方法,其特征在于,所述方法包括将氨基酸序列如SEQ IDNO:1所示的葡萄糖氧化酶GoxM10进行D497N突变的步骤。

9.根据权利要求8所述的改善葡萄糖氧化酶的酸稳定性的方法,其特征在于,所述方法包括:

将氨基酸序列如SEQ IDNO:1所示的葡萄糖氧化酶GoxM10进行H113S/D497N突变的步骤;或

将氨基酸序列如SEQ IDNO:1所示的葡萄糖氧化酶GoxM10进行D193N/D497N突变的步骤;或

将氨基酸序列如SEQ IDNO:1所示的葡萄糖氧化酶GoxM10进K362Q/D497N突变的步骤;或

将氨基酸序列如SEQ IDNO:1所示的葡萄糖氧化酶GoxM10进行D497N/R535N突变的步骤。

10.权利要求1或2所述的酸稳定性提高的葡萄糖氧化酶GoxM10突变体作为饲料添加剂和食品添加剂的应用。

酸稳定性提高葡萄糖氧化酶GoxM10的突变体D497N及其衍生突变体和应用

技术领域

[0001] 本发明属于饲料生物技术领域，具体涉及酸稳定性提高葡萄糖氧化酶GoxM10的突变体D497N及其衍生突变体和应用。

背景技术

[0002] 葡萄糖氧化酶(Gox;EC1.1.3.4)是一种特性良好的需氧脱氢酶，在有氧条件下利用氧分子作为电子受体，催化β-d-葡萄糖生成d-葡萄糖酸内酯和过氧化氢，随后d-葡萄糖酸内酯水解成葡萄糖酸和水。近年来Gox作为一种新型抗生素替代添加剂受到饲料行业的普遍关注。Gox作为抗生素和生长促进剂的替代品，在不损害人类健康的前提下对保证动物健康和生产性能至关重要。大量应用研究表明，Gox作为一种绿色饲料添加剂，可用于预防牲畜胃肠道感染和腹泻，并有促进动物生长的作用。

[0003] Gox能够在酸性环境中维持较高的活性，以便在动物胃肠道发挥最大作用是至关重要。所以为了满足Gox在饲料工业中的应用，Gox要具备良好的酸稳定性。现有技术已提高黑曲霉(*Aspergillus niger*)来源Gox的稳定性，获得了T_{50}增加7.5 ℃的突变体GoxM4，以及比GoxM4的T_m提高了9 ℃的突变体GoxM10。

发明内容

[0004] 本发明的目的是提供酸稳定性提高的葡萄糖氧化酶GoxM10的突变体。

[0005] 本发明的再一目的是提供编码上述突变体的基因。

[0006] 本发明的再一目的是提供包含上述突变体基因的重组载体。

[0007] 本发明的再一目的是提供包含上述突变体基因的重组菌株。

[0008] 本发明的再一目的是提供上述突变体的应用。

[0009] 本发明的再一目的是提供制备稳定性提高的葡萄糖氧化酶的方法。

[0010] 本发明的再一目的是提供提高葡萄糖氧化酶GoxM10的方法。

[0011] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶进行定点突变。

[0012] 根据本发明的具体实施方式，将氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶进行113、193、362、497、535、113/497、193/497、362/497、497/535氨基酸位点的突变，从而获得酸稳定性提高的葡萄糖氧化酶突变体。

[0013] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行H113S突变，得到氨基酸序列如SEQ ID NO:2所示的酸稳定提高的突变体。

[0014] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体H113S的基因，其核苷酸序列如SEQ ID NO:3所示。

[0015] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行D193N突变，得到氨基酸序列如SEQ ID NO:4所示的酸稳定性提高的突变体。

[0016] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体D193N的基因，其核苷酸序列如SEQ ID NO:5所示。

[0017] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行K362Q突变，得到氨基酸序列如SEQ ID NO:6所示的酸稳定性提高的突变体。

[0018] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体K362Q的基因，其核苷酸序列如SEQ ID NO:7所示。

[0019] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行D497N突变，得到氨基酸序列如SEQ ID NO:8所示的酸稳定性提高的突变体。

[0020] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体D497N的基因，其核苷酸序列如SEQ ID NO:9所示。

[0021] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行R535N突变，得到氨基酸序列如SEQ ID NO:10所示的酸稳定性提高的突变体。

[0022] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体R535N的基因，其核苷酸序列如SEQ ID NO:11所示。

[0023] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行H113S/D497N突变，得到氨基酸序列如SEQ ID NO:12所示的酸稳定性提高的突变体。

[0024] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体H113S/D497N的基因，其核苷酸序列如SEQID NO:13所示。

[0025] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行D193N/D497N突变，得到氨基酸序列如SEQ ID NO:14所示的酸稳定性提高的突变体。

[0026] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体D193N/D497N的基因，其核苷酸序列如SEQ ID NO:15所示。

[0027] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行K362Q/D497N突变，得到氨基酸序列如SEQ ID NO:16所示的酸稳定性提高的突变体。

[0028] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体K362Q/D497N的基因，其核苷酸序列如SEQ ID NO:17所示。

[0029] 根据本发明的具体实施方式，对氨基酸序列如SEQ ID NO:1所示的葡萄糖氧化酶GoxM10进行D497N/R535N突变，得到氨基酸序列如SEQ ID NO:18所示的酸稳定性提高的突变体。

[0030] 根据本发明的具体实施方式，还提供了编码上述酸稳定性提高的葡萄糖氧化酶突变体D497N/R535N的基因，其核苷酸序列如SEQ ID NO:19所示。

[0031] 根据本发明的具体实施方式，还提供了包含上述葡萄糖氧化酶突变体基因的重组载体，所述重组表达载体的出发载体为pPIC9，所述重组表达载体具体为pPIC9-*goxm10*-H113S，pPIC9-*goxm10*-D193N，pPIC9-*goxm10*-K362Q，pPIC9-*goxm10*-D497N，pPIC9-*goxm10*-R535N，pPIC9-*goxm10*-H113S/D497N，pPIC9-*goxm10*-D193N/D497N，pPIC9-*goxm10*-K362Q/D497N，pPIC9-*goxm10*-D497N/R535N。

[0032] 根据本发明的具体实施方式，还提供了包含上述葡萄糖氧化酶突变体基因的重组菌株，所述重组菌的出发菌株具体为GS115(pPIC9-*goxm10*)。

[0033] 根据本发明的制备具有稳定性提高的葡萄糖氧化酶的方法，包括以下步骤：

[0034] 1)制备包含上述突变体基因的重组载体；

[0035] 2)所述重组载体转化毕赤酵母GS115表达宿主；

[0036] 3)发酵培养所述宿主，并分离葡萄糖氧化酶。

[0037] 本发明提供了上述酸稳定性改进的葡萄糖氧化酶突变体的应用，具体可以应用于食品和饲料领域中。

[0038] 本发明的突变体与GoxM10相比，酸稳定性均明显提高。突变体D193N、D497N和D193N/D497N的最适pH降低1个单位，双点突变体H113S/D497N、K362Q/D497N和D497N/R535N的最适反应pH为5.5，与GoxM10相比下降了0.5个单位，其他突变体的最适pH和GoxM10一致均为6.0。pH 2.5条件下处理30 min时，突变体H113S、D193N、K362Q、D497N、R535N、H113S/D497N、D193N/D497N、K362Q/D497N、D497N/R535N的相对剩余酶活力分别为22%、26%、26%、34%、24%、27%、35%、25%、28%，高于GoxM10(21%)；在pH 2.75和37 ℃条件下处理60 min，突变体H113S、D193N、K362Q、D497N、R535N、H113S/D497N、D193N/D497N、K362Q/D497N、D497N/R535N的相对剩余酶活力分别为26%、28%、26%、32%、29%、47%、49%、32%、43%左右，高于GoxM10的相对剩余酶活力24%。

[0039] 本发明提供的葡萄糖氧化酶突变体能很好的满足食品和饲料等领域中的应用，有着非常广阔的应用前景。

附图说明

[0040] 图1显示GoxM10和突变体在pH 2.5条件下处理30 min的酸稳定性对比；

[0041] 图2显示GoxM10和突变体在pH 2.75条件下处理60 min的酸稳定性对比；

[0042] 图3显示GoxM10和突变体的最适pH对比。

具体实施方式

[0043] 试验材料和试剂

[0044] 1、菌株及载体：表达宿主为*Pichia pastoris* GS115，表达质粒载体为pPIC9。

[0045] 2、酶类及其它生化试剂：内切酶/高保真DNA聚合酶和重组酶。

[0046] 3、大肠杆菌LB培养基(1%蛋白胨、0.5%酵母提取物、1% NaCl，pH自然)。毕赤酵母YPD培养基(1%酵母提取物，2%蛋白胨，2%葡萄糖，pH自然)；BMGY(1%酵母提取物，2%蛋白胨，10%无氨基酵母氮源，0.1%生物素，pH自然)；BMMY(1%酵母提取物，2%蛋白胨，10%无氨基酵母氮源，0.1%生物素，1%甲醇，pH自然)。

[0047] 说明：以下实施例中未作具体说明的分子生物学实验方法，均参照《分子克隆实验指南》(第三版)J.萨姆布鲁克一书中所列的具体方法进行，或者按照试剂盒和产品说明书进行。

[0048] 实施例1、重组菌株*GS115*(pPIC9-*goxm10*)的制备

[0049] 1.扩增高热稳定性葡萄糖氧化酶GoxM10的核酸序列*goxm10*

[0050] 采用PCR的方法扩增*goxm10*基因片段，采用双酶切方法获得载体pPIC9核酸片段，

通过重组酶将两者连接，获得重组质粒pPIC9-*goxm10*，并转化毕赤酵母GS115，获得重组毕赤酵母菌株GS115(pPIC9-*goxm10*)。PCR所用引物如下：

[0051] GoxM10-F(SEQ ID NO: 20)，GoxM10-R(SEQ ID NO: 21)。

[0052] 其中，GoxM10-F及GoxM10-R用于扩增GoxM10的基因编码序列；载体pPIC9通过将保存的菌种接到液体LB培养基过夜培养后，质粒提取得到。

[0053] 扩增结束后，将PCR产物以及提取质粒进行核酸电泳检测，*goxm10*与载体pPIC9条带大小分别为1746bp、8088bp，将载体用*Eco*RI和*Not*I进行酶切后，将PCR产物与酶切产物分别回收纯化。

[0054] 2.构建重组菌株GS115(pPIC9-*goxm10*)

[0055] 将回收的*goxm10*与pPIC9基因片段通过重组酶进行重组连接，然后将重组产物转化大肠杆菌JM109感受态，并涂布于LB(含100 μg/mL Amp)进行筛选。待测序正确后，利用*Bgl*Ⅱ限制性内切酶将重组质粒pPIC9-*goxm10*进行酶切，回收酶切产物后电击转化毕赤酵母GS115感受态细胞，得到重组表达菌株GS115(pPIC9-*goxm10*)。

[0056] 实施例2、重组突变菌株GS115的制备

[0057] 1.稳定性提高的重组质粒的构建

[0058] 根据突变体设计突变引物，以质粒pPIC9-*goxm10*为模板，通过点突变试剂盒引入突变氨基酸，含突变氨基酸的PCR产物用*Dpn*Ⅰ消化处理以去除模板，消化后的PCR产物转化进入大肠杆菌JM109感受态细胞，并对其进行测序验证，获得含葡萄糖氧化酶突变质粒的大肠杆菌pPIC9-*goxm10*-H113S，pPIC9-*goxm10*-D193N，pPIC9-*goxm10*-K362Q，pPIC9-*goxm10*-D497N，pPIC9-*goxm10*-R535N， pPIC9-*goxm10*-H113S/D497N，pPIC9-*goxm10*-D193N/D497N，pPIC9-*goxm10*-K362Q/D497N，pPIC9-*goxm10*-D497N/R535N。所用引物如下所示：

[0059] Gox-H113S-F(SEQ ID NO:22)，Gox-H113S-R(SEQ ID NO:23)；Gox-D193N-F(SEQ ID NO:24)，Gox-D193N-R(SEQ ID NO:25)；Gox-K362Q-F(SEQ ID NO:26)，Gox-K362Q-R(SEQ ID NO:27)；Gox-D497N-F(SEQ ID NO:28)，Gox-D497N-R(SEQ ID NO:29)；

[0060] Gox-R535N-F(SEQ ID NO:30)，Gox-R535N-R(SEQ ID NO:31)。

[0061] 2.酸稳定性和热稳定重组菌株GS115构建

[0062] 利用*Bgl*Ⅱ将测序正确的突变质粒进行酶切，回收酶切产物后电击转化毕赤酵母GS115感受态细胞，得到重组表达菌株GS115(pPIC9-*goxm10*-H113S)，GS115(pPIC9-*goxm10*-D193N)，GS115(pPIC9-*goxm10*-K362Q)，GS115(pPIC9-*goxm10*-D497N)，GS115(pPIC9-*goxm10*-R535N)， GS115(pPIC9-*goxm10*-H113S/D497N)，GS115(pPIC9-*goxm10*-D193N/D497N)，GS115(pPIC9-*goxm10*-K362Q/D497N)，GS115(pPIC9-*goxm10*-D497N/R535N)。

[0063] 实施例3、葡萄糖氧化酶GoxM10及高酸稳定性和热稳定性突变体酶蛋白的获得

[0064] 1.GoxM10及突变体的诱导表达

[0065] 以1%的接种量将上述得到的重组酵母表达菌株接种至50 mL YPD培养基中进行种子液培养，200 rpm，30 ℃培养48 h后，以1%接种量转接至400 mL BMGY培养基中，200 rpm，30 ℃培养48 h，离心收集菌体转接到200 mL BMMY培养基中，每24 h补加1%的甲醇进行诱导表达，共培养72 h。

[0066] 2.GoxM10及突变体的纯化

[0067] 将诱导表达后的菌液12000 rpm，10 min离心，收集上清后用10 kDa的膜包进行

浓缩，再用10 mM磷酸氢二钠-柠檬酸缓冲液(pH 6.5)进行透析，然后将透析后的粗酶液用阴离子柱纯化，纯化用A液为10 mM磷酸氢二钠-柠檬酸缓冲液(pH 6.5)，B液为A液加1 M NaCl，纯化蛋白，收集洗脱液。

[0068] 3.GoxM10和突变体的酶学性质测定

[0069] (1)GoxM10和突变体的酸稳定性测定

[0070] 1采用两种测定方法评估GoxM10和突变体的pH稳定性。方法一：把相同浓度的GoxM10和突变体酶液置于准确配置的pH 2.5、2.75、3.0、4.0、5.0、6.0、7.0和8.0的0.1 M的磷酸氢二钠-柠檬酸缓冲液，然后于37 ℃保温处理1 h。保温结束后在标准条件下测定其剩余酶活力，以未处理样品的酶活力记为100%。方法二：把相同浓度的GoxM10和突变体酶液置于pH 2.5的0.1 M的磷酸氢二钠-柠檬酸缓冲液，然后于37 ℃保温处理10 min、20 min、30 min、40 min、50 min和60 min。保温结束后在标准条件下测定GoxM10及其突变体酶液的相对剩余酶活。如图1所示，pH 2.5条件下处理30 min时，突变体H113S、D193N、K362Q、D497N、R535N、H113S/D497N、D193N/D497N、K362Q/D497N、D497N/R535N的相对剩余酶活力分别为22%、26%、26%、34%、24%、27%、35%、25%、28%，与GoxM10(21%)相比分别提高了约5%、24%、24%、62%、14%、29%、67%、19%、33%。如图2所示，在pH 2.75和37 ℃条件下处理60 min，突变体H113S、D193N、K362Q、D497N、R535N、H113S/D497N、D193N/D497N、K362Q/D497N、D497N/R535N的相对剩余酶活力分别为26%、28%、26%、32%、29%、47%、49%、32%、43%左右，与GoxM10(24%)相比分别提高了约8%、17%、8%、33%、21%、96%、104%、33%、79%。

[0071] (4)GoxM10和突变体的最适pH测

[0072] 首先，分别配置不同pH梯度(3.0、4.0、5.0、6.0、7.0、8.0)的Gox酶活力测定的底物混合液，然后，在30 ℃下测定GoxM10及其突变体的酶活力，把最适反应pH条件下的酶活力设定为100%，然后计算其余pH条件下的相对酶活力，即可得到GoxM10及其突变体的最适反应pH。如图3所示，突变体D193N、D497N和D193N/D497N的最适pH为5，与GoxM10相比下降一个单位，突变体H113S/D497N、K362Q/D497N和D497N/R535N的最适反应pH为5.5，与GoxM10相比下降了0.5个单位，突变体H113S、K362Q、R535N的最适反应pH与GoxM10相比均为6.0。

[0073] 以上实施例仅用于解释本申请的技术方案，不限定本申请的保护范围。

[0001] 序列表

[0002] <110> 中国农业科学院北京畜牧兽医研究所

[0003] <120> 酸稳定性提高葡萄糖氧化酶GoxM10的突变体D497N及其衍生突变体和应用

[0004] <160> 31

[0005] <170> SIPOSequenceListing 1.0

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[0007] <211> 581

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[0015] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu

[0016] 35 40 45

[0017] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn

[0018] 50 55 60

[0019] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr

[0020] 65 70 75 80

[0021] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn

[0022] 85 90 95

[0023] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro

[0024] 100 105 110

[0025] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly

[0026] 115 120 125

[0027] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala

[0028] 130 135 140

[0029] Arg Ala Pro Asn Ala Lys Gln Ile Ala Ala Gly His Tyr Phe Asn Ala

[0030] 145 150 155 160

[0031] Ser Cys His Gly Ile Asn Gly Thr Val His Ala Gly Pro Arg Asp Thr

[0032] 165 170 175

[0033] Gly Asp Asp Tyr Ser Pro Ile Val Lys Ala Leu Met Ser Ala Val Glu

[0034] 180 185 190

[0035] Asp Arg Gly Val Pro Thr Lys Lys Asp Leu Gly Cys Gly Asp Pro His

[0036] 195 200 205

[0037] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser

[0038] 210 215 220

[0039] Asp Ala Ala Arg Glu Trp Leu Leu Pro Asn Tyr Gln Arg Pro Asn Leu

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[0042] 245 250 255

[0043] Ala Thr Thr Pro Arg Ala Val Gly Val Glu Phe Gly Thr His Lys Gly

[0044] 260 265 270

[0045] Asn Phe His Asn Val Thr Ala Lys His Glu Val Leu Leu Ala Ala Gly

[0046] 275 280 285

[0047] Ser Ala Val Ser Pro Thr Ile Leu Glu Tyr Ser Gly Ile Gly Met Lys

[0048] 290 295 300

[0049] Ser Ile Leu Glu Pro Leu Gly Ile Lys Thr Val Val Asp Leu Pro Val

[0050] 305 310 315 320

[0051] Gly Leu Asn Leu Gln Asp Gln Thr Thr Ser Thr Val Arg Ser Arg Ile

[0052] 325 330 335

[0053] Thr Ser Ala Gly Ala Gly Gln Gly Gln Ala Ala Trp Phe Ala Thr Phe

[0054] 340 345 350

[0055] Asn Glu Thr Phe Gly Asp Tyr Thr Glu Lys Ala His Glu Leu Leu Asn

[0056] 355 360 365

[0057] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe

[0058] 370 375 380

[0059] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp

[0060] 385 390 395 400

[0061] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala

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[0063] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly

[0064] 420 425 430

[0065] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr

[0066] 435 440 445

[0067] Asp Pro Gln Tyr Phe Leu Asn Glu Leu Asp Leu Leu Gly Gln Ala Ala

[0068] 450 455 460

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[0071] Tyr Phe Ala Gly Glu Thr Ile Pro Gly Asp Asn Leu Ala Tyr Asp Ala

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[0093] 20 25 30

[0094] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu

[0095] 35 40 45

[0096] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn

[0097] 50 55 60

[0098] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr

[0099] 65 70 75 80

[0100] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn

[0101] 85 90 95

[0102] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro

[0103] 100 105 110

[0104] Ser Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly

[0105] 115 120 125

[0106] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala

[0107] 130 135 140

[0108] Arg Ala Pro Asn Ala Lys Gln Ile Ala Ala Gly His Tyr Phe Asn Ala

[0109] 145 150 155 160

[0110] Ser Cys His Gly Ile Asn Gly Thr Val His Ala Gly Pro Arg Asp Thr

[0111] 165 170 175

[0112] Gly Asp Asp Tyr Ser Pro Ile Val Lys Ala Leu Met Ser Ala Val Glu

[0113] 180 185 190

[0114] Asp Arg Gly Val Pro Thr Lys Lys Asp Leu Gly Cys Gly Asp Pro His

[0115] 195 200 205

[0116] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser

[0117] 210 215 220

[0118] Asp Ala Ala Arg Glu Trp Leu Leu Pro Asn Tyr Gln Arg Pro Asn Leu

[0119] 225 230 235 240

[0120] Ser Val Leu Thr Gly Gln Tyr Val Gly Lys Val Leu Leu Ser Gln Asn

[0121] 245 250 255

[0122] Ala Thr Thr Pro Arg Ala Val Gly Val Glu Phe Gly Thr His Lys Gly

[0123] 260 265 270

[0124] Asn Phe His Asn Val Thr Ala Lys His Glu Val Leu Leu Ala Ala Gly

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[0139] 385 390 395 400
[0140] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
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[0143] 420 425 430
[0144] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
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[0149] 465 470 475 480
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[0154] Tyr His Gly Val Gly Thr Cys Ser Met Met Pro Lys Glu Met Gly Gly
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[0156] Val Val Asp Asn Ala Ala Arg Val Tyr Gly Val Gln Gly Leu Arg Val
[0157] 530 535 540
[0158] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
[0159] 545 550 555 560
[0160] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
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[0171] gacatcaccg ttttggtcat tgagtccggt tcttacgaat ctgatagagg tcctatcatt 180

[0172] gaagacttga acgcttacgg taaaatcttc ggatcttccg ttgaccacgc ttacgagact 240

[0173] gtctgccttg ccactaacaa tagaaccgct ttgattagag ctggtaacgg tttgggtggt 300

[0174] tctactttgg ttaacggagg tacttggacc agaccatcta aggctcaagt tgactcttgg 360

[0175] gagaccgtct tcggtaacga aggttggaat tgggattctg tcgcagctta ctccttgcag 420

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[0178] tctcctatcg tcaaggcctt gatgtccgct gttgaagaca gaggtgtccc aactaagaag 600

[0179] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660

[0180] caagtcagat ccgatgctgc ccgtgaatgg ttgcttccaa actaccaaag acctaacttg 720

[0181] caggttttga ccggtcaata cgttggtaag gtccttttgt ctcaaaacgc cactacccca 780

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[0189] attgttaagg ataacgtcgc ttactctgaa ttgttcttgg acactgccgg tgaggcttcc 1260

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[0200] <211> 581

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[0206] Thr Val Asp Tyr Ile Ile Ala Gly Gly Gly Leu Thr Gly Leu Val Val

[0207] 20 25 30

[0208] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu

[0209] 35 40 45

[0210] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn
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[0212] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr
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[0214] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn
[0215] 85 90 95
[0216] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro
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[0218] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly
[0219] 115 120 125
[0220] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala
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[0251] 370 375 380

[0252] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp
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[0254] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
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[0256] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly
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[0258] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
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[0263] 465 470 475 480
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[0272] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
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[0293] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660

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[0304] ttcgacgtct gggacttgct gccattcact agaggatacg ttcacatctt ggacaaggac 1320
[0305] ccatacttga gacacttcgc ttacgatcct caatacttct tgaacgagtt ggacttgctt 1380
[0306] ggtcaggctg ccgctactca attggctaga aacatctcta actccggtgc catgcaaact 1440
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[0311] gtcttctacg ctatggcttt gaagatcgca gacgctgttt tggctgacta cgcctccatg 1740
[0312] caataa 1746
[0313] <210> 6
[0314] <211> 581
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[0322] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu
[0323] 35 40 45
[0324] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn
[0325] 50 55 60
[0326] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr
[0327] 65 70 75 80
[0328] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn
[0329] 85 90 95
[0330] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro
[0331] 100 105 110
[0332] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly
[0333] 115 120 125
[0334] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala
[0335] 130 135 140

[0336] Arg Ala Pro Asn Ala Lys Gln Ile Ala Ala Gly His Tyr Phe Asn Ala
[0337] 145 150 155 160
[0338] Ser Cys His Gly Ile Asn Gly Thr Val His Ala Gly Pro Arg Asp Thr
[0339] 165 170 175
[0340] Gly Asp Asp Tyr Ser Pro Ile Val Lys Ala Leu Met Ser Ala Val Glu
[0341] 180 185 190
[0342] Asp Arg Gly Val Pro Thr Lys Lys Asp Leu Gly Cys Gly Asp Pro His
[0343] 195 200 205
[0344] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser
[0345] 210 215 220
[0346] Asp Ala Ala Arg Glu Trp Leu Leu Pro Asn Tyr Gln Arg Pro Asn Leu
[0347] 225 230 235 240
[0348] Ser Val Leu Thr Gly Gln Tyr Val Gly Lys Val Leu Leu Ser Gln Asn
[0349] 245 250 255
[0350] Ala Thr Thr Pro Arg Ala Val Gly Val Glu Phe Gly Thr His Lys Gly
[0351] 260 265 270
[0352] Asn Phe His Asn Val Thr Ala Lys His Glu Val Leu Leu Ala Ala Gly
[0353] 275 280 285
[0354] Ser Ala Val Ser Pro Thr Ile Leu Glu Tyr Ser Gly Ile Gly Met Lys
[0355] 290 295 300
[0356] Ser Ile Leu Glu Pro Leu Gly Ile Lys Thr Val Val Asp Leu Pro Val
[0357] 305 310 315 320
[0358] Gly Leu Asn Leu Gln Asp Gln Thr Thr Ser Thr Val Arg Ser Arg Ile
[0359] 325 330 335
[0360] Thr Ser Ala Gly Ala Gly Gln Gly Gln Ala Ala Trp Phe Ala Thr Phe
[0361] 340 345 350
[0362] Asn Glu Thr Phe Gly Asp Tyr Thr Glu Gln Ala His Glu Leu Leu Asn
[0363] 355 360 365
[0364] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe
[0365] 370 375 380
[0366] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp
[0367] 385 390 395 400
[0368] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
[0369] 405 410 415
[0370] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly
[0371] 420 425 430
[0372] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
[0373] 435 440 445
[0374] Asp Pro Gln Tyr Phe Leu Asn Glu Leu Asp Leu Leu Gly Gln Ala Ala
[0375] 450 455 460
[0376] Ala Thr Gln Leu Ala Arg Asn Ile Ser Asn Ser Gly Ala Met Gln Thr
[0377] 465 470 475 480

[0378] Tyr Phe Ala Gly Glu Thr Ile Pro Gly Asp Asn Leu Ala Tyr Asp Ala
[0379] 485 490 495
[0380] Asp Leu Arg Ala Trp Val Glu Tyr Ile Pro Tyr His Phe Arg Pro Asn
[0381] 500 505 510
[0382] Tyr His Gly Val Gly Thr Cys Ser Met Met Pro Lys Glu Met Gly Gly
[0383] 515 520 525
[0384] Val Val Asp Asn Ala Ala Arg Val Tyr Gly Val Gln Gly Leu Arg Val
[0385] 530 535 540
[0386] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
[0387] 545 550 555 560
[0388] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
[0389] 565 570 575
[0390] Tyr Ala Ser Met Gln
[0391] 580
[0392] <210> 7
[0393] <211> 1746
[0394] <212> DNA
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[0399] gacatcaccg ttttggtcat tgagtccggt tcttacgaat ctgatagagg tcctatcatt 180
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[0401] gtctgccttg ccactaacaa tagaaccgct ttgattagag ctggtaacgg tttgggtggt 300
[0402] tctactttgg ttaacggagg tacttggacc agaccacaca aggctcaagt tgactcttgg 360
[0403] gagaccgtct tcggtaacga aggttggaat tgggattctg tcgcagctta ctccttgcag 420
[0404] gccgagagag cccgtgctcc aaacgctaag caaatcgccg caggtcacta cttcaacgcc 480
[0405] tcctgtcacg gtattaacgg aactgttcac gctggtccaa gagacaccgg tgacgattac 540
[0406] tctcctatcg tcaaggcctt gatgtccgct gttgaagaca gaggtgtccc aactaagaag 600
[0407] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660
[0408] caagtcagat ccgatgctgc ccgtgaatgg ttgcttccaa actaccaaag acctaacttg 720
[0409] caggttttga ccggtcaata cgttggtaag gtccttttgt ctcaaaacgc cactacccca 780
[0410] agagctgttg gtgtcgagtt cggaactcac aagggtaact ttcacaatgt taccgctaaa 840
[0411] cacgaagtcc ttttggcagc tggttccgct gtttctccaa ctatcttgga gtactctggt 900
[0412] atcggaatga agtccatttt ggaaccactt ggtattaaga ccgtcgttga cttgcctgtt 960
[0413] ggtctgaact tgcaagacca gactacctct actgtcagat cccgtattac ctccgccggt 1020
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[0417] attgttaagg ataacgtcgc ttactctgaa ttgttcttgg acactgccgg tgaggcttcc 1260
[0418] ttcgacgtct gggacttgct gccattcact agaggatacg ttcacatctt ggacaaggac 1320
[0419] ccatacttga gacacttcgc ttacgatcct caatacttct tgaacgagtt ggacttgctt 1380

[0420] ggtcaggctg ccgctactca attggctaga aacatctcta actccggtgc catgcaaact 1440
[0421] tactttgctg gtgaaaccat tccaggtgac aacttggcct acgatgctga cttgagagct 1500
[0422] tgggttgaat acattccata ccacttcaga cctaactacc atggtgtcgg aacctgttct 1560
[0423] atgatgccaa aggagatggg tggtgtcgtt gacaacgccg ctagagttta cggtgtccag 1620
[0424] ggattgagag ttatcgacgg ttctatccca cctactcaaa tgtcctctca cgttatgacc 1680
[0425] gtcttctacg ctatggcttt gaagatcgca gacgctgttt tggctgacta cgcctccatg 1740
[0426] caataa 1746
[0427] <210> 8
[0428] <211> 581
[0429] <212> PRT
[0430] <213> 人工序列(Artificial Sequence)
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[0434] Thr Val Asp Tyr Ile Ile Ala Gly Gly Gly Leu Thr Gly Leu Val Val
[0435] 20 25 30
[0436] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu
[0437] 35 40 45
[0438] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn
[0439] 50 55 60
[0440] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr
[0441] 65 70 75 80
[0442] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn
[0443] 85 90 95
[0444] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro
[0445] 100 105 110
[0446] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly
[0447] 115 120 125
[0448] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala
[0449] 130 135 140
[0450] Arg Ala Pro Asn Ala Lys Gln Ile Ala Ala Gly His Tyr Phe Asn Ala
[0451] 145 150 155 160
[0452] Ser Cys His Gly Ile Asn Gly Thr Val His Ala Gly Pro Arg Asp Thr
[0453] 165 170 175
[0454] Gly Asp Asp Tyr Ser Pro Ile Val Lys Ala Leu Met Ser Ala Val Glu
[0455] 180 185 190
[0456] Asp Arg Gly Val Pro Thr Lys Lys Asp Leu Gly Cys Gly Asp Pro His
[0457] 195 200 205
[0458] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser
[0459] 210 215 220
[0460] Asp Ala Ala Arg Glu Trp Leu Leu Pro Asn Tyr Gln Arg Pro Asn Leu
[0461] 225 230 235 240

[0462] Ser Val Leu Thr Gly Gln Tyr Val Gly Lys Val Leu Leu Ser Gln Asn
[0463] 245 250 255
[0464] Ala Thr Thr Pro Arg Ala Val Gly Val Glu Phe Gly Thr His Lys Gly
[0465] 260 265 270
[0466] Asn Phe His Asn Val Thr Ala Lys His Glu Val Leu Leu Ala Ala Gly
[0467] 275 280 285
[0468] Ser Ala Val Ser Pro Thr Ile Leu Glu Tyr Ser Gly Ile Gly Met Lys
[0469] 290 295 300
[0470] Ser Ile Leu Glu Pro Leu Gly Ile Lys Thr Val Val Asp Leu Pro Val
[0471] 305 310 315 320
[0472] Gly Leu Asn Leu Gln Asp Gln Thr Thr Ser Thr Val Arg Ser Arg Ile
[0473] 325 330 335
[0474] Thr Ser Ala Gly Ala Gly Gln Gly Gln Ala Ala Trp Phe Ala Thr Phe
[0475] 340 345 350
[0476] Asn Glu Thr Phe Gly Asp Tyr Thr Glu Lys Ala His Glu Leu Leu Asn
[0477] 355 360 365
[0478] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe
[0479] 370 375 380
[0480] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp
[0481] 385 390 395 400
[0482] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
[0483] 405 410 415
[0484] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly
[0485] 420 425 430
[0486] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
[0487] 435 440 445
[0488] Asp Pro Gln Tyr Phe Leu Asn Glu Leu Asp Leu Leu Gly Gln Ala Ala
[0489] 450 455 460
[0490] Ala Thr Gln Leu Ala Arg Asn Ile Ser Asn Ser Gly Ala Met Gln Thr
[0491] 465 470 475 480
[0492] Tyr Phe Ala Gly Glu Thr Ile Pro Gly Asp Asn Leu Ala Tyr Asp Ala
[0493] 485 490 495
[0494] Asn Leu Arg Ala Trp Val Glu Tyr Ile Pro Tyr His Phe Arg Pro Asn
[0495] 500 505 510
[0496] Tyr His Gly Val Gly Thr Cys Ser Met Met Pro Lys Glu Met Gly Gly
[0497] 515 520 525
[0498] Val Val Asp Asn Ala Ala Arg Val Tyr Gly Val Gln Gly Leu Arg Val
[0499] 530 535 540
[0500] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
[0501] 545 550 555 560
[0502] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
[0503] 565 570 575

[0504] Tyr Ala Ser Met Gln

[0505] 580

[0506] <210> 9

[0507] <211> 1746

[0508] <212> DNA

[0509] <213> 人工序列(Artificial Sequence)

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[0512] atcattgctg gtggtggatt gactggtttg gttgtcgctg ccagattgac tgagaaccca 120

[0513] gacatcaccg ttttggtcat tgagtccggt tcttacgaat ctgatagagg tcctatcatt 180

[0514] gaagacttga acgcttacgg taaaatcttc ggatcttccg ttgaccacgc ttacgagact 240

[0515] gtctgccttg ccactaacaa tagaaccgct ttgattagag ctggtaacgg tttgggtggt 300

[0516] tctactttgg ttaacggagg tacttggacc agaccacaca aggctcaagt tgactcttgg 360

[0517] gagaccgtct tcggtaacga aggttggaat tgggattctg tcgcagctta ctccttgcag 420

[0518] gccgagagag cccgtgctcc aaacgctaag caaatcgccg caggtcacta cttcaacgcc 480

[0519] tcctgtcacg gtattaacgg aactgttcac gctggtccaa gagacaccgg tgacgattac 540

[0520] tctcctatcg tcaaggcctt gatgtccgct gttgaagaca gaggtgtccc aactaagaag 600

[0521] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660

[0522] caagtcagat ccgatgctgc ccgtgaatgg ttgcttccaa actaccaaag acctaacttg 720

[0523] caggttttga ccggtcaata cgttggtaag gtccttttgt ctcaaaacgc cactacccca 780

[0524] agagctgttg gtgtcgagtt cggaactcac aagggtaact ttcacaatgt taccgctaaa 840

[0525] cacgaagtcc ttttggcagc tggttccgct gtttctccaa ctatcttgga gtactctggt 900

[0526] atcggaatga agtccatttt ggaaccactt ggtattaaga ccgtcgttga cttgcctgtt 960

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[0528] gctggacagg gtcaggctgc ctggtttgct actttcaacg agaccttcgg tgactacact 1080

[0529] gagaaggctc acgaattgct taacaccaaa ttggaacaat gggctgagga agccgttgct 1140

[0530] agaggtggtt tccacaacac taccgctctt ttgatccaat acgagaacta cagagactgg 1200

[0531] attgttaagg ataacgtcgc ttactctgaa ttgttcttgg acactgccgg tgaggcttcc 1260

[0532] ttcgacgtct gggacttgct gccattcact agaggatacg ttcacatctt ggacaaggac 1320

[0533] ccatacttga gacacttcgc ttacgatcct caatacttct tgaacgagtt ggacttgctt 1380

[0534] ggtcaggctg ccgctactca attggctaga aacatctcta actccggtgc catgcaaact 1440

[0535] tactttgctg gtgaaaccat tccaggtgac aacttggcct acgatgctaa cttgagagct 1500

[0536] tgggttgaat acattccata ccacttcaga cctaactacc atggtgtcgg aacctgttct 1560

[0537] atgatgccaa aggagatggg tggtgtcgtt gacaacgccg ctagagttta cggtgtccag 1620

[0538] ggattgagag ttatcgacgg ttctatccca cctactcaaa tgtcctctca cgttatgacc 1680

[0539] gtcttctacg ctatggcttt gaagatcgca gacgctgttt tggctgacta cgcctccatg 1740

[0540] caataa 1746

[0541] <210> 10

[0542] <211> 581

[0543] <212> PRT

[0544] <213> 人工序列(Artificial Sequence)

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[0549] 20 25 30
[0550] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu
[0551] 35 40 45
[0552] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn
[0553] 50 55 60
[0554] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr
[0555] 65 70 75 80
[0556] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn
[0557] 85 90 95
[0558] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro
[0559] 100 105 110
[0560] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly
[0561] 115 120 125
[0562] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala
[0563] 130 135 140
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[0565] 145 150 155 160
[0566] Ser Cys His Gly Ile Asn Gly Thr Val His Ala Gly Pro Arg Asp Thr
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[0568] Gly Asp Asp Tyr Ser Pro Ile Val Lys Ala Leu Met Ser Ala Val Glu
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[0572] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser
[0573] 210 215 220
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[0575] 225 230 235 240
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[0578] Ala Thr Thr Pro Arg Ala Val Gly Val Glu Phe Gly Thr His Lys Gly
[0579] 260 265 270
[0580] Asn Phe His Asn Val Thr Ala Lys His Glu Val Leu Leu Ala Ala Gly
[0581] 275 280 285
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[0583] 290 295 300
[0584] Ser Ile Leu Glu Pro Leu Gly Ile Lys Thr Val Val Asp Leu Pro Val
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[0586] Gly Leu Asn Leu Gln Asp Gln Thr Thr Ser Thr Val Arg Ser Arg Ile
[0587] 325 330 335

[0588] Thr Ser Ala Gly Ala Gly Gln Gly Gln Ala Ala Trp Phe Ala Thr Phe
[0589] 340 345 350
[0590] Asn Glu Thr Phe Gly Asp Tyr Thr Glu Lys Ala His Glu Leu Leu Asn
[0591] 355 360 365
[0592] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe
[0593] 370 375 380
[0594] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp
[0595] 385 390 395 400
[0596] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
[0597] 405 410 415
[0598] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly
[0599] 420 425 430
[0600] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
[0601] 435 440 445
[0602] Asp Pro Gln Tyr Phe Leu Asn Glu Leu Asp Leu Leu Gly Gln Ala Ala
[0603] 450 455 460
[0604] Ala Thr Gln Leu Ala Arg Asn Ile Ser Asn Ser Gly Ala Met Gln Thr
[0605] 465 470 475 480
[0606] Tyr Phe Ala Gly Glu Thr Ile Pro Gly Asp Asn Leu Ala Tyr Asp Ala
[0607] 485 490 495
[0608] Asp Leu Arg Ala Trp Val Glu Tyr Ile Pro Tyr His Phe Arg Pro Asn
[0609] 500 505 510
[0610] Tyr His Gly Val Gly Thr Cys Ser Met Met Pro Lys Glu Met Gly Gly
[0611] 515 520 525
[0612] Val Val Asp Asn Ala Ala Asn Val Tyr Gly Val Gln Gly Leu Arg Val
[0613] 530 535 540
[0614] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
[0615] 545 550 555 560
[0616] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
[0617] 565 570 575
[0618] Tyr Ala Ser Met Gln
[0619] 580
[0620] <210> 11
[0621] <211> 1746
[0622] <212> DNA
[0623] <213> 人工序列(Artificial Sequence)
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[0627] gacatcaccg ttttggtcat tgagtccggt tcttacgaat ctgatagagg tcctatcatt 180
[0628] gaagacttga acgcttacgg taaaatcttc ggatcttccg ttgaccacgc ttacgagact 240
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[0631] gagaccgtct tcggtaacga aggttggaat tgggattctg tcgcagctta ctccttgcag 420
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[0635] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660
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[0643] gagaaggctc acgaattgct taacaccaaa ttggaacaat gggctgagga agccgttgct 1140
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[0645] attgttaagg ataacgtcgc ttactctgaa ttgttcttgg acactgccgg tgaggcttcc 1260
[0646] ttcgacgtct gggacttgct gccattcact agaggatacg ttcacatctt ggacaaggac 1320
[0647] ccatacttga gacacttcgc ttacgatcct caatacttct tgaacgagtt ggacttgctt 1380
[0648] ggtcaggctg ccgctactca attggctaga aacatctcta actccggtgc catgcaaact 1440
[0649] tactttgctg gtgaaaccat tccaggtgac aacttggcct acgatgctga cttgagagct 1500
[0650] tgggttgaat acattccata ccacttcaga cctaactacc atggtgtcgg aacctgttct 1560
[0651] atgatgccaa aggagatggg tggtgtcgtt gacaacgccg ctaacgttta cggtgtccag 1620
[0652] ggattgagag ttatcgacgg ttctatccca cctactcaaa tgtcctctca cgttatgacc 1680
[0653] gtcttctacg ctatggcttt gaagatcgca gacgctgttt tggctgacta cgcctccatg 1740
[0654] caataa 1746
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[0656] <211> 581
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[0683] 180 185 190
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[0686] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser
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[0697] 290 295 300
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[0706] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe
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[0714] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
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[0724] Tyr His Gly Val Gly Thr Cys Ser Met Met Pro Lys Glu Met Gly Gly
[0725] 515 520 525
[0726] Val Val Asp Asn Ala Ala Arg Val Tyr Gly Val Gln Gly Leu Arg Val
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[0728] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
[0729] 545 550 555 560
[0730] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
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[0779] 35 40 45
[0780] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn
[0781] 50 55 60
[0782] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr
[0783] 65 70 75 80
[0784] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn
[0785] 85 90 95
[0786] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro
[0787] 100 105 110
[0788] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly
[0789] 115 120 125
[0790] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala
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[0816] Thr Ser Ala Gly Ala Gly Gln Gly Gln Ala Ala Trp Phe Ala Thr Phe
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[0818] Asn Glu Thr Phe Gly Asp Tyr Thr Glu Lys Ala His Glu Leu Leu Asn
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[0820] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe
[0821] 370 375 380
[0822] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp
[0823] 385 390 395 400
[0824] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
[0825] 405 410 415
[0826] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly
[0827] 420 425 430
[0828] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
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[0830] Asp Pro Gln Tyr Phe Leu Asn Glu Leu Asp Leu Leu Gly Gln Ala Ala
[0831] 450 455 460
[0832] Ala Thr Gln Leu Ala Arg Asn Ile Ser Asn Ser Gly Ala Met Gln Thr
[0833] 465 470 475 480
[0834] Tyr Phe Ala Gly Glu Thr Ile Pro Gly Asp Asn Leu Ala Tyr Asp Ala
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[0844] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
[0845] 565 570 575
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[0847] 580
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[0863] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660
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[0876] ggtcaggctg ccgctactca attggctaga aacatctcta actccggtgc catgcaaact 1440
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[0879] atgatgccaa aggagatggg tggtgtcgtt gacaacgccg ctagagttta cggtgtccag 1620
[0880] ggattgagag ttatcgacgg ttctatccca cctactcaaa tgtcctctca cgttatgacc 1680
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[0892] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu

[0893] 35 40 45

[0894] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn

[0895] 50 55 60

[0896] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr

[0897] 65 70 75 80

[0898] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn

[0899] 85 90 95

[0900] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro

[0901] 100 105 110

[0902] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly

[0903] 115 120 125

[0904] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala

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[0906] Arg Ala Pro Asn Ala Lys Gln Ile Ala Ala Gly His Tyr Phe Asn Ala

[0907] 145 150 155 160

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[0909] 165 170 175

[0910] Gly Asp Asp Tyr Ser Pro Ile Val Lys Ala Leu Met Ser Ala Val Glu

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[0947] 465 470 475 480
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[0961] 580
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[0970] gaagacttga acgcttacgg taaaatcttc ggatcttccg ttgaccacgc ttacgagact 240

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[0986] agaggtggtt tccacaacac taccgctctt ttgatccaat acgagaacta cagagactgg 1200

[0987] attgttaagg ataacgtcgc ttactctgaa ttgttcttgg acactgccgg tgaggcttcc 1260

[0988] ttcgacgtct gggacttgct gccattcact agaggatacg ttcacatctt ggacaaggac 1320

[0989] ccatacttga gacacttcgc ttacgatcct caatacttct tgaacgagtt ggacttgctt 1380

[0990] ggtcaggctg ccgctactca attggctaga aacatctcta actccggtgc catgcaaact 1440

[0991] tactttgctg gtgaaaccat tccaggtgac aacttggcct acgatgctaa cttgagagct 1500

[0992] tgggttgaat acattccata ccacttcaga cctaactacc atggtgtcgg aacctgttct 1560

[0993] atgatgccaa aggagatggg tggtgtcgtt gacaacgccg ctagagttta cggtgtccag 1620

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[0996] caataa 1746

[0997] <210> 18

[0998] <211> 581

[0999] <212> PRT

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[1006] Ala Ala Arg Leu Thr Glu Asn Pro Asp Ile Thr Val Leu Val Ile Glu

[1007] 35 40 45

[1008] Ser Gly Ser Tyr Glu Ser Asp Arg Gly Pro Ile Ile Glu Asp Leu Asn
[1009] 50 55 60
[1010] Ala Tyr Gly Lys Ile Phe Gly Ser Ser Val Asp His Ala Tyr Glu Thr
[1011] 65 70 75 80
[1012] Val Cys Leu Ala Thr Asn Asn Arg Thr Ala Leu Ile Arg Ala Gly Asn
[1013] 85 90 95
[1014] Gly Leu Gly Gly Ser Thr Leu Val Asn Gly Gly Thr Trp Thr Arg Pro
[1015] 100 105 110
[1016] His Lys Ala Gln Val Asp Ser Trp Glu Thr Val Phe Gly Asn Glu Gly
[1017] 115 120 125
[1018] Trp Asn Trp Asp Ser Val Ala Ala Tyr Ser Leu Gln Ala Glu Arg Ala
[1019] 130 135 140
[1020] Arg Ala Pro Asn Ala Lys Gln Ile Ala Ala Gly His Tyr Phe Asn Ala
[1021] 145 150 155 160
[1022] Ser Cys His Gly Ile Asn Gly Thr Val His Ala Gly Pro Arg Asp Thr
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[1026] Asp Arg Gly Val Pro Thr Lys Lys Asp Leu Gly Cys Gly Asp Pro His
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[1028] Gly Val Ser Met Phe Pro Asn Thr Leu His Glu Asp Gln Val Arg Ser
[1029] 210 215 220
[1030] Asp Ala Ala Arg Glu Trp Leu Leu Pro Asn Tyr Gln Arg Pro Asn Leu
[1031] 225 230 235 240
[1032] Ser Val Leu Thr Gly Gln Tyr Val Gly Lys Val Leu Leu Ser Gln Asn
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[1034] Ala Thr Thr Pro Arg Ala Val Gly Val Glu Phe Gly Thr His Lys Gly
[1035] 260 265 270
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[1038] Ser Ala Val Ser Pro Thr Ile Leu Glu Tyr Ser Gly Ile Gly Met Lys
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[1040] Ser Ile Leu Glu Pro Leu Gly Ile Lys Thr Val Val Asp Leu Pro Val
[1041] 305 310 315 320
[1042] Gly Leu Asn Leu Gln Asp Gln Thr Thr Ser Thr Val Arg Ser Arg Ile
[1043] 325 330 335
[1044] Thr Ser Ala Gly Ala Gly Gln Gly Gln Ala Ala Trp Phe Ala Thr Phe
[1045] 340 345 350
[1046] Asn Glu Thr Phe Gly Asp Tyr Thr Glu Lys Ala His Glu Leu Leu Asn
[1047] 355 360 365
[1048] Thr Lys Leu Glu Gln Trp Ala Glu Glu Ala Val Ala Arg Gly Gly Phe
[1049] 370 375 380

[1050] His Asn Thr Thr Ala Leu Leu Ile Gln Tyr Glu Asn Tyr Arg Asp Trp
[1051] 385 390 395 400
[1052] Ile Val Lys Asp Asn Val Ala Tyr Ser Glu Leu Phe Leu Asp Thr Ala
[1053] 405 410 415
[1054] Gly Glu Ala Ser Phe Asp Val Trp Asp Leu Leu Pro Phe Thr Arg Gly
[1055] 420 425 430
[1056] Tyr Val His Ile Leu Asp Lys Asp Pro Tyr Leu Arg His Phe Ala Tyr
[1057] 435 440 445
[1058] Asp Pro Gln Tyr Phe Leu Asn Glu Leu Asp Leu Leu Gly Gln Ala Ala
[1059] 450 455 460
[1060] Ala Thr Gln Leu Ala Arg Asn Ile Ser Asn Ser Gly Ala Met Gln Thr
[1061] 465 470 475 480
[1062] Tyr Phe Ala Gly Glu Thr Ile Pro Gly Asp Asn Leu Ala Tyr Asp Ala
[1063] 485 490 495
[1064] Asn Leu Arg Ala Trp Val Glu Tyr Ile Pro Tyr His Phe Arg Pro Asn
[1065] 500 505 510
[1066] Tyr His Gly Val Gly Thr Cys Ser Met Met Pro Lys Glu Met Gly Gly
[1067] 515 520 525
[1068] Val Val Asp Asn Ala Ala Asn Val Tyr Gly Val Gln Gly Leu Arg Val
[1069] 530 535 540
[1070] Ile Asp Gly Ser Ile Pro Pro Thr Gln Met Ser Ser His Val Met Thr
[1071] 545 550 555 560
[1072] Val Phe Tyr Ala Met Ala Leu Lys Ile Ala Asp Ala Val Leu Ala Asp
[1073] 565 570 575
[1074] Tyr Ala Ser Met Gln
[1075] 580
[1076] <210> 19
[1077] <211> 1746
[1078] <212> DNA
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[1083] gacatcaccg ttttggtcat tgagtccggt tcttacgaat ctgatagagg tcctatcatt 180
[1084] gaagacttga acgcttacgg taaaatcttc ggatcttccg ttgaccacgc ttacgagact 240
[1085] gtctgccttg ccactaacaa tagaaccgct ttgattagag ctggtaacgg tttgggtggt 300
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[1089] tcctgtcacg gtattaacgg aactgttcac gctggtccaa gagacaccgg tgacgattac 540
[1090] tctcctatcg tcaaggcctt gatgtccgct gttgaagaca gaggtgtccc aactaagaag 600
[1091] gacttgggtt gcggagaccc acatggtgtt tctatgttcc ctaacacctt gcacgaggac 660

[1092] caagtcagat ccgatgctgc ccgtgaatgg ttgcttccaa actaccaaag acctaacttg 720
[1093] caggttttga ccggtcaata cgttggtaag gtccttttgt ctcaaaacgc cactacccca 780
[1094] agagctgttg gtgtcgagtt cggaactcac aagggtaact ttcacaatgt taccgctaaa 840
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[1106] tgggttgaat acattccata ccacttcaga cctaactacc atggtgtcgg aacctgttct 1560
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[1109] gtcttctacg ctatggcttt gaagatcgca gacgctgttt tggctgacta cgcctccatg 1740
[1110] caataa 1746
[1111] <210> 20
[1112] <211> 30
[1113] <212> DNA
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[1117] <210> 21
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[1119] <212> DNA
[1120] <213> 人工序列(Artificial Sequence)
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[1122] ttgcatggag gcgtagtcag ccaaaacagc 30
[1123] <210> 22
[1124] <211> 32
[1125] <212> DNA
[1126] <213> 人工序列(Artificial Sequence)
[1127] <400> 22
[1128] tggaccagac catctaaggc tcaagttgac tc 32
[1129] <210> 23
[1130] <211> 32
[1131] <212> DNA
[1132] <213> 人工序列(Artificial Sequence)
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[1134] aacttgagcc ttagatggtc tggtccaagt ac 32

[1135] <210> 24

[1136] <211> 32

[1137] <212> DNA

[1138] <213> 人工序列(Artificial Sequence)

[1139] <400> 24

[1140] tccgctgttg aaaacgatgg tgtcccaact aa 32

[1141] <210> 25

[1142] <211> 32

[1143] <212> DNA

[1144] <213> 人工序列(Artificial Sequence)

[1145] <400> 25

[1146] tgggacacca tcgttttcaa cagcggacat ca 32

[1147] <210> 26

[1148] <211> 32

[1149] <212> DNA

[1150] <213> 人工序列(Artificial Sequence)

[1151] <400> 26

[1152] gactacactg agcaagctca cgaattgctt aa 32

[1153] <210> 27

[1154] <211> 32

[1155] <212> DNA

[1156] <213> 人工序列(Artificial Sequence)

[1157] <400> 27

[1158] caattcgtga gcttgctcag tgtagtcacc ga 32

[1159] <210> 28

[1160] <211> 32

[1161] <212> DNA

[1162] <213> 人工序列(Artificial Sequence)

[1163] <400> 28

[1164] caattcgtga gcttgctcag tgtagtcacc ga 32

[1165] <210> 29

[1166] <211> 32

[1167] <212> DNA

[1168] <213> 人工序列(Artificial Sequence)

[1169] <400> 29

[1170] ccaagcatcc aagttagcat cgtaggccaa gt 32

[1171] <210> 30

[1172] <211> 32

[1173] <212> DNA

[1174] <213> 人工序列(Artificial Sequence)

[1175] <400> 30

[1176] gacaacgccg ctaacgttta cggtgtccag gg 32

[1177] <210> 31

[1178] <211> 31

[1179] <212> DNA

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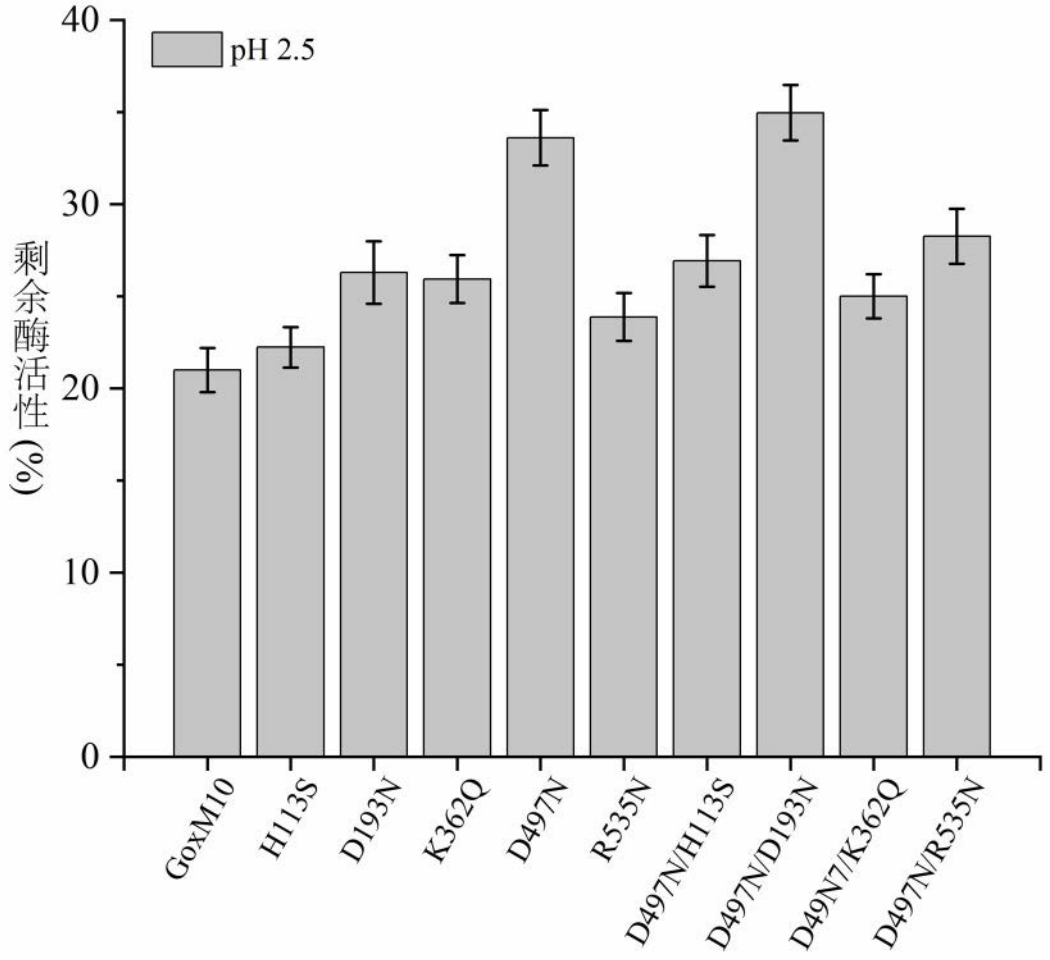
pH 2.5
剩余酶活性(%)
40
30
20
10
0
GoxM10
H113S
D193N
K362Q
D497N
R535N
D497N/H113S
D497N/D193N
D49N7/K362Q
D497N/R535N

图1

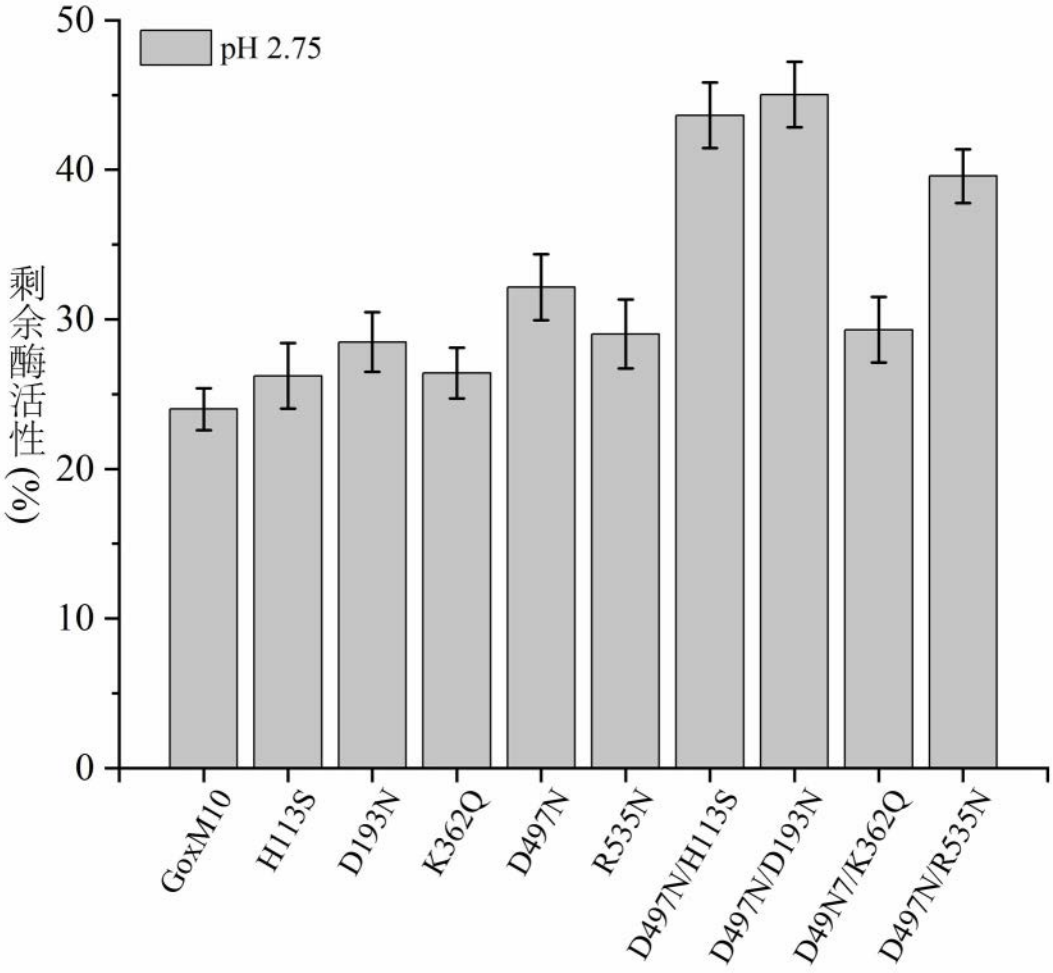
pH 2.75
剩余酶活性(%)
50
40
30
20
10
0
GoxM10
H113S
D193N
K362Q
D497N
R535N
D497N/H113S
D497N/D193N
D49N7/K362Q
D497N/R535N

图2

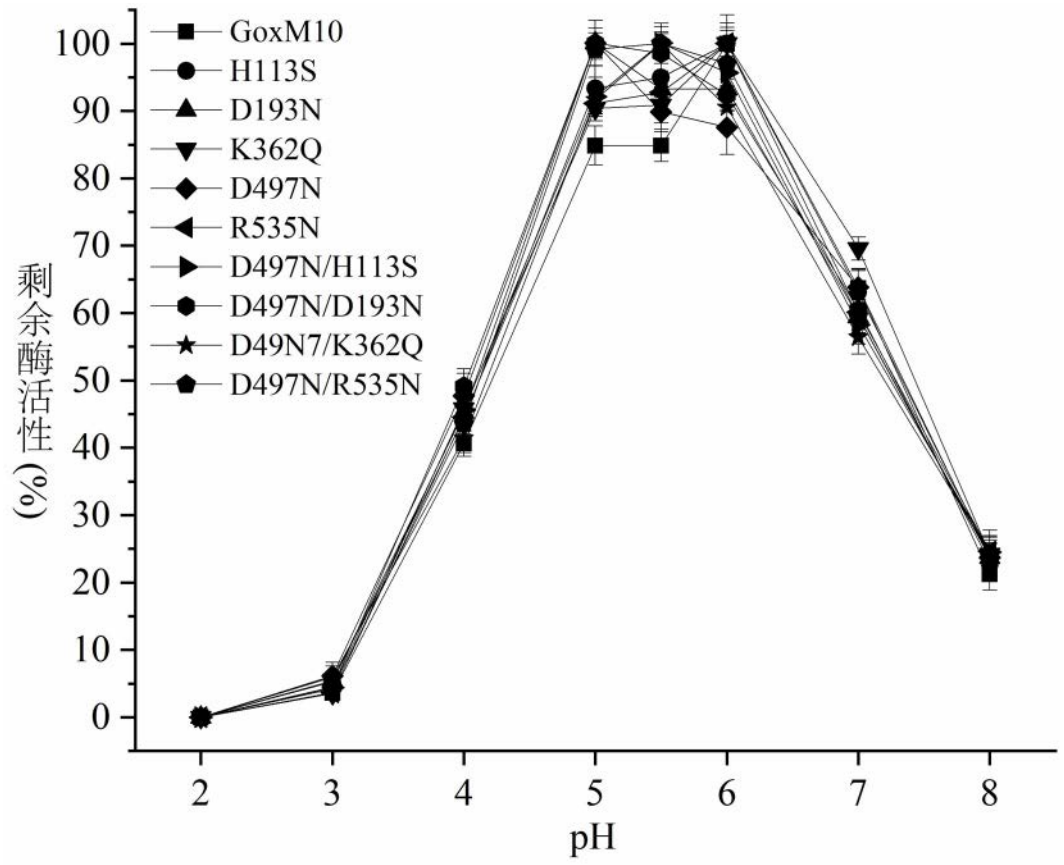
GoxM10
H113S
D193N
K362Q
D497N
R535N
D497N/H113S
D497N/D193N
D49N7/K362Q
D497N/R535N
剩余酶活性(%)
pH
0
10
20
30
40
50
60
70
80
90
100
2
3
4
5
6
7
8

图3