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High Activity Mutants of Butyrylcholinesterase for Cocaine Hydrolysis

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(54) **HIGH ACTIVITY MUTANTS OF BUTYRYLCHOLINESTERASE FOR COCAINE HYDROLYSIS**

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CPC **A61K 38/465** (2013.01); **C12N 9/18** (2013.01); **C12Y 301/01008** (2013.01)

(58) **Field of Classification Search**
CPC C12N 9/18
USPC 435/196; 536/23.2
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,049,121 B2 5/2006 Watkins et al.
7,438,904 B1 10/2008 Zhan et al.
2003/0153062 A1 8/2003 Watkins et al.
2004/0120939 A1 6/2004 Watkins et al.

OTHER PUBLICATIONS

Gao, et al.; Modeling effects of oxyanion hole on the ester hydrolyses catalyzed by human cholinesterases; *Phys. Chem. B*; 2005; 109; pp. 23070-23076.
Gao, et al; Computational design of a human butyrylcholinesterase mutant for accelerating cocaine hydrolysis based on the transition-state simulation; *Angew. Chem. Int. Ed.*; 2006; 45; pp. 653-657.
Gao, et al; Modeling evolution of hydrogen bonding and stabilization of transition states in the process of cocaine hydrolysis catalyzed by human butyrylcholinesterase; *Proteins*; 2006; 62; pp. 99-110.
Hamza, et al.; Molecular dynamics simulation of cocaine binding with human butyrylcholinesterase and its mutants; *J. Phys. Chem. B.*; 2005; 109; pp. 4776-4782.
Pan, et al.; Computational redesign of human butyrylcholinesterase for anti-cocaine medication; *G. Proc. Natl. Acad. Sci. USA*; 2005; 102; pp. 16656-16661.
Zhan, et al.; Fundamental reaction mechanism for cocaine metabolism in human butyrylcholinesterase; *J. Am. Chem. Soc.*; 2003; 125; pp. 2462-2474.
Zhan, et al.; Catalytic Mechanism and energy barriers for butyrylcholinesterase-catalyzed hydrolysis of cocaine; *Biophysical Journal*; 2005; 89; 3863-3872.
Xie, et al.; An improved cocaine hydrolase: the A328Y mutant of human butyrylcholinesterase is 4-fold more efficient; *Molecular Pharm.*; 1999; 55; pp. 83-91.

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(57) **ABSTRACT**

Butyrylcholinesterase (BChE) polypeptide variants of the presently-disclosed subject matter have enhanced catalytic efficiency for (–)-cocaine, as compared to wild-type BChE. Pharmaceutical compositions of the presently-disclosed subject matter include a BChE polypeptide variant having an enhanced catalytic efficiency for (–)-cocaine. A method of the presently-disclosed subject matter for treating a cocaine-induced condition includes administering to an individual an effective amount of a BChE polypeptide variant, as disclosed herein, to lower blood cocaine concentration.

2 Claims, No Drawings

HIGH ACTIVITY MUTANTS OF BUTYRYLCHOLINESTERASE FOR COCAINE HYDROLYSIS

RELATED APPLICATIONS

This application is a division of and claims benefit to U.S. patent application Ser. No. 14/470,751, now allowed, filed Aug. 27, 2014, which is a division of and claims benefit to U.S. patent application Ser. No. 13/479,899, filed May 24, 2013, now issued as U.S. Pat. No. 8,846,887, which is a division of U.S. patent application Ser. No. 13/005,213, filed Jan. 12, 2011, now issued as U.S. Pat. No. 8,206,703, which is a division of U.S. patent application Ser. No. 12/767,128, now allowed, filed Apr. 26, 2010, now issued as U.S. Pat. No. 7,892,537, which is a division of U.S. patent application Ser. No. 12/685,341, filed Jan. 11, 2010, now issued as U.S. Pat. No. 7,740,840, which is a continuation-in-part of U.S. patent application Ser. No. 12/192,394 filed Aug. 15, 2008, now issued as U.S. Pat. No. 7,731,957, which is a division of U.S. patent application Ser. No. 11/243,111, filed Oct. 4, 2005, now issued as U.S. Pat. No. 7,438,904, the disclosures of which are incorporated herein by this reference.

GOVERNMENT INTEREST

Subject matter described herein was made with government support under Grant Number R01DA013930 awarded by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH). The government has certain rights in the described subject matter.

TECHNICAL FIELD

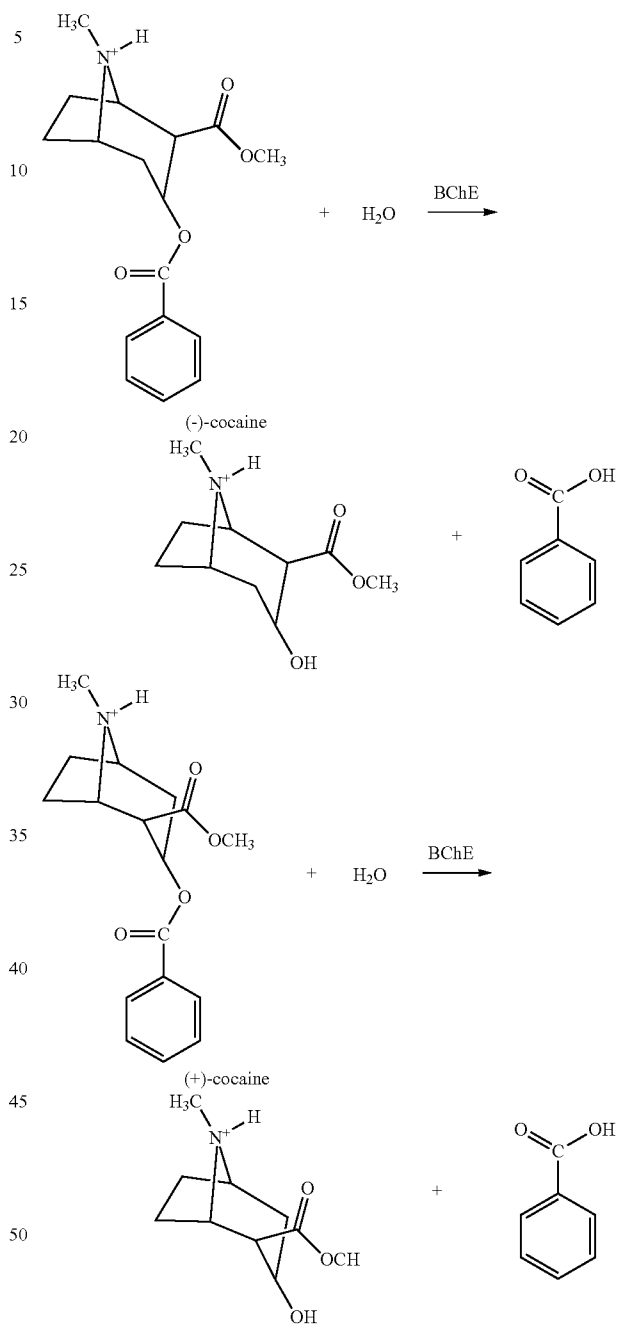
The presently-disclosed subject matter relates to butyrylcholinesterase variant polypeptides, and in particular, butyrylcholinesterase mutants having amino acid substitutions.

INTRODUCTION

Cocaine abuse is a major medical and public health problem that continues to defy treatment. The disastrous medical and social consequences of cocaine addiction, such as violent crime, loss in individual productivity, illness, and death, have made the development of an effective pharmacological treatment a high priority. However, cocaine mediates its reinforcing and toxic effects by blocking neurotransmitter reuptake and the classical pharmacodynamic approach has failed to yield small-molecule receptor antagonists due to the difficulties inherent in blocking a blocker. An alternative to receptor-based approaches is to interfere with the delivery of cocaine to its receptors and accelerate its metabolism in the body.

The dominant pathway for cocaine metabolism in primates is butyrylcholinesterase (BChE)-catalyzed hydrolysis at the benzoyl ester group (Scheme 1).

Scheme 1. Schematic representation of BChE-catalyzed hydrolysis at the benzoyl ester group.



Only 5% of the cocaine is deactivated through oxidation by the liver microsomal cytochrome P450 system. Cocaine hydrolysis at benzoyl ester group yields ecgonine methyl ester, whereas the oxidation produces norcocaine. The metabolite ecgonine methyl ester is a biologically inactive metabolite, whereas the metabolite norcocaine is hepatotoxic and a local anesthetic. BChE is synthesized in the liver and widely distributed in the body, including plasma, brain, and lung. Extensive experimental studies in animals and humans demonstrate that enhancement of BChE activity by administration of exogenous enzyme substantially decreases cocaine half-life.

Enhancement of cocaine metabolism by administration of BChE has been recognized to be a promising pharmacokinetic approach for treatment of cocaine abuse and dependence. However, the catalytic activity of this plasma enzyme is three orders-of-magnitude lower against the naturally occurring (-)-cocaine than that against the biologically inactive (+)-cocaine enantiomer. (+)-cocaine can be cleared from plasma in seconds and prior to partitioning into the central nervous system (CNS), whereas (-)-cocaine has a plasma half-life of approximately 45-90 minutes (for a relatively low dose of cocaine), long enough for manifestation of the CNS effects which peak in minutes. Under the overdose condition, BChE is saturated with (-)-cocaine and, thus, the plasma half-life of (-)-cocaine will be longer. Hence, BChE mutants with high activity against (-)-cocaine are highly desired for use in humans. Although some BChE mutants with increased catalytic activity over wild-type BChE have previously been generated, there exists a need for mutant BChE with even higher catalytic activity.

SUMMARY

The presently-disclosed subject matter meets some or all of the above-identified needs, as will become evident to those of ordinary skill in the art after a study of information provided in this document.

This Summary describes several embodiments of the presently-disclosed subject matter, and in many cases lists variations and permutations of these embodiments. This Summary is merely exemplary of the numerous and varied embodiments. Mention of one or more representative features of a given embodiment is likewise exemplary. Such an embodiment can typically exist with or without the feature(s) mentioned; likewise, those features can be applied to other embodiments of the presently-disclosed subject matter, whether listed in this Summary or not. To avoid excessive repetition, this Summary does not list or suggest all possible combinations of such features.

The presently-disclosed subject matter includes butyrylcholinesterase (BChE) polypeptide variants. In some embodiments the amino acid sequence of the BChE polypeptide variant includes an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32, as set forth herein.

The presently-disclosed subject matter further includes a pharmaceutical composition that includes a butyrylcholinesterase polypeptide variant and a suitable pharmaceutical carrier.

The presently-disclosed subject matter further includes a method of treating a cocaine-induced condition, which includes administering to an individual an effective amount of BChE polypeptide variant or a pharmaceutical composition comprising a BChE polypeptide variant, as described herein, to lower blood cocaine concentration. In some embodiments, the BChE polypeptide variant exhibits a one-hundred-fold or more increase in cocaine hydrolysis catalytic efficiency compared to wild-type butyrylcholinesterase.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID NO: 1 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 2;

SEQ ID NO: 2 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285A, S287G, A328W, and Y332G;

SEQ ID NO: 3 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 4;

SEQ ID NO: 4 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285S, S287G, A328W, and Y332G;

SEQ ID NO: 5 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 6;

SEQ ID NO: 6 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285Q, S287G, A328W, and Y332G;

SEQ ID NO: 7 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 8;

SEQ ID NO: 8 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227P, S287G, A328W, and Y332G.

SEQ ID NO: 9 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 10;

SEQ ID NO: 10 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, P285G, S287G, A328W, and Y332G;

SEQ ID NO: 11 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 12;

SEQ ID NO: 12 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227A, L286M, S287G, A328W, and Y332G;

SEQ ID NO: 13 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 14;

SEQ ID NO: 14 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, P285Q, S287G, A328W, and Y332G;

SEQ ID NO: 15 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 16;

SEQ ID NO: 16 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, P285I, S287G, A328W, and Y332G;

SEQ ID NO: 17 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 18;

SEQ ID NO: 18 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227G, S287G, A328W, and Y332G;

SEQ ID NO: 19 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 20;

SEQ ID NO: 20 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, P285S, S287G, A328W, and Y332G;

SEQ ID NO: 21 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 22;

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SEQ ID NO: 22 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227V, S287G, A328W, and Y332G;

SEQ ID NO: 23 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 24;

SEQ ID NO: 24 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, P285G, S287G, A328W, and Y332G;

SEQ ID NO: 25 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 26;

SEQ ID NO: 26 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227I, S287G, A328W, and Y332G;

SEQ ID NO: 27 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 28;

SEQ ID NO: 28 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, F227L, S287G, A328W, and Y332G;

SEQ ID NO: 29 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 30;

SEQ ID NO: 30 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid substitutions, as compared to wild type BChE: A199S, L286M, S287G, A328W, and Y332G;

SEQ ID NO: 31 is a nucleotide sequence encoding a butyrylcholinesterase (BChE) polypeptide variant of SEQ ID NO: 32; and

SEQ ID NO: 32 is an amino acid sequence encoding a BChE polypeptide variant having the following amino acid

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substitutions, as compared to wild type BChE: A199S, F227A, P285K, S287G, A328W, and Y332G.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

The details of one or more embodiments of the presently-disclosed subject matter are set forth in this document. Modifications to embodiments described in this document, and other embodiments, will be evident to those of ordinary skill in the art after a study of the information provided in this document. The information provided in this document, and particularly the specific details of the described exemplary embodiments, is provided primarily for clearness of understanding and no unnecessary limitations are to be understood therefrom. In case of conflict, the specification of this document, including definitions, will control.

The presently-disclosed subject matter includes butyrylcholinesterase (BChE) polypeptide variants. The BChE polypeptide variants disclosed herein each have enhanced catalytic efficiency for (–)-cocaine, as compared to wild-type BChE. The presently-disclosed subject matter further includes a pharmaceutical composition including a butyrylcholinesterase polypeptide variant, as described herein, and a suitable pharmaceutical carrier. The presently-disclosed subject matter further includes a method of treating a cocaine-induced condition comprising administering to an individual an effective amount of a butyrylcholinesterase polypeptide variant, as disclosed herein, to lower blood cocaine concentration.

In some embodiments, the BChE polypeptide variant is selected from a BChE polypeptide variants set forth in Table 1. Table 1 also includes the SEQ ID NOs associated with the identified BChE polypeptide variants, as well as a summary of the approximate fold increase in catalytic efficiency against (–)-cocaine for the identified BChE polypeptide variants, as compared to wild type BChE.

TABLE 1

BChE Polypeptide Variants and Associated SEQ TD NOs										
Variant	Amino Acid Substitution						Catalytic Efficiency (k_{cat}/K_M) against (–)-cocaine (Approximate Fold Increase) ^a	Nucleic Acid SEQ ID	Amino Acid SEQ ID	
	Number	199	227	285	286	287				328
1	A199S	F227A	P285A	—	S287G	A328W	Y332G	4080	1	2
2	A199S	F227A	P285S	—	S287G	A328W	Y332G	3700	3	4
3	A199S	F227A	P285Q	—	S287G	A328W	Y332G	3590	5	6
4	A199S	F227P	—	—	S287G	A328W	Y332G	1860	7	8
5	A199S	F227A	P285G	—	S287G	A328W	Y332G	2420	9	10
6	A199S	F227A	—	L286M	S287G	A328W	Y332G	2120	11	12
7	A199S	—	P285Q	—	S287G	A328W	Y332G	2220	13	14
8	A199S	—	P285I	—	S287G	A328W	Y332G	830	15	16
9	A199S	F227G	—	—	S287G	A328W	Y332G	2010	17	18
10	A199S	—	P285S	—	S287G	A328W	Y332G	1240	19	20
11	A199S	F227V	—	—	S287G	A328W	Y332G	950	21	22
12	A199S	—	P285G	—	S287G	A328W	Y332G	1250	23	24
13	A199S	F227I	—	—	S287G	A328W	Y332G	1240	25	26
14	A199S	F227L	—	—	S287G	A328W	Y332G	1100	27	28
15	A199S	—	—	L286M	S287G	A328W	Y332G	740	29	30
16	A199S	F227A	P285K	—	S287G	A328W	Y332G	1540	31	32

^aThe approximate ratio of the k_{cat}/K_M value for the BChE mutant to that for the wild-type BChE against (–)-cocaine.

The terms "polypeptide", "protein", and "peptide", which are used interchangeably herein, refer to a polymer of the protein amino acids, or amino acid analogs, regardless of its size or function. Although "protein" is often used in reference to relatively large polypeptides, and "peptide" is often used in reference to small polypeptides, usage of these terms in the art overlaps and varies. The term "polypeptide" as used herein refers to peptides, polypeptides, and proteins, unless otherwise noted. The terms "protein", "polypeptide", and "peptide" are used interchangeably herein when referring to a gene product. Thus, exemplary polypeptides include gene products, naturally occurring proteins, homologs, orthologs, paralog, fragments and other equivalents, variants, and analogs of the foregoing.

The term "variant" refers to an amino acid sequence that is different from the reference polypeptide by one or more amino acids, e.g., one or more amino acid substitutions. For example a butyrylcholinesterase (BChE) polypeptide variant differs from wild-type BChE by one or more amino acid substitutions, i.e., mutations.

The terms "polypeptide fragment" or "fragment", when used in reference to a reference polypeptide, refers to a polypeptide in which amino acid residues are deleted as compared to the reference polypeptide itself, but where the remaining amino acid sequence is usually identical corresponding positions in the reference polypeptide. Such deletions can occur at the amino-terminus, carboxy-terminus of the reference polypeptide, or alternatively both. A fragment can also be a "functional fragment," in which case the fragment retains some or all of the activity of the reference polypeptide as described herein. For example, a functional fragment of a particular BChE polypeptide variant retains some or all of the cocaine hydrolysis activity, i.e., the catalytic efficiency for (-)-cocaine, of the particular BChE polypeptide variant. In this regard, the term "BChE polypeptide variant" is inclusive of functional fragments of the BChE polypeptide variant. Such fragments are typically are at least about 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, or 550 amino acids long. One or more residues from about 1 to 67 and/or one or more residues from about 443 to 574 can be removed without substantially affecting the catalytic activity of the BChE polypeptide variant. As such, the term "BChE polypeptide variant" is inclusive of functional fragments wherein one or more residues from 1 to 67 and/or one or more residues from 443 to 574 is truncated relative to the full-length BChE polypeptide variant.

The BChE polypeptide variant (e.g., SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32) can be formulated in a pharmaceutical composition along with a suitable pharmaceutical carrier known to one skilled in the art.

The present BChE variant polypeptides can be used in treating a cocaine-induced condition by administering to an individual, an effective amount of a BChE variant polypeptides, (e.g., SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32), to lower blood cocaine concentration. The BChE polypeptide variant can be administered in the form of a pharmaceutical composition in which the BChE polypeptide variant is included with a suitable pharmaceutical carrier. Treatment of a cocaine-induced condition using one of the aforementioned BChE polypeptide variants can be in a manner that will be understood by those skilled in the art.

The preferred dose for administration of a BChE polypeptide variant or pharmaceutical composition in accordance with the presently-described subject matter is that amount which will be effective in lowering (-)-cocaine concentration in a patient's bloodstream, and one would readily recognize that this amount will vary greatly depending on the nature of cocaine consumed, e.g., injected or inhaled, and the condition

of a patient. An "effective amount" of butyrylcholinesterase polypeptide variant or pharmaceutical composition to be used in accordance with the presently-disclosed subject matter is intended to mean a nontoxic but sufficient amount of the agent, such that the desired prophylactic or therapeutic effect is produced. Thus, the exact amount of the enzyme or a particular agent that is required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the particular carrier or adjuvant being used and its mode of administration, and the like. Similarly, the dosing regimen should also be adjusted to suit the individual to whom the composition is administered and will once again vary with age, weight, metabolism, etc. of the individual. Accordingly, the "effective amount" of any particular butyrylcholinesterase polypeptide variant, or pharmaceutical composition thereof, will vary based on the particular circumstances, and an appropriate effective amount may be determined in each case of application by one of ordinary skill in the art using only routine experimentation.

The presently-disclosed subject matter is further illustrated by the following specific but non-limiting examples. The following examples may include compilations of data that are representative of data gathered at various times during the course of development and experimentation related to the presently-disclosed subject matter.

EXAMPLES

Embodiments of the BChE polypeptide variants of the presently-disclosed subject matter were made and studied using the following experimental procedure.

Site-directed mutagenesis of human BChE cDNA was performed by the QuikChange method of Braman, J.; Papworth, C.; Greener, A. *Methods Mol. Biol.* 1996, 57, 5731, incorporated herein by this reference. Mutations were generated from wild-type human BChE in a pRc/CMV expression plasmid in accordance with Xie, W.; Altamirano, C. V.; Bartels, C. F.; Speirs, R. J.; Cashman, J. R.; Lockridge, O. *Mol. Pharmacol.* 1999, 55, 83, each of which is incorporated herein by this reference. The expression plasmid pRc/CMV was kindly provided by Dr. O. Lockridge, University of Nebraska Medical Center (Omaha, Nebr.).

Using plasmid DNA as template and primers with specific base-pair alterations, mutations were made by polymerase chain reaction with Pfu DNA polymerase, for replication fidelity. The PCR product was treated with Dpn I endonuclease to digest the parental DNA template. Cloned pfu DNA polymerase and Dpn I endonuclease were obtained from Stratagene (La Jolla, Calif.). Modified plasmid DNA was transformed into *Escherichia coli*, amplified, and purified. The DNA sequences of the mutants were confirmed by DNA sequencing. All oligonucleotides were synthesized by the Integrated DNA Technologies, Inc. The QIAprep Spin Plasmid Miniprep Kit and Qiagen plasmid purification kit and QIAquick PCR purification kit were obtained from Qiagen (Santa Clarita, Calif.).

BChE mutants were expressed in human embryonic kidney cell line 293T/17. Cells were grown to 80-90% confluence in 6-well dishes and then transfected by Lipofectamine 2000 complexes of 4 µg plasmid DNA per each well. Cells were incubated at 37° C. in a CO₂ incubator for 24 hours and cells were moved to 60-mm culture vessel and cultured for four more days. The culture medium [10% fetal bovine serum in Dulbecco's modified Eagle's medium (DMEM)] was harvested for a BChE activity assay.

Human embryonic kidney 293T/17 cells were from ATCC (Manassas, Va.). Dulbecco's modified Eagle's medium (DMEM) was purchased from Fisher Scientific (Fairlawn, N.J.). Oligonucleotide primers were synthesized by the Inte-

grated DNA Technologies and Analysis Facility of the University of Kentucky. 3, 3', 5, 5'-Tetramethylbenzidine (TMB) was obtained from Sigma (Saint Louis, Mo.). Anti-butyrylcholinesterase (mouse monoclonal antibody, Product #HAH002-01) was purchased from AntibodyShop (Gentofte, Denmark) and Goat anti-mouse IgG HRP conjugate from Zymed (San Francisco, Calif.).

To measure cocaine and benzoic acid, the product of cocaine hydrolysis by BChE, sensitive radiometric assays based on toluene extraction of [³H]-(-)-cocaine labeled on its benzene ring were used in accordance with Zheng, F.; Yang, W.; Ko, M.-C.; Lin, J.; Cho, H.; Gao, D.; Tong, M.; Tai, H.-H.; Woods, J. H.; Zhan, C.-G. "Most Efficient Cocaine Hydrolase Designed by Virtual Screening of Transition States", *J. Am. Chem. Soc.* 2008, 130, 12148-12155, which is incorporated herein by this reference. ³H-(-)-cocaine (50 Ci/mmol) was purchased from PerkinElmer Life Sciences (Boston, Mass.).

In brief, to initiate reactions, 100 nCi of [³H]-(-)-cocaine was mixed with 100 μl of culture medium. Reactions proceeded at room temperature (25° C.) with varying concentrations of (-)-cocaine. Reactions were stopped by adding 300 μl of 0.02 M HCl, which neutralized the liberated benzoic acid while ensuring a positive charge on the residual cocaine. [³H]benzoic acid was extracted by 1 ml of toluene and measured by scintillation counting. Finally, the measured (-)-cocaine concentration-dependent radiometric data were analyzed by using the standard Michaelis-Menten kinetics so that the catalytic efficiency (k_{cat}/K_M) was determined, along with the use of an enzyme-linked immunosorbent assay (ELISA) described in b Zheng, F.; Yang, W.; Ko, M.-C.; Liu, J.; Cho, H.; Gao, D.; Tong, M.; Tai, H.-H.; Woods, J. H.; Zhan, C.-G. "Most Efficient Cocaine Hydrolase Designed by Virtual Screening of Transition States", *J. Am. Chem. Soc.* 2008, 130, 12148-12155.

The catalytic efficiency (k_{cat}/K_M) of the BChE polypeptide variants of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32 are set forth in Table 2.

TABLE 2

Catalytic Efficiency (k_{cat}/K_M) of BChE Polypeptide Variants			
Variant Number	Amino Acid SEQ ID NO:	Catalytic Efficiency against (-)-cocaine ($M^{-1} \text{ min}^{-1}$)	Catalytic Efficiency against (-)-cocaine (Approximate Fold Increase) ^a
1	2	3.72×10^9	4080
2	4	3.37×10^9	3700
3	6	3.27×10^9	3590
4	8	1.69×10^9	1860
5	10	2.20×10^9	2420
6	12	1.93×10^9	2120
7	14	2.02×10^9	2220
8	16	7.56×10^8	830
9	18	1.83×10^9	2010
10	20	1.13×10^9	1240
11	22	8.65×10^8	950
12	24	1.14×10^9	1250
13	26	1.13×10^9	1240
14	28	1.00×10^9	1100
15	30	6.74×10^8	740
16	32	1.40×10^9	1540

^aThe approximate ratio of the k_{cat}/K_M value for the BChE mutant to that for the wild-type BChE against (-)-cocaine

The catalytic efficiencies (k_{cat}/K_M) of the BChE polypeptide variants were found to be between about 6.74×10^8 and $3.72 \times 10^9 M^{-1} \text{ min}^{-1}$, which is about 740 to about 4080 times the k_{cat}/K_M value ($9.11 \times 10^5 M^{-1} \text{ min}^{-1}$) of the wild-type BChE.

Enzyme-linked immunosorbent assays (ELISA) were performed as follows. The ELISA buffers used were the same as those described in the literature such as Brock, A.; Mortensen,

V.; Loft, A. G. R.; Nergaard-Pedersen, B. *J. Clin. Chem. Clin. Biochem.* 1990, 28, 221-224; and Khattab, A. D.; Walker, C. H.; Johnston, G.; Siddiqui, M. K. Saphier, P. W. *Environmental Toxicology and Chemistry* 1994, 13, 1661-1667, both of which are incorporated herein by this reference. The coating buffer was 0.1 M sodium carbonate/bicarbonate buffer, pH 9.5. The diluent buffer (EIA buffer) was potassium phosphate monobasic/potassium phosphate monohydrate buffer, pH 7.5, containing 0.9% sodium chloride and 0.1% bovine serum albumin. The washing buffer (PBS-T) was 0.01 M potassium phosphate monobasic/potassium phosphate monohydrate buffer, pH 7.5, containing 0.05% (v/v) Tween-20. All the assays were performed in triplicate. Each well of an ELISA microliter plate was filled with 100 μl of the mixture buffer consisting of 20 μl culture medium and 80 μl coating buffer. The plate was covered and incubated overnight at 4° C. to allow the antigen to bind to the plate. The solutions were then removed and the wells were washed four times with PBS-T. The washed wells were filled with 200 μl diluent buffer and kept shaking for 1.5 h at room temperature (25° C.). After washing with PBS-T for four times, the wells were filled with 100 μl antibody (1:8000) and were incubated for 1.5 h, followed by washing for four times. Then, the wells were filled with 100 μl goat anti-mouse IgG HRP conjugate complex diluted to a final 1:3000 dilution, and were incubated at room temperature for 1.5 h, followed by washing for four times. The enzyme reactions were started by addition of 100 μl substrate (TMB) solution. The reactions were stopped after 15 min by the addition of 100 μl of 2 M sulfuric acid, and the absorbance was read at 460 nm using a Bio-Rad ELISA plate reader.

While the terms used herein are believed to be well understood by one of ordinary skill in the art, the definitions set forth herein are provided to facilitate explanation of the presently-disclosed subject matter.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the presently-disclosed subject matter belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the presently-disclosed subject matter, representative methods, devices, and materials are now described.

Following long-standing patent law convention, the terms "a", "an", and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a cell" includes a plurality of such cells, and so forth.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently-disclosed subject matter.

As used herein, the term "about," when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments $\pm 50\%$, in some embodiments $\pm 40\%$, in some embodiments $\pm 30\%$, in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in some embodiments $\pm 5\%$, in some embodiments $\pm 1\%$, in some embodiments $\pm 0.5\%$, and in some embodiments $\pm 0.1\%$ from the specified amount, and such variations are appropriate to perform the disclosed method.

Throughout this document, various references are mentioned. All such references are incorporated herein by reference.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 32

<210> SEQ ID NO 1
 <211> LENGTH: 1722
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 1

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gcacctaaac caaaaaatgc cactgtattg atatggattt atggtgggtg ttttcaaact    360
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aatatagcag cctttggtgg aaatcctaaa agtgaactc tctttggaga aagttccgga    600
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<210> SEQ ID NO 2
 <211> LENGTH: 574
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 2

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 Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
 35 40 45
 Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
 50 55 60
 Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
 65 70 75 80
 Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
 85 90 95
 Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
 100 105 110
 Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
 115 120 125
 Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
 130 135 140
 Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
 145 150 155 160
 Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
 165 170 175
 Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
 180 185 190
 Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205
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 210 215 220
 Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240
 Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255
 Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270
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 Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335
 Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
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 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
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 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415

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 450 455 460
 Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480
 Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495
 Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510
 Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525
 Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
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<210> SEQ ID NO 3
 <211> LENGTH: 1722
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 3

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<210> SEQ ID NO 4
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 4

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Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105         110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115         120         125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130         135         140
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145         150         155         160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165         170         175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180         185         190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
195         200         205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
210         215         220
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225         230         235         240
Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
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Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
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 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
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 485 490 495
 Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
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 Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525
 Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
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<210> SEQ ID NO 5

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 5

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tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagtga gactgtttat atctaaatgt atggattcca    300
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<210> SEQ ID NO 6
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 6

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20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105         110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr

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130					135					140					
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145					150					155					160
Glu	Ala	Pro	Gly	Asn	Met	Gly	Leu	Phe	Asp	Gln	Gln	Leu	Ala	Leu	Gln
				165					170					175	
Trp	Val	Gln	Lys	Asn	Ile	Ala	Ala	Phe	Gly	Gly	Asn	Pro	Lys	Ser	Val
			180						185					190	
Thr	Leu	Phe	Gly	Glu	Ser	Ser	Gly	Ala	Ala	Ser	Val	Ser	Leu	His	Leu
			195				200					205			
Leu	Ser	Pro	Gly	Ser	His	Ser	Leu	Phe	Thr	Arg	Ala	Ile	Leu	Gln	Ser
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Gly	Ser	Ala	Asn	Ala	Pro	Trp	Ala	Val	Thr	Ser	Leu	Tyr	Glu	Ala	Arg
225					230					235					240
Asn	Arg	Thr	Leu	Asn	Leu	Ala	Lys	Leu	Thr	Gly	Cys	Ser	Arg	Glu	Asn
				245					250					255	
Glu	Thr	Glu	Ile	Ile	Lys	Cys	Leu	Arg	Asn	Lys	Asp	Pro	Gln	Glu	Ile
			260					265						270	
Leu	Leu	Asn	Glu	Ala	Phe	Val	Val	Pro	Tyr	Gly	Thr	Gln	Leu	Gly	Val
		275					280					285			
Asn	Phe	Gly	Pro	Thr	Val	Asp	Gly	Asp	Phe	Leu	Thr	Asp	Met	Pro	Asp
		290				295					300				
Ile	Leu	Leu	Glu	Leu	Gly	Gln	Phe	Lys	Lys	Thr	Gln	Ile	Leu	Val	Gly
305					310					315					320
Val	Asn	Lys	Asp	Glu	Gly	Thr	Trp	Phe	Leu	Val	Gly	Gly	Ala	Pro	Gly
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Phe	Ser	Lys	Asp	Asn	Asn	Ser	Ile	Ile	Thr	Arg	Lys	Glu	Phe	Gln	Glu
			340					345						350	
Gly	Leu	Lys	Ile	Phe	Phe	Pro	Gly	Val	Ser	Glu	Phe	Gly	Lys	Glu	Ser
		355				360						365			
Ile	Leu	Phe	His	Tyr	Thr	Asp	Trp	Val	Asp	Asp	Gln	Arg	Pro	Glu	Asn
		370				375					380				
Tyr	Arg	Glu	Ala	Leu	Gly	Asp	Val	Val	Gly	Asp	Tyr	Asn	Phe	Ile	Cys
385					390					395					400
Pro	Ala	Leu	Glu	Phe	Thr	Lys	Lys	Phe	Ser	Glu	Trp	Gly	Asn	Asn	Ala
				405					410					415	
Phe	Phe	Tyr	Tyr	Phe	Glu	His	Arg	Ser	Ser	Lys	Leu	Pro	Trp	Pro	Glu
			420					425						430	
Trp	Met	Gly	Val	Met	His	Gly	Tyr	Glu	Ile	Glu	Phe	Val	Phe	Gly	Leu
		435					440					445			
Pro	Leu	Glu	Arg	Arg	Asp	Asn	Tyr	Thr	Lys	Ala	Glu	Glu	Ile	Leu	Ser
		450				455					460				
Arg	Ser	Ile	Val	Lys	Arg	Trp	Ala	Asn	Phe	Ala	Lys	Tyr	Gly	Asn	Pro
465					470					475					480
Asn	Glu	Thr	Gln	Asn	Asn	Ser	Thr	Ser	Trp	Pro	Val	Phe	Lys	Ser	Thr
				485					490					495	
Glu	Gln	Lys	Tyr	Leu	Thr	Leu	Asn	Thr	Glu	Ser	Thr	Arg	Ile	Met	Thr
			500						505					510	
Lys	Leu	Arg	Ala	Gln	Gln	Cys	Arg	Phe	Trp	Thr	Ser	Phe	Phe	Pro	Lys
			515						520					525	
Val	Leu	Glu	Met	Thr	Gly	Asn	Ile	Asp	Glu	Ala	Glu	Trp	Glu	Trp	Lys
			530			535						540			

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Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
565 570

<210> SEQ ID NO 7
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 7

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gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagt 60
tttgggtgca cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga 120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa 180
tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag 240
atgtggaacc caaacactga cctcagttaa gactgtttat atctaaatgt atggattcca 300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg tttcaaact 360
ggaacatcat ctttcatagt ttatgatggc aagtttctgg ctcggttga aagagtatt 420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct 480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggtcaaaaa 540
aatatagcag cctttggtgg aaatcctaaa agtgaactc tctttggaga aagttccgga 600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc 660
attctgcaaa gtggttcccc gaatgctcct tgggcggtaa catctcttta tgaagctagg 720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780
atcaagtgtc ttagaataaa agatccocaa gaaattcttc tgaatgaagc atttgtgtc 840
ccctatggga ctcttttggg tgtaaacttt ggtccgaccg tggatggtga tttctcact 900
gacatgccag acatattact tgaacttggc caatttaaaa aaaccagat tttggtgggt 960
gttaataaag atgaagggac atgggtttta gtcggtggtg ctctgggctt cagcaaagat 1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga 1080
gtgagtgagt ttggaaaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actaccgtga ggccttgggt gatgtgttg gggattataa tttcatatgc 1200
cctgccttgg agttcaccaa gaagtctca gaatgggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagatgc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat ctttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
ttaaagcatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 8
<211> LENGTH: 574
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 8

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
 1 5 10 15

Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
 20 25 30

Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
 35 40 45

Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
 50 55 60

Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
 65 70 75 80

Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
 85 90 95

Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
 100 105 110

Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
 115 120 125

Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
 130 135 140

Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
 145 150 155 160

Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
 165 170 175

Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
 180 185 190

Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205

Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
 210 215 220

Gly Ser Pro Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240

Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
 275 280 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys

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385		390		395		400									
Pro	Ala	Leu	Glu	Phe	Thr	Lys	Lys	Phe	Ser	Glu	Trp	Gly	Asn	Asn	Ala
				405					410					415	
Phe	Phe	Tyr	Tyr	Phe	Glu	His	Arg	Ser	Ser	Lys	Leu	Pro	Trp	Pro	Glu
			420					425					430		
Trp	Met	Gly	Val	Met	His	Gly	Tyr	Glu	Ile	Glu	Phe	Val	Phe	Gly	Leu
		435					440					445			
Pro	Leu	Glu	Arg	Arg	Asp	Asn	Tyr	Thr	Lys	Ala	Glu	Glu	Ile	Leu	Ser
	450					455					460				
Arg	Ser	Ile	Val	Lys	Arg	Trp	Ala	Asn	Phe	Ala	Lys	Tyr	Gly	Asn	Pro
465					470					475					480
Asn	Glu	Thr	Gln	Asn	Asn	Ser	Thr	Ser	Trp	Pro	Val	Phe	Lys	Ser	Thr
				485					490					495	
Glu	Gln	Lys	Tyr	Leu	Thr	Leu	Asn	Thr	Glu	Ser	Thr	Arg	Ile	Met	Thr
			500					505					510		
Lys	Leu	Arg	Ala	Gln	Gln	Cys	Arg	Phe	Trp	Thr	Ser	Phe	Phe	Pro	Lys
		515					520					525			
Val	Leu	Glu	Met	Thr	Gly	Asn	Ile	Asp	Glu	Ala	Glu	Trp	Glu	Trp	Lys
	530					535					540				
Ala	Gly	Phe	His	Arg	Trp	Asn	Asn	Tyr	Met	Met	Asp	Trp	Lys	Asn	Gln
545					550					555					560
Phe	Asn	Asp	Tyr	Thr	Ser	Lys	Lys	Glu	Ser	Cys	Val	Gly	Leu		
				565					570						

<210> SEQ ID NO 9

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 9

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tttgggtggca cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagttaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtgggtgg ttttcaaact    360
ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggtccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttgggtg aaatcctaaa agtgtaacct tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattggt caccagagcc    660
attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg    720
aacagaacgt tgaacttagc taaattgact ggttgcctca gagagaatga gactgaaata    780
atcaagtgtc ttagaataaa agatcccaaa gaaattcttc tgaatgaagc atttgtgtc    840
ccctatggga ctggtttggg tgtaaacctt ggtccgaccg tggatgggtga ttttctcact    900
gacatgccag acatattact tgaacttgga caatttaaaa aaaccagat tttggtgggt    960
gttaataaag atgaagggac atggttttta gtcggtggtg ctctctggctt cagcaaagat   1020

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aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga 1080
gtgagtgagt ttggaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actacctgga gcccttgggt gatgttgttg gggattataa tttcatatgc 1200
cctgccttgg agttcaccaa gaagtctca gaatggggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat ctttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt aactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 10
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 10

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Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10          15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
                20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
                35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
        50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
        65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
                100         105         110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
        115         120         125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
        130         135         140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
        145         150         155         160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
                165         170         175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
                180         185         190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
        195         200         205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
        210         215         220
Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
        225         230         235         240

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Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255

Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270

Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Gly Leu Gly Val
 275 280 285

Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

<210> SEQ ID NO 11
 <211> LENGTH: 1722
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 11

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 ttggtggca cggtaacagc cttcttgga attccctatg cacagccacc tcttggtaga 120
 cttgattca aaaagccaca gtctctgacc aagtggctctg atatttgaa tgccacaaaa 180

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tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag 240
atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca 300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact 360
ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcgggttga aagagtatt 420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct 480
gaggctccag ggaacatggg tttatattgat caacagttgg ctcttcagtg ggttcaaaaa 540
aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga 600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc 660
attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg 720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780
atcaagtgtc ttagaaaaa agatccccaa gaaattcttc tgaatgaagc atttgtgtgc 840
ccctatggga ctctatggg tgtaaacctt ggtccgaccg tggatggtga ttttctcact 900
gacatgccag acatattact tgaacttggc caatttaaaa aaaccagat tttggtgggt 960
gttaataaag atgaagggac atggttttta gtcggtggtg ctctctggctt cagcaaagat 1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga 1080
gtgagtgagt ttgaaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc 1200
ctcgcttgg agttcaccaa gaagtctca gaatggggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgetca acaatgtcga 1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt aactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 12

<211> LENGTH: 574

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 12

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Glu Asp Asp Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10          15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95

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Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
 100 105 110
 Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
 115 120 125
 Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
 130 135 140
 Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
 145 150 155 160
 Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
 165 170 175
 Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
 180 185 190
 Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205
 Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
 210 215 220
 Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240
 Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255
 Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270
 Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Met Gly Val
 275 280 285
 Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300
 Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320
 Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335
 Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350
 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380
 Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400
 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415
 Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430
 Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445
 Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460
 Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480
 Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495
 Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510

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Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
515 520 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
530 535 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
565 570

<210> SEQ ID NO 13
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 13

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gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt      60
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cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagtcaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg tttcaaact     360
ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctccgggtga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttggtgg aaatcctaaa agtghtaact tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattggt caccagagcc    660
attctgcaaa gtgggtcctt taatgctcct tgggcggtaa catctcttta tgaagctagg    720
aacagaacgt tgaacttagc taaattgact gggtgctcta gagagaatga gactgaaata    780
atcaagtgtc ttagaataaa agatccccc aaaattcttc tgaatgaagc atttgtgtgc    840
ccctatggga ctccagttggg tgtaaaactt ggcccgaccg tggatggtga ttttctcact    900
gacatgccag acatattact tgaacttggg caatttaaaa aaaccagat tttggtgggt    960
gttaataaag atgaagggac atggttttta gtcggtggtg ctcttggtct cagcaaagat   1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga   1080
gtgagtgagt ttggaaggga atccatcctt tttcattaca cagactgggt agatgatcag   1140
agacctgaaa actaccgtga gcccttgggt gatgttgttg gggattataa tttcatatgc   1200
cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620
tgggagtgga aagcaggatt ccctcgtctg aacaattaca tgatggactg gaaaaatcaa   1680
tttaacgatt aactagcaa gaaagaaagt tgtgtgggtc tc                          1722

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<210> SEQ ID NO 14
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 14

Glu Asp Asp Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10           15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105        110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115        120        125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130        135        140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145        150        155        160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165        170        175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180        185        190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
195        200        205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
210        215        220
Gly Ser Phe Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225        230        235        240
Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
245        250        255
Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
260        265        270
Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Gln Leu Gly Val
275        280        285
Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
290        295        300
Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305        310        315        320
Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
325        330        335
Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
340        345        350
Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
355        360        365

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Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

<210> SEQ ID NO 15

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 15

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gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60
tttgggtgga cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga      120
cttcgattca aaaagccaca gtctctgacc aagtggctcg atatttggaa tgccacaaaa      180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag      240
atgtggaacc caaacactga cctcagtga gactgtttat atctaaatgt atggattcca      300
gcacctaaac caaaaaatgc cactgtattg atatggattt atgggtgtgg tttcaaact      360
ggaacatcat ctttcatagt ttatgatggc aagtttctgg ctcggttga aagagttatt      420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct      480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa      540
aatatagcag cctttggtgg aaatcctaaa agtgaactc tctttggaga aagttccgga      600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattggt caccagagcc      660
attctgcaaa gtgggtcctt taatgctcct tgggcggtaa catctcttta tgaagctagg      720
aacagaacgt tgaacttagc taaattgact ggttgcteta gagagaatga gactgaaata      780
atcaagtgtc ttagaaataa agatccccaa gaaattcttc tgaatgaagc atttgttgtc      840
ccctatggga ctatcttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact      900

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gacatgccag acatattact tgaacttggga caatttataaa aaaccagat tttggtgggt 960
gttaataaaag atgaaggagac atggttttta gtcggtgggt ctctggctt cagcaaagat 1020
aacaatagta tcataactag aaaagaattt caggaagggt taaaaatatt tttccagga 1080
gtgagtgagt ttggaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc 1200
cctgccttgg agttcaccaa gaagtctca gaatggggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
ttaaagcatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 16
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 16

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```

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10           15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105         110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115         120         125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130         135         140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145         150         155         160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165         170         175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180         185         190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
195         200         205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser

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210			215			220									
Gly	Ser	Phe	Asn	Ala	Pro	Trp	Ala	Val	Thr	Ser	Leu	Tyr	Glu	Ala	Arg
225				230						235					240
Asn	Arg	Thr	Leu	Asn	Leu	Ala	Lys	Leu	Thr	Gly	Cys	Ser	Arg	Glu	Asn
			245						250						255
Glu	Thr	Glu	Ile	Ile	Lys	Cys	Leu	Arg	Asn	Lys	Asp	Pro	Gln	Glu	Ile
			260						265						270
Leu	Leu	Asn	Glu	Ala	Phe	Val	Val	Pro	Tyr	Gly	Thr	Ile	Leu	Gly	Val
			275						280						285
Asn	Phe	Gly	Pro	Thr	Val	Asp	Gly	Asp	Phe	Leu	Thr	Asp	Met	Pro	Asp
290						295						300			
Ile	Leu	Leu	Glu	Leu	Gly	Gln	Phe	Lys	Lys	Thr	Gln	Ile	Leu	Val	Gly
305					310						315				320
Val	Asn	Lys	Asp	Glu	Gly	Thr	Trp	Phe	Leu	Val	Gly	Gly	Ala	Pro	Gly
			325						330						335
Phe	Ser	Lys	Asp	Asn	Asn	Ser	Ile	Ile	Thr	Arg	Lys	Glu	Phe	Gln	Glu
			340						345						350
Gly	Leu	Lys	Ile	Phe	Phe	Pro	Gly	Val	Ser	Glu	Phe	Gly	Lys	Glu	Ser
			355						360						365
Ile	Leu	Phe	His	Tyr	Thr	Asp	Trp	Val	Asp	Asp	Gln	Arg	Pro	Glu	Asn
370						375						380			
Tyr	Arg	Glu	Ala	Leu	Gly	Asp	Val	Val	Gly	Asp	Tyr	Asn	Phe	Ile	Cys
385					390						395				400
Pro	Ala	Leu	Glu	Phe	Thr	Lys	Lys	Phe	Ser	Glu	Trp	Gly	Asn	Asn	Ala
			405						410						415
Phe	Phe	Tyr	Tyr	Phe	Glu	His	Arg	Ser	Ser	Lys	Leu	Pro	Trp	Pro	Glu
			420						425						430
Trp	Met	Gly	Val	Met	His	Gly	Tyr	Glu	Ile	Glu	Phe	Val	Phe	Gly	Leu
			435						440						445
Pro	Leu	Glu	Arg	Arg	Asp	Asn	Tyr	Thr	Lys	Ala	Glu	Glu	Ile	Leu	Ser
			450			455						460			
Arg	Ser	Ile	Val	Lys	Arg	Trp	Ala	Asn	Phe	Ala	Lys	Tyr	Gly	Asn	Pro
465					470						475				480
Asn	Glu	Thr	Gln	Asn	Asn	Ser	Thr	Ser	Trp	Pro	Val	Phe	Lys	Ser	Thr
			485						490						495
Glu	Gln	Lys	Tyr	Leu	Thr	Leu	Asn	Thr	Glu	Ser	Thr	Arg	Ile	Met	Thr
			500						505						510
Lys	Leu	Arg	Ala	Gln	Gln	Cys	Arg	Phe	Trp	Thr	Ser	Phe	Phe	Pro	Lys
			515						520						525
Val	Leu	Glu	Met	Thr	Gly	Asn	Ile	Asp	Glu	Ala	Glu	Trp	Glu	Trp	Lys
			530			535						540			
Ala	Gly	Phe	His	Arg	Trp	Asn	Asn	Tyr	Met	Met	Asp	Trp	Lys	Asn	Gln
545					550						555				560
Phe	Asn	Asp	Tyr	Thr	Ser	Lys	Lys	Glu	Ser	Cys	Val	Gly	Leu		
			565						570						

<210> SEQ ID NO 17

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 17

gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt

60

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tttgggtggca cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga 120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa 180
tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag 240
atgtggaacc caaacactga cctcagtga gactgtttat atctaaatgt atggattcca 300
gcacctaaac caaaaaatgc cactgtattg atatggattt atgggtgggg tttcaaact 360
ggaacatcat ctttcatagt ttatgatggc aagtttctgg ctcggttga aagagtatt 420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct 480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggtcaaaaa 540
aatatagcag cctttggggg aaatcctaaa agtgaactc tctttggaga aagttccgga 600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc 660
attctgcaaa gtggttccgg taatgctcct tgggcggtaa catctcttta tgaagctagg 720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780
atcaagtgtc ttagaataaa agatccccaa gaaattcttc tgaatgaagc atttgtgtc 840
ccctatggga ctctttggg tgtaaacttt ggtccgaccg tggatggtga tttctcact 900
gacatgccag acatattact tgaacttggg caatttaaaa aaaccagat tttgggtggg 960
gttaataaag atgaagggac atggttttta gtcggtggtg ctctgggctt cagcaaagat 1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga 1080
gtgagtgagt ttggaaaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actaccgtga ggccttgggt gatgtgttg gggattataa tttcatatgc 1200
cctgccttgg agttcaccaa gaagtctca gaatgggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat cttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 18
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 18

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Glu Asp Asp Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10           15

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Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20           25           30

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Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35           40           45

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Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50           55           60

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Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
 65 70 80
 Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
 85 90 95
 Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
 100 105 110
 Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
 115 120 125
 Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
 130 135 140
 Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
 145 150 155 160
 Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
 165 170 175
 Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
 180 185 190
 Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205
 Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
 210 215 220
 Gly Ser Gly Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240
 Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255
 Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270
 Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
 275 280 285
 Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300
 Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320
 Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335
 Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350
 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380
 Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400
 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415
 Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430
 Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445
 Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460
 Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480
 Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr

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	485		490		495										
Glu	Gln	Lys	Tyr	Leu	Thr	Leu	Asn	Thr	Glu	Ser	Thr	Arg	Ile	Met	Thr
			500					505					510		
Lys	Leu	Arg	Ala	Gln	Gln	Cys	Arg	Phe	Trp	Thr	Ser	Phe	Phe	Pro	Lys
		515					520					525			
Val	Leu	Glu	Met	Thr	Gly	Asn	Ile	Asp	Glu	Ala	Glu	Trp	Glu	Trp	Lys
	530					535					540				
Ala	Gly	Phe	His	Arg	Trp	Asn	Asn	Tyr	Met	Met	Asp	Trp	Lys	Asn	Gln
545					550					555				560	
Phe	Asn	Asp	Tyr	Thr	Ser	Lys	Lys	Glu	Ser	Cys	Val	Gly	Leu		
				565					570						

<210> SEQ ID NO 19

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 19

```

gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt    60
tttgggtggca cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagttaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtgggtg ttttcaaact    360
ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctccgggtga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggtccag ggaacatggg tttatttggat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttgggtg aaatcctaaa agtgtaaact tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660
attctgcaaa gtggttcctt taatgctcct tggggcgtta catctcttta tgaagctagg    720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780
atcaagtgtc ttagaaataa agatccccc aaaaattcttc tgaatgaagc atttgtgtgc    840
ccctatggga cttccttggg tgtaaaactt ggtccgaccg tggatgggtga ttttctcact    900
gacatgccag acatattact tgaacttggc caatttaaaa aaaccagat tttggtgggt    960
gttaataaag atgaagggac atggttttta gtcggtggtg ctctctggctt cagcaaagat   1020
aacaatagta tcataactag aaaagaattt caggaagggt taaaaatatt tttccagga   1080
gtgagtgagt ttgaaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200
cctgccttgg agttcaccaa gaagtcttca gaatggggaa ataatgcctt tttctactat   1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320
gaaattgaat ttgtcttttg tttacctctg gaaagaagag ataattacac aaaagccgag   1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca   1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat   1500
ctaaccctga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga   1560

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ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

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```

<210> SEQ ID NO 20
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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```

<400> SEQUENCE: 20

```

```

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10           15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20           25           30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35           40           45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50           55           60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65           70           75           80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85           90           95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100          105          110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115          120          125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130          135          140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145          150          155          160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165          170          175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180          185          190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
195          200          205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
210          215          220
Gly Ser Phe Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225          230          235          240
Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
245          250          255
Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
260          265          270
Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Ser Leu Gly Val
275          280          285
Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
290          295          300
Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
305          310          315          320
Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
325          330          335

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Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350
 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380
 Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400
 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415
 Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430
 Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445
 Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460
 Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480
 Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495
 Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510
 Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525
 Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540
 Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560
 Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

<210> SEQ ID NO 21

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 21

```

gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt    60
tttgggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagttaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360
ggaacatcat ctttacctgt ttatgatggc aagtttctgg ctgggttga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttggtgg aaatcctaaa agtgtaaact tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660
attctgcaaa gtggttccgt taatgctcct tgggcggtaa catctcttta tgaagctagg    720

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aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780
atcaagtgtc ttagaataaa agatccccaa gaaattcttc tgaatgaagc atttgtgtc 840
ccctatggga ctcccttggg tgtaaacctt ggtccgaccg tggatggtga tttctcaact 900
gacatgccag acatattact tgaacttggg caatttaaaa aaaccagat tttggtgggt 960
gttaataaag atgaaggggac atggtttcta gtcggtggtg ctccctggctt cagcaaagat 1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga 1080
gtgagtgagt ttggaagga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc 1200
ctcgccttgg agttcaccaa gaagtctca gaatggggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctcaa acttccgttg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtcttggg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccacgcgttg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt aactagcaa gaaagaaagt tgtgtgggtc tc 1722

```

<210> SEQ ID NO 22

<211> LENGTH: 574

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 22

```

Glu Asp Asp Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10           15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105         110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115         120         125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130         135         140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145         150         155         160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165         170         175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180         185         190

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Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205
 Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
 210 215 220
 Gly Ser Val Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240
 Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255
 Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270
 Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
 275 280 285
 Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300
 Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320
 Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335
 Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350
 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380
 Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400
 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415
 Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430
 Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445
 Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460
 Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480
 Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495
 Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510
 Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525
 Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540
 Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560
 Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

<210> SEQ ID NO 23
 <211> LENGTH: 1722
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 23

```

gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt    60
tttgggtggca cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgtgtgca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagtgaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtgggtg ttttcaaact    360
ggaacatcat ctttacctgt ttatgatggc aagtttctgg ctcggttga aagagtattt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggctccag ggaacatggg tttatattgat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttgggtg aaatcctaaa agtghtaact tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattggt caccagagcc    660
attctgcaaa gtgggtcctt taatgctcct tgggcggtaa catctcttta tgaagctagg    720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780
atcaagtgtc ttagaataaa agatccocaa gaaattcttc tgaatgaagc atttgttgtc    840
ccctatggga ctgggttggg tgtaaacttt ggtccgaccg tggatggtga ttttctcact    900
gacatgccag acatattact tgaacttggg caatttaaaa aaaccagat tttggtgggt    960
gttaataaaag atgaagggac atggttttta gtcggtggtg ctcttggtt cagcaaagat   1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga   1080
gtgagtgtgag ttgaaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200
cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaaata tgggaatcca   1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaaatat   1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgtctca acaatgtcga   1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa   1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa   1680
tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc                          1722

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<210> SEQ ID NO 24

<211> LENGTH: 574

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 24

```

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10          15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
                20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser

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35					40					45					
Leu	Thr	Lys	Trp	Ser	Asp	Ile	Trp	Asn	Ala	Thr	Lys	Tyr	Ala	Asn	Ser
50					55					60					
Cys	Cys	Gln	Asn	Ile	Asp	Gln	Ser	Phe	Pro	Gly	Phe	His	Gly	Ser	Glu
65					70					75					80
Met	Trp	Asn	Pro	Asn	Thr	Asp	Leu	Ser	Glu	Asp	Cys	Leu	Tyr	Leu	Asn
				85					90					95	
Val	Trp	Ile	Pro	Ala	Pro	Lys	Pro	Lys	Asn	Ala	Thr	Val	Leu	Ile	Trp
			100						105					110	
Ile	Tyr	Gly	Gly	Gly	Phe	Gln	Thr	Gly	Thr	Ser	Ser	Leu	His	Val	Tyr
		115					120						125		
Asp	Gly	Lys	Phe	Leu	Ala	Arg	Val	Glu	Arg	Val	Ile	Val	Val	Ser	Met
		130				135					140				
Asn	Tyr	Arg	Val	Gly	Ala	Leu	Gly	Phe	Leu	Ala	Leu	Pro	Gly	Asn	Pro
145					150					155					160
Glu	Ala	Pro	Gly	Asn	Met	Gly	Leu	Phe	Asp	Gln	Gln	Leu	Ala	Leu	Gln
				165					170						175
Trp	Val	Gln	Lys	Asn	Ile	Ala	Ala	Phe	Gly	Gly	Asn	Pro	Lys	Ser	Val
			180						185					190	
Thr	Leu	Phe	Gly	Glu	Ser	Ser	Gly	Ala	Ala	Ser	Val	Ser	Leu	His	Leu
		195					200						205		
Leu	Ser	Pro	Gly	Ser	His	Ser	Leu	Phe	Thr	Arg	Ala	Ile	Leu	Gln	Ser
		210					215					220			
Gly	Ser	Phe	Asn	Ala	Pro	Trp	Ala	Val	Thr	Ser	Leu	Tyr	Glu	Ala	Arg
225					230					235					240
Asn	Arg	Thr	Leu	Asn	Leu	Ala	Lys	Leu	Thr	Gly	Cys	Ser	Arg	Glu	Asn
				245					250					255	
Glu	Thr	Glu	Ile	Ile	Lys	Cys	Leu	Arg	Asn	Lys	Asp	Pro	Gln	Glu	Ile
			260					265						270	
Leu	Leu	Asn	Glu	Ala	Phe	Val	Val	Pro	Tyr	Gly	Thr	Gly	Leu	Gly	Val
		275					280						285		
Asn	Phe	Gly	Pro	Thr	Val	Asp	Gly	Asp	Phe	Leu	Thr	Asp	Met	Pro	Asp
		290				295						300			
Ile	Leu	Leu	Glu	Leu	Gly	Gln	Phe	Lys	Lys	Thr	Gln	Ile	Leu	Val	Gly
305					310					315					320
Val	Asn	Lys	Asp	Glu	Gly	Thr	Trp	Phe	Leu	Val	Gly	Gly	Ala	Pro	Gly
				325					330					335	
Phe	Ser	Lys	Asp	Asn	Asn	Ser	Ile	Ile	Thr	Arg	Lys	Glu	Phe	Gln	Glu
				340					345					350	
Gly	Leu	Lys	Ile	Phe	Phe	Pro	Gly	Val	Ser	Glu	Phe	Gly	Lys	Glu	Ser
		355					360					365			
Ile	Leu	Phe	His	Tyr	Thr	Asp	Trp	Val	Asp	Asp	Gln	Arg	Pro	Glu	Asn
		370				375						380			
Tyr	Arg	Glu	Ala	Leu	Gly	Asp	Val	Val	Gly	Asp	Tyr	Asn	Phe	Ile	Cys
385					390					395					400
Pro	Ala	Leu	Glu	Phe	Thr	Lys	Lys	Phe	Ser	Glu	Trp	Gly	Asn	Asn	Ala
				405					410					415	
Phe	Phe	Tyr	Tyr	Phe	Glu	His	Arg	Ser	Ser	Lys	Leu	Pro	Trp	Pro	Glu
				420					425					430	
Trp	Met	Gly	Val	Met	His	Gly	Tyr	Glu	Ile	Glu	Phe	Val	Phe	Gly	Leu
				435				440					445		
Pro	Leu	Glu	Arg	Arg	Asp	Asn	Tyr	Thr	Lys	Ala	Glu	Glu	Ile	Leu	Ser
				450			455						460		

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Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

<210> SEQ ID NO 25

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 25

```

gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt      60
tttgggtgga cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctcg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagtga gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atgggtgggg tttcaaact     360
ggaacatcat ctttacetat ttatgatggc aagtttctgg ctcggttga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggtcaaaaa    540
aatatagcag cctttggggg aaatcctaaa agtgaactc tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660
attctgcaaa gtggttccat caatgctcct tgggcggtaa catctcttta tgaagctagg    720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780
atcaagtgtc ttagaataaa agatccccaa gaaattcttc tgaatgaagc atttgtgtgc    840
ccctatggga ctcccttggg tgtaaacctt ggtccgaccg tggatggtga tttctcact    900
gacatgccag acatattact tgaacttggg caatttaaaa aaaccagat tttggtgggt    960
gttaataaag atgaagggac atgggtttta gtcggtggtg ctctgggctt cagcaaagat   1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga   1080
gtgagtgagt ttggaaggga atccatcctt tttcattaca cagactgggt agatgatcag   1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200
cctgccttgg agttcaccaa gaagtcttca gaatggggaa ataatgcctt tttctactat   1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat   1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag   1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaaata tgggaatcca   1440

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aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt acactagcaa gaaagaaagt tgtgtgggctc tc 1722

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<210> SEQ ID NO 26
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 26

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```

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10          15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105        110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115        120        125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130        135        140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145        150        155        160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165        170        175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180        185        190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
195        200        205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
210        215        220
Gly Ser Ile Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225        230        235        240
Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
245        250        255
Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
260        265        270
Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
275        280        285
Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
290        295        300
Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly

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305		310		315		320
Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly						
		325		330		335
Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu						
		340		345		350
Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser						
		355		360		365
Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn						
		370		375		380
Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys						
		385		390		395
Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala						
		405		410		415
Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu						
		420		425		430
Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu						
		435		440		445
Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser						
		450		455		460
Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro						
		465		470		475
Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr						
		485		490		495
Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr						
		500		505		510
Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys						
		515		520		525
Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys						
		530		535		540
Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln						
		545		550		555
Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu						
		565		570		

<210> SEQ ID NO 27

<211> LENGTH: 1722

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 27

```

gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt      60
tttgggtggca cggtaacagc ctttcttggga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagttttc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagttaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtggtgg ttttcaaact    360
ggaacatcat ctttcatatgt ttatgatggc aagtttctgg ctccgggttga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggctccag ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600

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gcagcttcag ttagcctgca ttgctttct cctggaagcc attcattggt caccagagcc 660
attctgcaaa gtggttcctt gaatgctcct tgggcggtaa catctcttta tgaagctagg 720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata 780
atcaagtgtc ttagaaataa agatccocaa gaaattcttc tgaatgaagc atttgtgtgc 840
ccctatggga ctcttttggg tgtaaacctt ggtccgaccg tggatggtga ttttctcact 900
gacatgccag acatattact tgaacttgga caatttaaaa aaaccagat tttggtgggt 960
gttaataaag atgaagggac atggttttta gtcggtggtg ctctgggctt cagcaaagat 1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga 1080
gtgagtgagt ttggaaggga atccatcctt tttcattaca cagactgggt agatgatcag 1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc 1200
cctgccttgg agttcaccaa gaagtctca gaatgggaa ataatgcctt tttctactat 1260
tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaatttga gtagatccat agtgaacggg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga 1560
ttctggacat ctttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt acactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 28

<211> LENGTH: 574

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 28

```

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10          15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
                20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
                35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
                50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
                85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
                100         105         110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
                115         120         125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
                130         135         140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145         150         155         160

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Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
 165 170 175
 Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
 180 185 190
 Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205
 Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
 210 215 220
 Gly Ser Leu Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240
 Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255
 Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270
 Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Gly Val
 275 280 285
 Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300
 Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320
 Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335
 Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350
 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380
 Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400
 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415
 Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430
 Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445
 Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460
 Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480
 Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495
 Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510
 Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525
 Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540
 Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560
 Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

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<210> SEQ ID NO 29
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 29
gaagatgaca tcataattgc aacaaagaat ggaaaagtca gagggatgaa cttgacagtt      60
tttgggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga      120
cttcgattca aaaagccaca gtctctgacc aagtggctcg atatttggaa tgccacaaaa      180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag      240
atgtggaacc caaacactga cctcagttaa gactgtttat atctaaatgt atggattcca      300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtgggtg ttttcaaact      360
ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctcggttga aagagttatt      420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct      480
gaggtccagc ggaacatggg tttatttgat caacagttgg ctcttcagtg ggttcaaaaa      540
aatatagcag cctttggtgg aaatcctaaa agtgtaactc tctttggaga aagttccgga      600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc      660
attctgcaaa gtggttcctt taatgctcct tggggggtaa catctcttta tgaagctagg      720
aacagaacgt tgaacttagc taaattgact gggtgctcta gagagaatga gactgaaata      780
atcaagtgtc ttagaaaaaa agatcccaaa gaaattcttc tgaatgaagc atttgtgtgc      840
ccctatggga ctccctatggg tgtaaaactt ggtccgaccg tggatgggtg ttttctcact      900
gacatgccag acatattact tgaacttggc caatttaaaa aaaccagat tttggtgggt      960
gttaataaag atgaaggggc atggttttta gtcggtgggt ctctctggctt cagcaaagat      1020
aacaatagta tcataactag aaaagaattt caggaaggtt taaaaatatt tttccagga      1080
gtgagtgagt ttggaagga atccatcctt tttcattaca cagactgggt agatgatcag      1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc      1200
cctgccttgg agttcaccaa gaagtcttca gaatggggaa ataatgcctt tttctactat      1260
tttgaacacc gatcctcaa acttccgtgg ccagaatgga tgggagtgat gcatggctat      1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag      1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca      1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat      1500
ctaaccttga atacagagtc aacaagaata atgacgaaac tacgtgctca acaatgtcga      1560
ttctggacat ctttttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa      1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa      1680
tttaacgatt aactagcaa gaaagaaagt tgtgtgggtc tc                               1722

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<210> SEQ ID NO 30
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

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<400> SEQUENCE: 30

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Glu Asp Asp Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10          15

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Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
 20 25 30
 Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
 35 40 45
 Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
 50 55 60
 Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
 65 70 75 80
 Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
 85 90 95
 Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
 100 105 110
 Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
 115 120 125
 Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
 130 135 140
 Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
 145 150 155 160
 Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
 165 170 175
 Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
 180 185 190
 Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
 195 200 205
 Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
 210 215 220
 Gly Ser Phe Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
 225 230 235 240
 Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
 245 250 255
 Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
 260 265 270
 Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Pro Met Gly Val
 275 280 285
 Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300
 Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320
 Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335
 Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350
 Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365
 Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380
 Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400
 Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415
 Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430

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Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
435 440 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
450 455 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
465 470 475 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
485 490 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
500 505 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
515 520 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
530 535 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
565 570

<210> SEQ ID NO 31
<211> LENGTH: 1722
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 31

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gaagatgaca tcataattgc aacaagaat ggaaaagtca gagggatgaa cttgacagtt      60
tttgggtggca cggtaacagc ctttcttgga attccctatg cacagccacc tcttggtaga    120
cttcgattca aaaagccaca gtctctgacc aagtggctctg atatttggaa tgccacaaaa    180
tatgcaaatt cttgctgtca gaacatagat caaagtttcc caggcttcca tggatcagag    240
atgtggaacc caaacactga cctcagtcaa gactgtttat atctaaatgt atggattcca    300
gcacctaaac caaaaaatgc cactgtattg atatggattt atggtgggtg ttttcaaact    360
ggaacatcat ctttacatgt ttatgatggc aagtttctgg ctccgggtga aagagttatt    420
gtagtgtcaa tgaactatag ggtgggtgcc ctaggattct tagctttgcc aggaaatcct    480
gaggctccag ggaacatggg tttatattgat caacagttgg ctcttcagtg ggttcaaaaa    540
aatatagcag cctttgggtg aaatcctaaa agtgtaactc tctttggaga aagttccgga    600
gcagcttcag ttagcctgca tttgctttct cctggaagcc attcattgtt caccagagcc    660
attctgcaaa gtggttccgc taatgctcct tgggcggtaa catctcttta tgaagctagg    720
aacagaacgt tgaacttagc taaattgact ggttgctcta gagagaatga gactgaaata    780
atcaagtgtc ttagaataaa agatccoccaa gaaattcttc tgaatgaagc atttgtgtgc    840
ccctatggga ctaaattggg tgtaaacttt ggtccgaccg tggatgggtg ttttctcact    900
gacatgccag acatattact tgaacttggc caatttaaaa aaaccagat tttggtgggt    960
gttaataaag atgaagggac atggttttta gtcgggtggg ctctctggctt cagcaaagat   1020
aacaatagta tcataactag aaaagaattt caggaagggt taaaaatatt tttccagga   1080
gtgagtgagt ttgaaagga atccatcctt tttcattaca cagactgggt agatgatcag   1140
agacctgaaa actaccgtga ggccttgggt gatgttgttg gggattataa tttcatatgc   1200
cctgccttgg agttcaccaa gaagttctca gaatggggaa ataatgcctt tttctactat   1260

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tttgaacacc gatcctccaa acttccgtgg ccagaatgga tgggagtgat gcatggctat 1320
gaaattgaat ttgtctttgg tttacctctg gaaagaagag ataattacac aaaagccgag 1380
gaaattttga gtagatccat agtgaaacgg tgggcaaatt ttgcaaaata tgggaatcca 1440
aatgagactc agaacaatag cacaagctgg cctgtcttca aaagcactga acaaaaatat 1500
ctaaccttga atacagagtc aacaagaata atgacgaac tacgtgctca acaatgtcga 1560
ttctggacat cattttttcc aaaagtcttg gaaatgacag gaaatattga tgaagcagaa 1620
tgggagtgga aagcaggatt ccatcgctgg aacaattaca tgatggactg gaaaaatcaa 1680
tttaacgatt aactagcaa gaaagaaagt tgtgtgggtc tc 1722

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<210> SEQ ID NO 32

<211> LENGTH: 574

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: mutant of human BChE

<400> SEQUENCE: 32

```

Glu Asp Asp Ile Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met
1           5           10           15
Asn Leu Thr Val Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro
20          25          30
Tyr Ala Gln Pro Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser
35          40          45
Leu Thr Lys Trp Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser
50          55          60
Cys Cys Gln Asn Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu
65          70          75          80
Met Trp Asn Pro Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn
85          90          95
Val Trp Ile Pro Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp
100         105        110
Ile Tyr Gly Gly Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr
115        120        125
Asp Gly Lys Phe Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met
130        135        140
Asn Tyr Arg Val Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro
145        150        155        160
Glu Ala Pro Gly Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln
165        170        175
Trp Val Gln Lys Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val
180        185        190
Thr Leu Phe Gly Glu Ser Ser Gly Ala Ala Ser Val Ser Leu His Leu
195        200        205
Leu Ser Pro Gly Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser
210        215        220
Gly Ser Ala Asn Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg
225        230        235        240
Asn Arg Thr Leu Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn
245        250        255
Glu Thr Glu Ile Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile
260        265        270
Leu Leu Asn Glu Ala Phe Val Val Pro Tyr Gly Thr Lys Leu Gly Val
275        280        285

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Asn Phe Gly Pro Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp
 290 295 300

Ile Leu Leu Glu Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly
 305 310 315 320

Val Asn Lys Asp Glu Gly Thr Trp Phe Leu Val Gly Gly Ala Pro Gly
 325 330 335

Phe Ser Lys Asp Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu
 340 345 350

Gly Leu Lys Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser
 355 360 365

Ile Leu Phe His Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn
 370 375 380

Tyr Arg Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys
 385 390 395 400

Pro Ala Leu Glu Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala
 405 410 415

Phe Phe Tyr Tyr Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu
 420 425 430

Trp Met Gly Val Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu
 435 440 445

Pro Leu Glu Arg Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser
 450 455 460

Arg Ser Ile Val Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro
 465 470 475 480

Asn Glu Thr Gln Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr
 485 490 495

Glu Gln Lys Tyr Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr
 500 505 510

Lys Leu Arg Ala Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys
 515 520 525

Val Leu Glu Met Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys
 530 535 540

Ala Gly Phe His Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln
 545 550 555 560

Phe Asn Asp Tyr Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
 565 570

What is claimed is:

1. An isolated nucleic acid molecule comprising a nucleic acid sequence which encodes a butyrylcholinesterase variant peptide, said nucleic acid sequence comprising SEQ ID NO: 5.

2. An isolated nucleic acid molecule comprising a nucleic acid sequence which encodes a butyrylcholinesterase variant peptide comprising the amino acid sequence of SEQ ID NO: 6.

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