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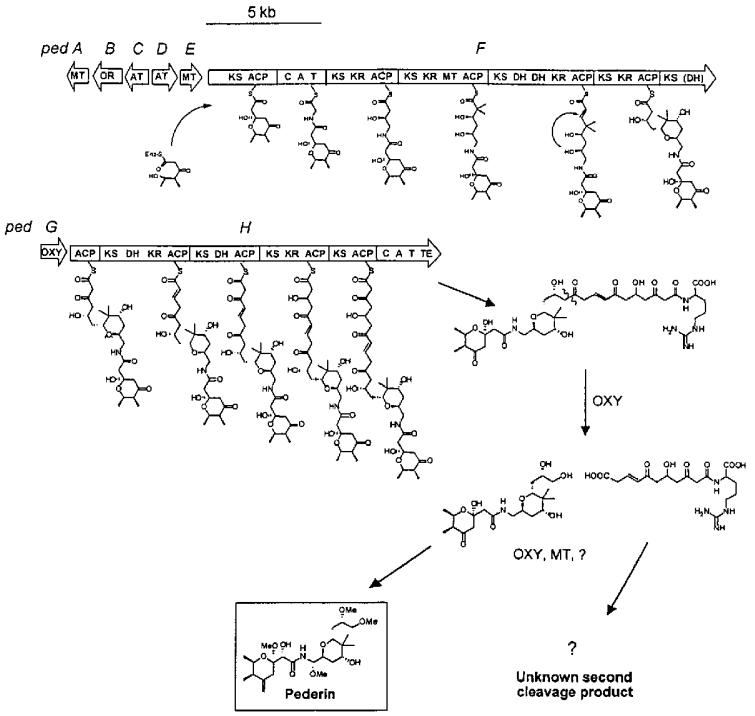
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**(54) Title:** NOVEL GENE CLUSTER OF PEDERIN BIOSYNTHESIS GENES




**(57) Abstract:** The present invention relates to the cloning, sequencing and analysing of a gene cluster encoding a modular polyketide synthase enzyme involved in the biosynthesis of the antitumor compound pederin. This novel cluster represents the first example of genes from an unculturable symbiont encoding the biosynthesis of a drug candidate.

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

Specification

# NOVEL GENE CLUSTER OF PEDERIN BIOSYNTHESIS GENES

The present invention relates to the cloning, sequencing and analysing of a gene cluster encoding a modular polyketide synthase enzyme involved in the biosynthesis of the antitumor compound pederin.

In particular, the present invention relates to a novel isolated nucleic acid comprising a pederin biosynthetic gene cluster, fragments of this gene cluster, corresponding polypeptides, vectors and recombinant host cells or transgenic organisms comprising said nucleic acids, a method for producing pederin and the use of said nucleic acids for preparing a modified pederin biosynthesis gene cluster or modified pederin molecules.

Thus, the invention relates to novel genes and isolated nucleic acids encoding polypeptides/proteins exhibiting functional activities involved in the pederin biosynthesis, such polypeptides themselves, and methods or uses to prepare pederin or modified pederin derivatives.

Invertebrates, particularly those from marine environments, are an important source of natural products with high therapeutic potential. The low availability of most of these metabolites, however, represents a serious impediment to drug development. As many invertebrates are difficult to cultivate and chemical synthesis is usually not economical, alternative and ecologically friendly sources of natural products are urgently needed. The actual producers of many drug candidates isolated from invertebrates may well be symbiotic bacteria, but so far no producing symbiont has ever been successfully cultured. Genes from bacterial secondary metabolism are usually clustered, which can simplify their cloning and transfer into a heterologous host. Het-

erologous expression in a culturable bacterium could therefore generate renewable sources of rare symbiont-derived drug candidates isolated from invertebrates.

The highly active antitumor compounds of the pederin group (Fig. 1) represent the strongest evidence for such a bacterial biosynthesis (Narquizian, R., Kocienski, P. J., The pederin family of antitumor agents: structures, synthesis and biological activity. The Role of Natural Products in Drug Discovery. Ernst Schering Research Foundation Workshop Series, **32**, Springer-Verlag, Heidelberg, Germany, 25-56 (2000)). While almost all of these metabolites were isolated from marine sponges, pederin is exclusively known from terrestrial *Paederus* and *Paederidus* beetles. These notorious insects carry pederin as vesicant deterrant in their hemolymph and cause severe dermatitis when accidentally crushed on the human skin. In all *Paederus* species studied so far, up to 90% of the females contain high levels of pederin, and only these (+)-females transfer this trait to their female offspring. Pederin-free (-)-females do not produce (+)-offspring, unless they are fed eggs of (+)-females. This non-Mendelian mode of inheritance can be prevented if the (+)-eggs are previously treated with antibiotics, which strongly suggests bacterially mediated pederin biosynthesis. In stark contrast to the large number of suspected symbiont drug candidates from marine invertebrates, pederin is the only terrestrial example known to date.

The structure of pederin and early labelling studies suggest that the metabolite is largely synthesised from malonyl- and methylmalonyl-coenzyme A (CoA) units by a type I polyketide synthase (PKS). Such megasynthases consist of repeated modules, along which the growing polyketide chain is processed in an assembly line-like fashion. Normally, each module minimally carries ketosynthase (KS), acyltransferase (AT) and acyl carrier protein (ACP) domains to perform exactly one chain elongation

cycle, and optional additional domains to catalyze further modifications.

As pointed out above, drug development from natural sources is commonly hampered by low yields and the difficulty of sustaining invertebrate cultures. To obtain insight into the true producer and to find alternative sources for these rare drug candidates, it was the object of the present invention to establish a way to provide pederin in a more convenient and economic fashion.

This object was solved by cloning, sequencing and analysing the pederin genes.

In a first aspect, the present invention provides an isolated nucleic acid comprising a pederin biosynthetic gene cluster or being complementary to a sequence comprising a pederin biosynthetic gene cluster. This cluster represents the first example of genes from an unculturable symbiont encoding the biosynthesis of a drug candidate.

This gene cluster is preferably derived from *Paederus* or *Paederidus* rove beetles, and in particular from a bacterial symbiont of *Paederus* or *Paederidus* rove beetles.

The isolated nucleic acid preferably comprises nucleic acid fragments forming individual units and/or modules of the pederin biosynthetic gene cluster as it is shown in more detail in Fig. 3. As depicted in Fig. 3, the cluster contains the units *ped*A to *ped*H which are either coding units for individual enzymes or for one or several polyketide synthase or nonribosomal peptide synthetase modules. The *ped*F unit, for example, comprises five polyketide synthase modules and one peptide synthetase module and/or the *ped*H unit comprises four polyketide synthase modules and one peptide synthetase module. Each polyketide synthase module comprises at least one ketosynthase domain and one acyl car-

rier protein domain. The isolated nucleic acid preferably comprises one or more of the *ped*A to *ped*H units essentially consisting of the nucleic acid sequences encoding the protein sequences shown in SEQ ID NO: 2 to 9.

In a particularly preferred embodiment, the isolated nucleic acid according to the present invention comprises:

- a nucleotide sequence as shown in SEQ ID NO:1; or
- a nucleotide sequence which is the complement of SEQ ID NO:1; or
- a nucleotide sequence hybridising under highly stringent conditions to SEQ ID NO:1 or to the complement thereof; or
- a nucleotide sequence having at least 80% sequence identity with SEQ ID NO:1 or with the complement thereof.

Under a further aspect, the present invention is directed to nucleic acid fragments selected from the group consisting of *ped*A, *ped*B, *ped*C, *ped*D, *ped*E, *ped*F, *ped*G and/or *ped*H as shown in Fig. 3. Especially important are the fragments essentially consisting of *ped*F and/or *ped*H. Further preferred are the nucleic acid fragments comprising one or more nucleotide sequences encoding the protein sequences as shown in SEQ ID NOs: 2 to 9. Also preferred are the corresponding parts of the nucleotide sequence SEQ ID NO:1.

Furthermore, the invention is directed to a polypeptide encoded by a nucleic acid as described above. The polypeptide preferably has functional activity in the synthesis of pederin and/or a polyketide and/or a peptide synthetase moiety.

In addition, the invention also provides a vector comprising a nucleic acid consisting essentially of the pederin biosynthetic gene cluster or a vector comprising a nucleic acid as described above as well as a recombinant host cell or a transgenic organ-

ism comprising said nucleic acid or containing said vector. In a preferred embodiment, the host cell used is a bacterial cell. As bacterial cells, *Pseudomonas, Acinetobacter, Bacillus or Streptomyces* cells are particularly preferred.

Finally, a method for producing pederin using a recombinant host cell or a transgenic organism as described above is provided, comprising the steps of:

- culturing the recombinant host cell under conditions to express the pederin biosynthetic gene cluster; and
- isolating the produced pederin.

The inventive nucleic acids can be used in the preparation of a modified pederin biosynthesis gene cluster or in the preparation of a modified pederin molecule. Modified pederin molecules might be used as an alternative antitumor agent and might be even more potent antitumor agents as the original pederin.

In the following, reference is made to the figures further illustrating the present invention.

**Fig. 1** shows some members of the pederin family of antitumor compounds isolated from terrestrial beetles and marine sponges.

**Fig. 2** illustrates the PCR amplification of PKS gene fragments from beetle total DNA. a, TLC analysis of the ethanolic beetle extracts. The arrow indicates the position of pederin. Small amounts of pederin found in males and (-)-females are due to pederin transfer from (+)-females to the offspring. b, Agarose gel of the PCR products obtained from total DNA of the same beetle specimens that were used for pederin extraction. L, 1 kb DNA ladder; B, blind PCR control without template DNA; 1 *Paederus fuscipes*, (+)-female, collected at Jena, Germany; 2 *P. fuscipes*, (-)-female, Jena; *P. fuscipes*, male, Jena; 4, *P. fuscipes*, (+)-female, collected at Aydın, Turkey; 5, *P. fuscipes*, (-)-female,

Aydın; 6, *P. fuscipes*, male, Aydın; 7, *Paederidus rubrothoracicus*, (+)-female, Aydın; 8, *Pd. rubrothoracicus*, (-)-female, Aydın; 9, *Pd. rubrothoracicus*, male, Aydın; 10, *Paederus litoralis*, (+)-female, Jena; 11, *P. litoralis*, male, Jena. No (-)-female of *P. litoralis* was available.

**Fig. 3** is a map of the sequenced *ped* genes and the proposed pederin biosynthesis pathway. MT, methyltransferase, OR, oxidoreductase, AT, acyltransferase; KS, ketosynthase domain; ACP, acyl carrier protein domain; KR, ketoreductase domain; DH, dehydratase domain; (DH), putative nonfunctional dehydratase domain, OXY, oxygenase; C, nonribosomal peptide synthetase condensation domain; A, nonribosomal peptide synthetase adenylation domain; T, nonribosomal peptide synthetase thiolation domain, TE, thioesterase domain.

**Fig. 4** shows a comparison of the first modules of PedF and the first module of the avermectin AVES2 protein which is a regular type I polyketide synthase. The shaded area in AVES2-1 indicates the AT region that is deleted in PedF1. Conserved motifs are shown as vertical bars. Motifs are: 1, EPIAIV; 2, DPQQRL; 3, CSSS; 4, HGTGTxLGD; 5, GxGGxNAHVILEE; 6, YTL; 7, GHSxG; 8, YPF; 9, GxDS.

The sequences mentioned in this application are listed in the attached sequence listing. These sequences are shortly summarized in the following:

SEQ ID NO:1: nucleic acid sequence of the pederin biosynthetic gene cluster
SEQ ID NO:2: protein sequence of PedA putative methyltransferase
SEQ ID NO:3: protein sequence of PedB putative FMN-dependent oxidoreductase

SEQ ID NO:4: protein sequence of PedC putative acetyltransferase

SEQ ID NO:5: protein sequence of PedD putative acetyltransferase

SEQ ID NO:6: protein sequence of PedE putative methyltransferase

SEQ ID NO:7: protein sequence of PedF mixed type I polyketide synthase/nonribosomal peptide synthase (module 1 PKS (KS-ACP), module 2 NRPS (C-A-T), module 3 PKS (KS-KR-ACP), module 4 PKS (KS-KR-MT-ACP), module 5 PKS (KS-KR-DH-DH-ACP), module 6 PKS (KS-KR-ACP), module 7 incomplete PKS (KS-DH))

SEQ ID NO:8: protein sequence of PedG putative flavin-binding monooxygenase

SEQ ID NO:9: protein sequence of PedH mixed type I polyketide synthase/nonribosomal peptide synthase (module 1 incomplete PKS (ACP), module 2 PKS (KS-DH-KR-ACP), KS-DH-ACP), module 3 PKS (KS-DH-ACP), module 4 PKS (KS-KR-ACP), module 5 PKS (KS-ACP), module 6 NRPS (C-A-T-TE))

SEQ ID NO:10 and SEQ ID NO:11: nucleic acid sequences of degenerate primers used during the cloning of the *ped* genes

SEQ ID NO:12 to SEQ ID NO:19: nucleic acid sequences of primers used during the cloning of the *ped* genes

The present invention will now be described in further detail with reference to a particular example.

According to the example of the present invention, pederin biosynthesis genes were cloned from total DNA of *Paederus fuscipes* beetles, which use this compound for chemical defense. Sequence analysis of the gene cluster and adjacent regions revealed the presence of open reading frames with typical bacterial architecture and homologies. The cluster is present only in female beetles with high pederin content and encodes a mixed modular polyketide synthase - nonribosomal peptide synthetase. Notably, none of the modules contains regions with homology to acyltransferase

domains, but two copies of isolated monodomain acyltransferase genes were found at the upstream end of the cluster. This architecture suggests a novel mechanism of extender unit selection, distinct from previously described modular polyketide systems. The cluster represents the first example of cloned genes from an unculturable invertebrate symbiont that encodes the biosynthesis of a potential drug candidate.

To clone the pederin cluster, a PCR strategy was pursued involving degenerate primers based on universally conserved motifs of KS domains. Total DNA, isolated from different beetle specimens, was used as a PCR template. Analysis of three species of the genera *Paederus* and *Paederidus* collected at two different locations consistently revealed that only those adult beetles with a high pederin content gave the PCR product expected to arise from the presence of PKS genes (Fig. 2). Amplification products were also obtained by using eggs from (+)-females of a fourth species, *P. riparius*, from a third locality (data not shown). Sequencing of the amplified DNA showed, in all cases, the exclusive presence of the same group of three to four different sequences possessing strong homology to KS domains of bacterial type I PKSs. This is shown in the following Table 1.

**Table 1 Comparison of DNA sequences obtained by PCR from different beetle specimens.**

| Sequence name | *P. fuscipes* adults (Jena, Germany) | *P. fuscipes* adults (Aydın, Turkey) | *P. litoralis* adults (Jena, Germany) | *P. riparius* eggs (Bayreuth, Germany) | *Paederidus rubrothoracicus* (Aydın, Turkey) | Highest homology |
|---|---|---|---|---|---|---|
| PKS1 | + | + | + | + | + | *B. subtilis* Pks (54%) |
| PKS2 | + | + | + | + | + | *B. subtilis* Pks (67%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| PKS3 | + | + | + | – | + | *B. subtilis* Pks (53%) |
| PKS4 | + | – | – | + | + | *B. subtilis* Pks (44%) |

Note: + and - indicate present and absent sequences, respectively.

The perfect correlation between pederin content and PKS sequences, independent of species and locality of collection, suggests that the amplified fragments belong to different modules of the pederin cluster. These DNA fragments were therefore used to locate the cluster.

To this end, a metagenomic cosmid library was constructed from total DNA of *P. fuscipes* beetles. By screening this library with specific PCR primers derived from the amplified sequences (see Methods below), three positive cosmids were identified. Sequencing of a 52,7 kb region revealed the presence of ORFs homologous to type I PKS genes, designated as *ped* genes. All of the amplified KS sequences could be found on these ORFs. Additional regions covering ca. 60 kb outside of the cluster were obtained on two cosmids isolated by chromosome walking and subjected to extensive spot sequencing. All putative genes present on these cosmids exhibit typical bacterial features: they are tightly packed, free of introns and polyadenylation sites, and preceded by Shine-Dalgarno patterns in appropriate distances to the start codons. Furthermore, when subjected to database homology searches, each of the translated ORFs exhibited the highest similarity to bacterial proteins. Among the homologies to 65 different ORFs analysed, 15 are exclusively known from prokaryotes, such as enzymes used in vitamin $B_{12}$ biosynthesis, type II fatty acid synthase components and regulatory proteins of the LuxR and LysR families. From these findings the inventor concluded that the *ped* cluster is located on a bacterial genome.

Fig. 3 summarizes the results from an analysis of the completely sequenced 52,7 kb region. The predicted gene products of the ORFs *pedF* and *pedH* are giant proteins of 8601 and 6266 amino acids (aa), respectively, resembling mixed modular PKSs/nonribosomal peptide synthetases (NRPSs). Strikingly, AT homologies are completely absent on these proteins. Alignment with other known type I PKSs revealed that a continuous ~300 aa region of each AT domain, including the active site GHS motif, are deleted in *pedF* and *pedH*, with no other homologies replacing them (Fig. 4), which leads to a considerable shortening of each module. In modular PKSs, the AT domain is crucial in the selection of the correct acyl-CoA unit in each extension cycle, raising the interesting question how this process is controlled during assembly of pederin from two different acyl-CoA units. The ORFs *pedC* and *pedD*, located upstream of *pedF* and encoding deduced proteins with homology to monodomain ATs, could play a possible role in selectivity control. It is tempting to speculate that each of these isolated ATs recognises a different extension unit and is bound and used iteratively by cognate PKS modules. The *ped* cluster would then encode a type I protein complemented by repetitive type II enzymes. Intriguingly, a similar PKS system containing such putative "super ATs" is encoded on the genome of *Bacillus subtilis*. The gene products of the *pks* cluster consist of a large number of PKS modules without AT domains and, encoded at the upstream end of the cluster, three isolated ATs. The secondary metabolite generated by these proteins is not known. Sequence comparison with other known PKS clusters reveals that the *ped* and the *B. subtilis pks* clusters are more closely related to each other than to any other known PKS cluster. The two clusters could therefore belong to a phylogenetically distinct subgroup of functionally novel type I PKS systems.

With few exceptions, the order of encoded modules in type I PKS clusters strictly correlates with the sequence of biosynthetic steps. In most cases the core structure of the metabolite can

therefore be predicted from the gene architecture and vice versa. Except for the missing first three modules, which could not be found in the sequenced region, the pederin structure is perfectly mirrored in *pedF* (Fig. 3). The single ORF should thus be responsible for the formation of the largest part of the pederin molecule except for the six-membered ring bearing the exomethylene group. Characteristic features of the cluster include (i) O-methyltransferase and oxygenase tailoring genes upstream and downstream of *pedF*, most likely involved in the final biosynthetic steps, (ii) a rare methyltransferase domain in PedF that should catalyse the formation of the uncommon geminal dimethyl group, as known from epothilone biosynthesis, (iii) a repeated dehydratase domain in PedF that putatively performs a sequential elimination of water and intramolecular alcohol attack to generate the dimethylated tetrahydropyrane ring and (iv) a NRPS module in PedF that likely incorporates an amino acid to account for the amide bond. Previous studies have identified sequence patterns of NRPS activating domains that can be used to predict the amino acid incorporated by the corresponding module. The structure of pederin suggests that glycine is selected by the NRPS module of PedF. In accordance, a pattern analysis of the PedF NRPS module revealed 100% identity to the known consensus nonribosomal code for glycine.

Analysis of the modular architecture of the pederin cluster as shown in Fig. 3 further suggests that the biosynthesis of pederin proceeds via a larger intermediate that is cleaved oxidatively into two fragments. One of these fragments would be converted by further biosynthetic steps to pederin. The intermediate presumably is very similar to the longer-chain compounds derived from sponges like onnamide and icadamide B. Manipulation of the pederin cluster (e. g. by inactivating the cleaving oxygenase gene) should therefore also enable access to analogues of these marine drugs.

Taken together, these findings and the fact that the *ped* genes contained all of the amplified KS fragments and only occur in beetles with high pederin content, independent of species and geography, are compelling evidence that the cloned gene cluster indeed encodes pederin biosynthesis.

The present invention showed for the first time that genes responsible for the biosynthesis of rare invertebrate drug candidates can be cloned from unculturable bacterial symbionts. Since whole sets of type I PKS genes have been functionally expressed even in *E. coli*, a similar production of "invertebrate" natural products in a suitable host has now become a realistic scenario. The novel structure of the *ped* cluster, featuring small-sized modules and ATs with putatively high catalytic flexibility, furthermore offers fascinating possibilities for generating unnatural drug analogues by combinatorial biosynthesis.

**Methods.**

**Pederin analysis.** Beetle species were determined by R.L.L. Kellner and H. Başpınar. Beetles were stored individually in ethanol immediately after collection to preserve the DNA. For pederin analysis the ethanol was concentrated to 50 µl, and 10 µl were spotted on a silica gel TLC plate (Merck). The plate was then developed in ethyl acetate and stained with anisaldehyde reagent. A pink spot at $R_F = 0.22$ was specific for pederin.

**Cloning of the *ped* genes.** A QIAamp DNA mini kit (Qiagen) was used to extract DNA from adult beetles with known pederin content. This DNA was used as PCR template. For egg DNA templates, one egg was ground in PCR buffer at 0 °C using a Wheaton homogenizer (previously treated with concentrated HCl for 15 min and washed with sterile $H_2O$), transferred into a PCR tube, frozen and thawed three times and subsequently boiled for 5 min, then the remaining PCR components were added. For all initial reac-

tions, the primers KSDPQQF (5'-MGNGARGCNNWNSMNATGGAYCCNCARCANMG-3') (SEQ ID NO:10) and KSHGTGR (5'-GGRTCNCCNARNSWNGTNCCNGTNCC-RTG-3') (SEQ ID NO:11) and Platinum *Taq* DNA Polymerase High Fidelity (Invitrogen) were used (M=A+C, R=A+G, W=A+T, S=C+G, Y=C+T, N=A+T+C+G). Each PCR experiment was performed at least in triplicate except for the rarer *P. litoralis* adults, where only two reactions could be run for each sex. PCR products were ligated into the pGEM-T Easy vector (Promega) and digested with *Rsa*I. Plasmids showing a unique restriction pattern were sequenced using the BigDye Terminator Ready Mix (Applied Biosystems) and an ABI 3700 sequencer (Applied Biosystems). From these sequences the following primer pairs specific for single modules were designed: 5'-TGGCATCGTGGGGAAAGGCTG-3' (SEQ ID NO:12) - 5'-GGCGCAGGTGCTGACACGC-3' (SEQ ID NO:13) (KS1F - KS1R), 5'-TTAGCC-ATCGAGAGTTACAGCTC-3' (SEQ ID NO:14) - 5'-AATCGCCGATAGCCATCGCCG-3' (SEQ ID NO:15) (KS2F - KS2R), 5'-GACGCCATGGATGCACTGCAC-3' (SEQ ID NO:16) - 5'-TATTGGATGCTCAGCACCGCAC-3' (SEQ ID NO:17) (KS3F - KS3R) and 5'-GGGCTCAGTTTCCACCCTTATG-3' (SEQ ID NO:18) - 5'-CCGGCGCTGCAGAGCCAGG-3' (SEQ ID NO:19) (KS4F - KS4R). A cosmid library was prepared from total DNA of 10 *P. fuscipes* (+)-females collected in Aydın, Turkey, using the pWEB cosmid cloning kit (Epicentre). The library was plated at concentrations to yield about 300 colonies per plate. The bacteria from each plate were combined, and the complete plasmid DNA isolated from 12 plate pools was screened by diagnostic PCR using the specific primers. Positive pools were plated at numbers of 50 per plate and rescreened. This procedure was repeated until single positive colonies could be identified. Positive cosmids were sonicated, end-repaired by BAL-31 and Klenow fragment and size-fractionated by gel electrophoresis to yield fragments of 1-2 kb lengths. These fragments were ligated into the *Eco*RV site of pBluescript II SK- (Stratagene) and end sequenced. Remaining gaps were filled by using specifically designed primers and by targeted subcloning. Sequence analysis was performed by using

BLASTX, PROSITE, FRAMEPLOT and the Lasergene DNASTAR software package.

## Claims

1. An isolated nucleic acid comprising a pederin biosynthetic gene cluster or being complementary to a sequence comprising a pederin biosynthetic gene cluster.

2. An isolated nucleic acid according to claim 1 which is derived from *Paederus* or *Paederidus* rove beetles and in particular from bacterial symbionts of these beetles.

3. The isolated nucleic acid according to claim 1 or 2 comprising nucleic acid fragments forming individual units and/or modules of the pederin biosynthetic gene cluster as shown in Fig. 3.

4. The isolated nucleic acid according to any of claims 1 to 3, comprising the units *ped*A to *ped*H as shown in Fig. 3.

5. The isolated nucleic acid according to claim 4, wherein the *ped*A unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:2, and/or the *ped*B unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:3, and/or the *ped*C unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:4, and/or the *ped*D unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:5, and/or the *ped*E unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:6, and/or the *ped*F unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:7, and/or the *ped*G unit essentially consists

of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:8, and/or the *ped*H unit essentially consists of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:9.

6. The isolated nucleic acid according to claims 1 to 5, comprising:
   - a nucleotide sequence as shown in SEQ ID NO:1; or
   - a nucleotide sequence which is the complement of SEQ ID NO:1; or
   - a nucleotide sequence hybridising under highly stringent conditions to SEQ ID NO:1 or to the complement thereof; or
   - a nucleotide sequence having at least 80% sequence identity with SEQ ID NO:1 or with the complement thereof.

7. A nucleic acid fragment according to claim 3 selected from the group consisting of *ped*A and/or *ped*B and/or *ped*C and/or *ped*D and/or *ped*E and/or *ped*F and/or *ped*G and/or *ped*H as shown in Fig. 3.

8. A nucleic acid fragment according to claim 7, essentially consisting of a nucleotide sequence coding for a protein sequence as shown in SEQ ID NO:2 and/or SEQ ID NO:3 and/or SEQ ID NO:4 and/or SEQ ID NO:5 and/or SEQ ID NO:6 and/or SEQ ID NO:7 and/or SEQ ID NO:8 and/or SEQ ID NO:9 or coding for a protein sequence having at least 80% sequence identity with these sequences.

9. A polypeptide encoded by a nucleic acid as defined in any of claims 1 to 8.

10. A polypeptide according to claim 9 comprising a protein sequence according to any of the sequences as shown in

SEQ ID NO:2 to SEQ ID NO:9 or a protein sequence having at least 80% sequence identity with these sequences.

11. A polypeptide according to claim 9 or 10 having functional activity in the synthesis of pederin and/or a polyketide moiety and/or a nonribosomal peptide moiety.

12. A vector comprising a nucleic acid consisting essentially of the pederin biosynthetic gene cluster.

13. A vector comprising a nucleic acid according to any of claims 1 to 8.

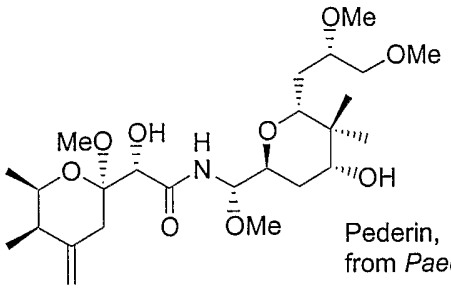
14. A recombinant host cell or a transgenic organism comprising a nucleic acid according to any of claims 1 to 8 or containing a vector according to any of claims 12 or 13.

15. A recombinant host cell according to claim 14 which is a bacterial cell and in particular is a *Pseudomonas*, *Acinetobacter*, *Bacillus* or *Streptomyces* cell.

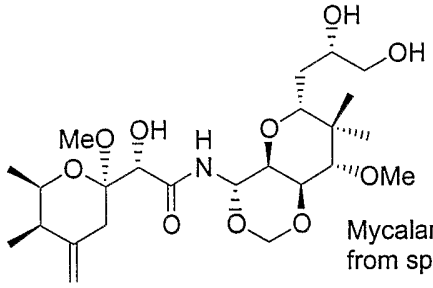
16. A method for producing pederin using a recombinant host cell or a transgenic organism according to claims 14 or 15 comprising the steps of:
- culturing the recombinant host cell or the transgenic organism under conditions to express the pederin biosynthetic gene cluster; and
- isolating the produced pederin.

17. Use of a nucleic acid according to any of claims 1 to 8 in the preparation of a modified pederin biosynthesis gene cluster.

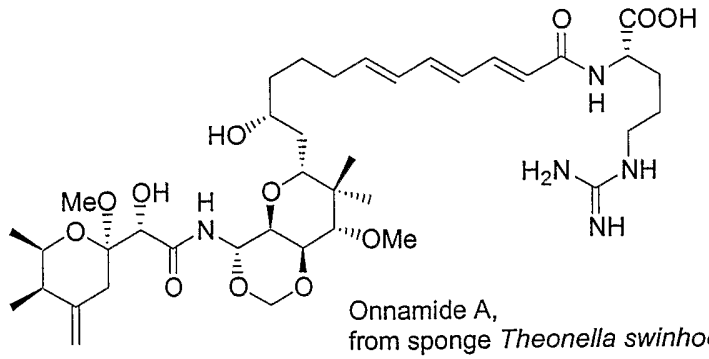
18. Use of a nucleic acid according to any of claims 1 to 8 in the preparation of a modified pederin molecule.




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from *Paederus* beetles




Mycalamide A,
from sponge *Mycale* sp.




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Fig. 1

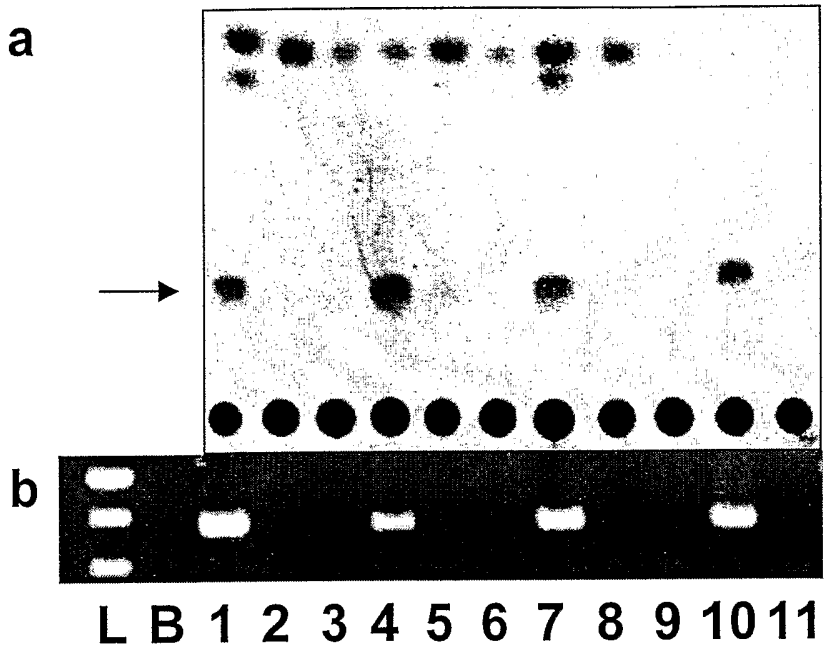



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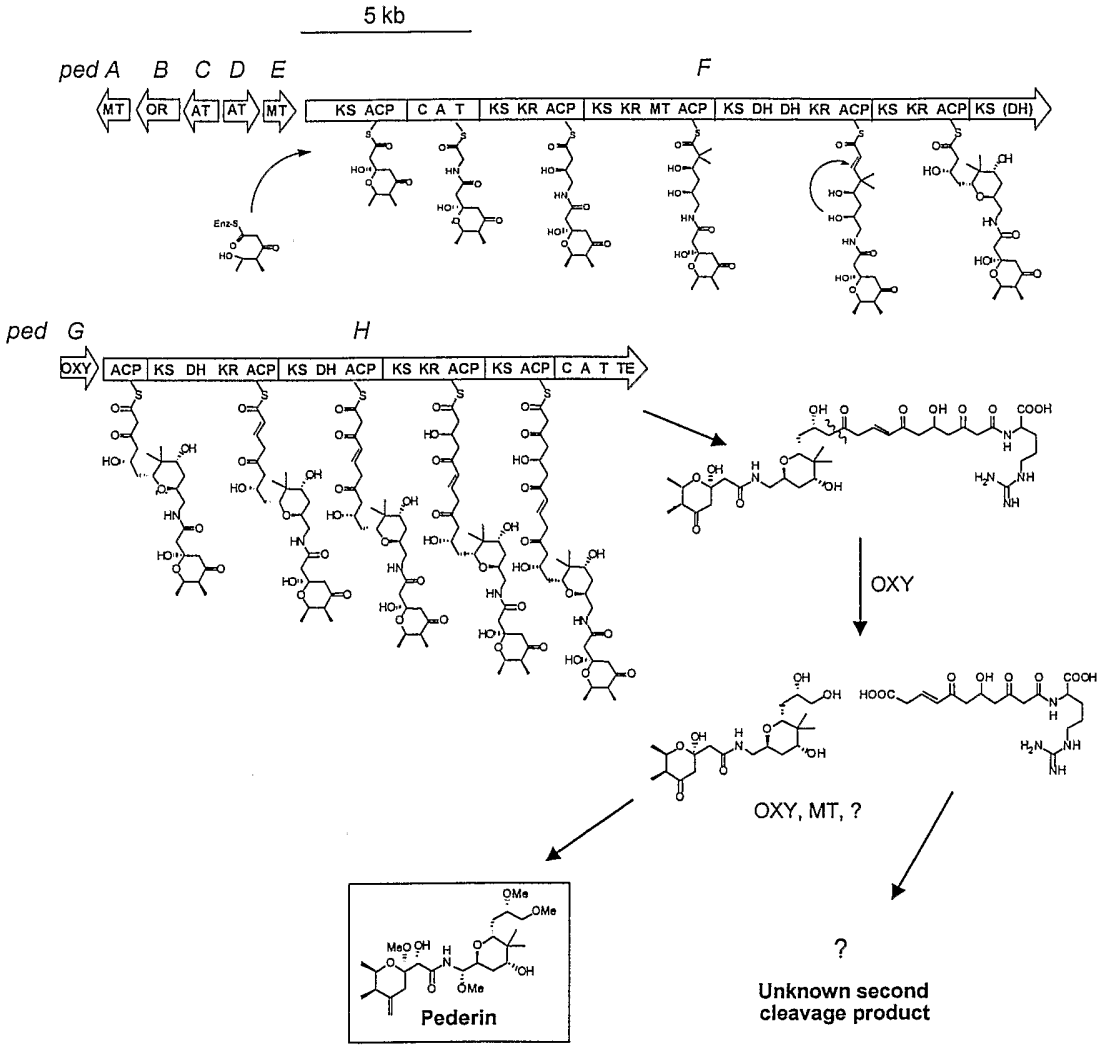

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Fig. 3

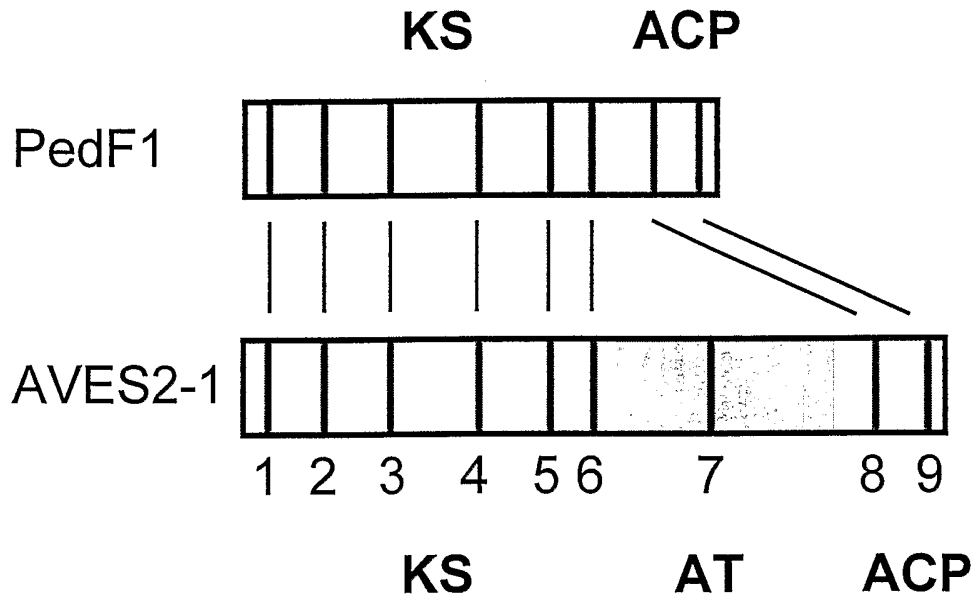



Fig. 4

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tgcaccgggg tgggagcctg                                           50000
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cgttgaaggt agcccgatc                                            52659
```

<210> 2
<211> 312
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedA putative methyltransferase

<400> 2

```
Met Leu Lys Gln Arg Leu Phe Glu Cys Ile Ser Ser His Val Asp Gly
 1               5                  10                  15

Ile Gly Tyr Val Pro Ile Asp Leu Gln Lys Ile Phe Asp Phe Gly Ala
            20                  25                  30

Ala Pro Ser Lys Asp Ala His Gly Ser Glu Ala Ser Asn Thr Asn Ser
        35                  40                  45

Asn Asp Glu Lys Glu Arg Leu Ala Ser His Ile Asn Gln His Tyr Asp
    50                  55                  60

His Thr Phe Phe Ser Glu Gly Leu Thr Ser Leu Leu Val Asp Gly Ser
65                  70                  75                  80

Asp Tyr Arg Asn Ile Gly Tyr Trp Asp Glu Thr Thr Thr Thr Gln His
                85                  90                  95

Glu Ala Ser Glu Arg Leu Gln Asp Ala Leu Leu Asp Phe Ile Pro Glu
            100                 105                 110

Lys Ser Gly Arg Ile Leu Asp Ala Ala Cys Gly Met Gly Ala Ser Thr
        115                 120                 125

Arg His Leu Leu Glu Tyr Tyr Pro Ala Asp Asn Ile Trp Ala Ile Asn
    130                 135                 140

Ile Ser Glu Lys Gln Ile Glu Ala Thr Arg Arg Asn Val Pro Gly Cys
145                 150                 155                 160

His Ala Gln Val Met Asn Ala Val Asp Leu Ser Phe Glu Glu Gly Phe
                165                 170                 175

Phe Asp Asn Ile Leu Cys Ile Glu Ala Ala Phe His Phe Glu Thr Arg
            180                 185                 190

Gln Lys Phe Leu Glu Glu Ala Arg Arg Ile Leu Arg Pro Gly Gly Arg
        195                 200                 205

Leu Val Leu Ser Asp Val Leu Phe Ser Ser Ser Glu Arg Leu Glu Gln
    210                 215                 220

Tyr Pro Ile Phe Pro Ser Ala Ile Asn His Leu Asn Asp Thr Glu Glu
225                 230                 235                 240

Tyr Arg Arg Leu Leu Lys Asp Thr Gly Phe Ser Gln Val Glu Ile Glu
                245                 250                 255

Asp Val Ser Asp Glu Val Trp Gly Ala His Phe Ile Tyr Ala Val Lys
            260                 265                 270

Arg Val His Glu Ala Phe Tyr Lys Gly Glu Leu Asp Ile Val Gln Leu
        275                 280                 285
```

```
Thr Glu Met Leu Trp Ser Tyr Tyr Gln Leu Asn Ser Ile Thr Lys His
    290                 295                 300

Cys Leu Phe Ile Cys Ala Gln Lys
305                 310
```

<210> 3
<211> 464
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedB putative FMN-dependent oxidoreductase

<400> 3

```
Met Ile Thr Ala Glu Lys Leu Gly Ser Arg Leu Phe Lys Glu Asp Tyr
  1               5                  10                  15

Gln Val Arg Tyr Ala Tyr Val Ala Gly Ala Met Ala Lys Ala Ile Gly
             20                  25                  30

Ser Ser Asp Leu Val Ile Ala Met Gly Lys Ala Gly Tyr Val Gly Phe
         35                  40                  45

Tyr Gly Ala Gly Gly Met Thr Leu Glu Glu Ile Glu Thr Ala Ile Gln
     50                  55                  60

Arg Ile Gln Gln Gly Leu Asn Arg Gly Glu Pro Tyr Gly Ile Asn Val
 65                  70                  75                  80

Leu Ala Asn Leu Ala Asp Leu Glu Lys Glu Asn His Leu Ile Asp Leu
                 85                  90                  95

Leu Leu Arg Tyr Gly Val Arg His Ile Glu Ala Ala Ala Phe Met Gln
            100                 105                 110

Ile Thr Pro Ala Leu Val Thr Phe Arg Leu Lys Gly Leu His Leu Asp
        115                 120                 125

Ala Ser Gly Lys Val Gln Ala Ala Asn Thr Leu Met Ala Lys Val Ser
    130                 135                 140

Arg Pro Glu Ile Ala Gln Leu Phe Leu Ser Pro Val Pro Ala Ser Ile
145                 150                 155                 160

Val Ser Leu Leu Leu Thr Glu Gly Arg Ile Asn Glu Gln Glu Ala Glu
                165                 170                 175

Leu Ala Gly Arg Ile Ala Val Ala Ser Asp Val Cys Val Glu Ala Asp
            180                 185                 190

Ser Gly Gly His Thr Asp Met Ala Val Thr Ser Val Val Leu Pro Arg
        195                 200                 205

Ile Ile Arg Leu Arg Asp Thr Leu Gln Gln Gln Tyr Arg Phe Gln Ser
    210                 215                 220

Pro Val Arg Val Gly Ser Ala Gly Gly Ile Gly Thr Pro Glu Ser Ala
225                 230                 235                 240

Ala Ser Ala Phe Met Leu Gly Ala Glu Phe Ile Val Thr Gly Ser Ile
                245                 250                 255
```

```
Asn Gln Cys Thr Val Gln Ala Gly Thr Ser Glu Thr Val Lys Lys Met
            260                 265                 270

Leu Gln Ser Ile Asp Val Gln Asp Thr Ala Tyr Ala Pro Ala Gly Asp
        275                 280                 285

Met Phe Glu Leu Gly Ser Lys Ile Gln Val Leu Lys Lys Ser Val Phe
    290                 295                 300

Phe Pro Val Arg Ala Asn Arg Leu Tyr Asp Leu Trp Arg Asn Asn Gly
305                 310                 315                 320

Ser Leu Glu Gln Leu Ala Pro Thr Val Arg Lys Glu Leu Gln Asp Lys
                325                 330                 335

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

Tyr Arg Lys Ala Ser Pro Ala His Ile Glu Lys Ala Glu Arg Asp Pro
        355                 360                 365

Lys Leu Lys Met Ala Leu Ile Phe Arg Trp Tyr Phe Val His Thr Met
    370                 375                 380

Arg Leu Ala Leu Glu Gly Asn His Glu Gln Arg Thr Asp Tyr Gln Ile
385                 390                 395                 400

His Thr Gly Pro Ala Leu Gly Ala Phe Asn Arg Trp Val Lys Asp Thr
                405                 410                 415

Pro Leu Glu Asp Trp Lys Asn Arg Asp Val Thr Lys Met Ala Asp Tyr
            420                 425                 430

Leu Met Asp Ala Cys Ala Glu Tyr Leu Asn Lys Arg Ile Ala Ser Leu
        435                 440                 445

Thr Thr Asn Arg Met Ser Phe Thr His Asp His Ala Ala Val Ser Thr
    450                 455                 460
```

<210> 4
<211> 334
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedC putative acyltransferase

<400> 4

```
Met Lys Asp Leu Gln Asn Ile Gln Asn Thr His Pro Val Val Trp Met
  1               5                  10                  15

Phe Ser Gly Gln Gly Ser Gln Tyr Phe Gln Met Gly Arg Gln Leu Tyr
            20                  25                  30

Glu Gln Asp Glu Thr Phe His Ala Trp Met Lys Ser Leu Asp Asp Asn
        35                  40                  45

Val Arg Asp Tyr Ile Gly Gln Ser Leu Leu Asp Ile Ile Tyr Asp Thr
    50                  55                  60
```

Gly His Glu Arg Ser Leu Pro Phe Asp Arg Leu Ile His Thr His Pro
65 70 75 80

Ala Leu Phe Met Val Gln Tyr Ala Leu Ala Lys Ser Leu Leu Ala Arg
85 90 95

Gly Leu Pro Ala Pro Asp Phe Leu Ile Gly Ala Ser Leu Gly Glu Phe
100 105 110

Ile Ala Ile Ser Leu Ala Gly Asp Thr His Val Glu Asn Ile Leu Phe
115 120 125

Asn Leu Ile Lys Gln Ala Arg Leu Phe Asp Glu Tyr Cys Asn Ala Gly
130 135 140

Ala Met Leu Leu Val Ile Asp His Ile Asp Thr Phe Ser Thr Thr Pro
145 150 155 160

Ala Phe Ser Lys Asp Cys Glu Leu Ala Gly Ile Asn Phe Asp His Cys
165 170 175

Phe Val Val Ser Gly Pro Arg Thr Gly Ile Leu Gln Thr Arg Lys Ser
180 185 190

Leu Thr Lys Gln Asn Ile Ala Cys Gln Leu Leu Pro Val Ser Ile Ala
195 200 205

Phe His Ser Ser Trp Met Asp Glu Val His Glu Ile Phe Ile Gln Gln
210 215 220

Phe Pro Glu Gln Ile Cys Arg Arg Leu His Thr Pro Val Ile Ser Cys
225 230 235 240

Ala Leu Pro Val Pro Glu Gln Leu Thr Arg Phe Ser Ser Thr Tyr Trp
245 250 255

Trp His Val Ile Arg Gln Pro Ile Ala Phe His Leu Ala Ile Asn Thr
260 265 270

Phe His Gln Ser Ser Pro Asn Ala Val Tyr Leu Asp Leu Gly Pro Ala
275 280 285

Gly Asn Met Ala Ala Ala Thr Lys Tyr Asn Leu Pro Ser Ser Ile His
290 295 300

Tyr Arg Ile Leu Pro Thr Met Thr Pro Phe Gly Arg Asp Leu Glu Asn
305 310 315 320

Ile Glu Ile Ala Arg Leu Arg Leu Leu Glu Leu Asp Gln Arg
325 330

<210> 5
<211> 364
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial
Symbiont of Paederus fuscipes

<220>
<223> PedD putative acyltransferase

<400> 5
Met Lys Ser Tyr Leu Phe Pro Gly Gln Gly Ser Gln His Leu Gly Met
1 5 10 15

PEDERIN.APP

```
Gly Glu Gln Leu Phe Asp Arg Phe Pro Asn Ile Ile Glu Ala Ala Asn
            20                  25                  30

Asp Ile Leu Gly Tyr Ser Ile Lys Thr Leu Cys Leu Glu Asp Pro Gln
        35                  40                  45

Arg Gln Leu Arg Leu Thr Gln Tyr Thr Gln Val Ala Leu Tyr Val Val
    50                  55                  60

Asn Ala Leu Thr Tyr Arg Gln His Leu Gln Gln Gly Gly Gly Leu Pro
65                  70                  75                  80

Asp Phe Val Ala Gly His Ser Leu Gly Glu Tyr Asn Ala Leu Glu Ser
                85                  90                  95

Ala Gly Val Phe Ser Phe Glu Asp Gly Leu Arg Leu Val Gln Lys Arg
            100                 105                 110

Gly Asp Leu Met Ser Gln Ala Pro Arg Gly Ala Met Ala Ala Ile Leu
        115                 120                 125

Gly Ile Ser Ala Asp Ser Val Ala Gly Ile Leu Ala Glu Gln Gly Leu
    130                 135                 140

Thr Arg Ile Asp Ile Ala Asn Tyr Asn Ala Pro Thr Gln Thr Ile Ile
145                 150                 155                 160

Ser Gly Leu Glu Ala Asp Ile Arg Asp Ala Gln Ala Val Phe Glu Ser
                165                 170                 175

Cys Gln Ala Met Tyr Val Pro Leu Asn Thr Ser Gly Ala Phe His Ser
            180                 185                 190

Arg Tyr Met Gln Ser Ala Arg Asp Glu Phe Ala Gln Phe Leu Glu Ala
        195                 200                 205

Phe Glu Phe Arg Asp Pro Gln Ile Pro Val Val Ala Asn Val Thr Ala
    210                 215                 220

Lys Pro Tyr Val Gly Thr Glu Val Val Arg Thr Leu Ala Asp Gln Leu
225                 230                 235                 240

Thr Gly Ser Val Arg Trp Leu Asp Ser Met Arg Phe Leu Leu Asp Gln
                245                 250                 255

Gly Val Thr Glu Phe Arg Glu Leu Gly Pro Gly Asp Val Leu Ser Lys
            260                 265                 270

Leu Val Glu Ser Ile Arg Ser Ser Ala Met Ser Lys Pro Val Ser Glu
        275                 280                 285

Phe Ala Ala Glu Asn Ser Gln Gln Leu Val Asp Glu Trp Asn Arg Thr
    290                 295                 300

Cys Pro Ile Gly Ser Arg Val Arg Val Lys Gly Tyr Asp Asp Ile Leu
305                 310                 315                 320

Val Thr Lys Ser Arg Ala Val Leu Leu Phe Gly His Arg Ala Ala Ile
                325                 330                 335

Tyr Met Glu Asn Tyr Gln Gly Tyr Phe Ala Leu Ser Glu Val Glu Pro
            340                 345                 350

Leu Ile Glu Gln Gln Pro Leu Val Glu Lys Val Trp
        355                 360
```

<210> 6

<211> 273
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedE putative methyltransferase

<400> 6
Met Gln Thr Ala Ile Ala Asp Val Glu Lys Val Ala Thr Leu Tyr Asp
1 5 10 15

Ser Ala Glu Gly Gln Val Gly Pro Ile Leu Phe Gly Gly His Met His
20 25 30

Trp Gly Tyr Trp Asp Glu Val Thr Gly Glu Gly Asn Phe Ala Asn Ala
35 40 45

Ala Glu Arg Leu Ala Gln Ile Met Ile Ala Lys Ala Pro Ile Lys Ala
50 55 60

Gly Gln Lys Phe Ile Asp Met Gly Cys Gly Phe Gly Glu Ser Ala Leu
65 70 75 80

Lys Leu Ala Lys Ala Lys Gly Cys Phe Val Asp Gly Ile Thr Ile Ser
85 90 95

Lys Glu Gln Gln Leu Ser Ala Ile Thr Arg Ala Glu Ala Glu Gln Leu
100 105 110

Gln Glu Arg Val Arg Phe Ile His Gly Ser Ala Leu Asn Ile Pro Cys
115 120 125

Glu Asp Gln Ser Tyr Asp Gly Gly Trp Phe Phe Glu Ser Ile Phe His
130 135 140

Met Gly His Arg Lys Ala Leu His Glu Ala Ala Arg Val Leu Lys Pro
145 150 155 160

Gly Ser Thr Leu Leu Leu Thr Asp Leu Pro Leu Leu Pro Glu Ser Thr
165 170 175

Glu Ala Phe Lys Glu Phe Val Trp Glu His Ile His Ser Arg Phe Val
180 185 190

Ser Arg Glu Asp Tyr Pro Glu Leu Leu Ala Glu Ala Glu Phe Glu Leu
195 200 205

Ile Glu Ile Asp Asp Ile Thr Asp Asn Val Met Pro Trp Leu Glu Pro
210 215 220

Lys Leu Lys Glu Ala Ile Glu Leu His Arg Pro Gln Val Glu Ala Ile
225 230 235 240

Ile Pro Asn Asp Thr Glu Lys Ala Ile Asp Asp Trp Leu Tyr Leu Phe
245 250 255

Glu Tyr Met Ser Glu Asn Leu Gly Tyr Met Ile Val Met Ala Lys Lys
260 265 270

Leu

<210> 7

<211> 8601
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedF mixed type I polyketide synthase/nonribosomal peptide synthase

<400> 7

```
Met Ser Val Asn Ile His Gln Gln Leu Lys Glu Ile Glu Asp Ala Leu
 1               5                  10                  15

Leu Asn Asn Ser Gly Val Ala Val Thr Leu Asp Val Glu Ser Ser Asp
            20                  25                  30

Lys Leu Arg Lys Arg Glu Ala Glu Asp Ser Pro Glu Ala Ile Ala Ile
        35                  40                  45

Val Gly Leu Ser Gly Tyr Phe Pro Gln Ser Ala Ser Val Asp Glu Phe
    50                  55                  60

Trp Arg His Leu Asp Gln Asp Ala Thr Leu Ile Glu Glu Ile Pro Asp
65                  70                  75                  80

Ser Arg Phe Asp Trp Arg Lys Val Phe Asp Pro Thr Gly Glu Arg Pro
                85                  90                  95

Gly Ser Ser Cys Ser Lys Trp Gly Gly Phe Ile Pro Asp Ile Arg Gly
            100                 105                 110

Phe Asp Pro Ala Phe Phe Asn Ile Pro Gly Ala Glu Ala Ile Thr Leu
        115                 120                 125

Asp Pro Arg Gln Arg Leu Leu Leu Met Ser Ala Tyr Gln Thr Leu Asn
    130                 135                 140

Asp Ala Gly Tyr Ala Ser Gln Ala Leu Arg Gln Ser Lys Thr Gly Val
145                 150                 155                 160

Phe Val Ala Leu Gln Asp Asn Glu Tyr Leu Gln Leu Leu Ala Asp Ala
                165                 170                 175

Gly Ile Asp Pro Gly Gln Trp Tyr Ala Gln Thr Cys Leu Leu Ala Asn
            180                 185                 190

Arg Ile Ser Tyr Phe Phe Asp Trp Arg Gly Thr Ser Glu Val Val Asp
        195                 200                 205

Ala Gln Cys Pro Gly Ala Ala Val Ala Ile His Arg Ala Val Ser Ala
    210                 215                 220

Leu Arg Asn Gly Glu Ile Glu Leu Ala Leu Val Gly Ala Ala Asn Leu
225                 230                 235                 240

Leu Leu Arg Pro Glu Pro Phe Val Leu Leu Ser Glu Ser Gly Gln Leu
                245                 250                 255

Ser Glu Ser Ala Ser Val His Ser Phe Gly Ala Gln Ala Gln Gly His
            260                 265                 270

Leu Arg Ala Glu Gly Val Cys Ser Leu Leu Leu Lys Pro Leu Thr Lys
        275                 280                 285

Ala Leu Ala Asp Gly Asp Pro Ile Tyr Ala Ser Ile Lys His Ser Ala
```

290 295 300

Val Asn Phe Asn Gly Gln Gly Gly Ala Ser Ile Ala Ala Pro Asn Val
305 310 315 320

Asp Ser His Val Asp Leu Ile Lys Ser Cys Tyr Gln Gln Ala Arg Val
325 330 335

Asp Pro Arg Gln Val Arg Tyr Ile Glu Ala Gln Gly Met Gly Asn Val
340 345 350

Leu Ala Asp Leu Val Glu Trp Gln Ala Phe Asn Arg Ala Leu Thr Asp
355 360 365

Ile Ala Arg Gln Gln Arg Val Ser Leu Pro Pro Gly Asn Cys Leu Ile
370 375 380

Ser Thr Leu Lys Pro Met Met Gly His Met Glu Ser Ala Ser Ala Leu
385 390 395 400

Gly Ala Leu Phe Lys Val Ile Arg Ser Leu His Thr Arg Thr Ile His
405 410 415

Lys Ile Ala His Phe Thr Gln Tyr His Pro Asp Met Asp Tyr Gln Gly
420 425 430

Gln Pro Cys Ala Ile Ala Gly Glu Thr Val Ala Trp Pro Gln Met Glu
435 440 445

Gly Leu Arg Leu Ala Gly Ile His Cys Tyr Gly Met Gly Gly Val Asn
450 455 460

Ala His Leu Leu Val Glu Glu Ser Val Ala Gly Tyr Tyr Asp Asp Ser
465 470 475 480

Glu Leu Gly Thr Val Ser Ser Leu Leu Glu His Val Leu Ile Val Leu
485 490 495

Ser Ala Lys Thr Ser Glu Ser Leu Arg Met Met Ala Arg Arg Leu Gln
500 505 510

Gln Phe Leu Gln Lys Ala Asp Ala Val Pro Ala Leu Arg Asp Ile Ala
515 520 525

Tyr Thr Leu Gln Val Gly Arg Asp Ala Phe Glu His Arg Leu Ala Leu
530 535 540

Val Val Asp Ser Gln Gln Gln Leu Ile Glu Gly Leu Glu Cys Tyr Leu
545 550 555 560

Glu Glu Arg Gln Pro Ser Gln Gly Glu Gly Ala Val Tyr Gln Gly Gln
565 570 575

Val Ala Ser Glu Ser Gln Ser Leu Pro Phe Thr Glu Asp Asp Leu Ala
580 585 590

Ala Val Ala Arg Cys Trp Val Ala Gly Gly Ala Val Leu Trp Pro Val
595 600 605

Pro Val Gly Pro Lys Lys Pro Arg Arg Val Arg Leu Pro Ala Tyr Pro
610 615 620

Phe Asp Lys Arg Ala Tyr Trp Val Asp Ser Ala Val Val Glu Ala Glu
625 630 635 640

Arg Ala Pro Asn Ser Lys Ala Pro Ala Ser Met Leu Ser Gly Glu Arg
645 650 655

Ser Ile Gly Asp Tyr Leu Arg Ala Lys Leu Gly Glu Val Leu Gln Val
660 665 670

Pro Val Glu Arg Ile Asp Pro Gln Gln His Leu Tyr Asp Leu Gly Val
675 680 685

Asp Ser Ile Val Ala Met Lys Leu Leu Arg Asn Leu Ala Arg Ala Phe
690 695 700

Gly Ile Pro Val Arg Gly Arg Asp Leu Leu Gln Tyr Ser Thr Val Gln
705 710 715 720

Ala Leu Ser Arg His Leu Ala Gln Tyr Leu Asp Arg Asp Gln Val Glu
725 730 735

Ser Val Gly Glu Asp Glu Glu Pro Arg Gln Leu Met Ala Ser Arg Arg
740 745 750

Cys Ser Leu Ser Glu Gly Gln Lys Gly Leu Trp Val Leu Gln Gln Leu
755 760 765

Ala Ser Arg Met Thr Ala Tyr Asn Ile Pro Leu Cys Val Arg Ile Ala
770 775 780

Gln Val Leu Asp Ile Thr Ala Leu Arg Glu Ala Phe Ala Trp Leu Leu
785 790 795 800

Glu Gln Tyr Pro Ile Leu Thr Ser Val Phe Val Gln Asp Asn Gly Glu
805 810 815

Leu Phe Arg Glu Cys His Val Ala Ala Ala Leu Pro Phe Trp Gln Glu
820 825 830

Glu Thr Asn Thr Leu Asp Gln Ala Gln Val Arg Met Arg Leu Lys Cys
835 840 845

Leu Ala Lys Gln Pro Phe Glu Leu Glu Lys Gly Pro Leu Val Arg Leu
850 855 860

His Val Leu Ser Cys Gly Glu His Asp His Tyr Leu Leu Leu Cys Val
865 870 875 880

His His Ile Val Phe Asp Gly Gly Ser Phe Leu Pro Val Phe Gly Gly
885 890 895

Leu Leu Gln Thr Tyr Gln Leu Ile Ser Gln Gly Gln Thr Leu Ala Lys
900 905 910

Ser Thr Arg Thr Gly Glu Gln Tyr Ala Asp Phe Val Leu Trp Glu Gln
915 920 925

Arg Met Leu Ala Ser Ala Glu Gly Gln Arg His Arg Ala Tyr Trp Lys
930 935 940

Arg Gln Leu Ser Gly Glu Leu Pro Val Leu Ser Leu Phe Thr Asp Asn
945 950 955 960

Pro Arg Asp Ala Gly Gln Arg Phe Thr Gly Asp Thr Tyr Gly Phe Gln
965 970 975

Leu Asp Val Asn Leu Ser Arg Lys Ile Arg Asn Phe Ala Lys Gln Gln
980 985 990

Arg Leu Asn Leu Ser Thr Leu Phe Leu Ala Leu Phe Lys Leu Leu Leu
995 1000 1005

His Arg Tyr Ser Gly Gln Ser Glu Leu Ile Ile Gly Met Pro Glu Gln
1010 1015 1020

```
Gly Arg Ser Glu Glu Arg Phe Glu Gly Val Val Gly Tyr Phe Val Asn
1025                1030                1035                1040

Met Leu Pro Ile Arg Ser Arg Gly Val Gly Ser Lys Pro Leu Ala Glu
                1045                1050                1055

Phe Ala Arg Asp Leu Gln Leu Ser Met Ala Asp Ala Met Asp His Ala
            1060                1065                1070

Val Tyr Pro Phe Pro Val Met Val Arg Asp Leu Gly Arg Ala Pro Ala
        1075                1080                1085

Glu Asp Leu Ala Pro Ile Phe Gln Val Ala Phe Glu Tyr Gln Asn Val
    1090                1095                1100

Phe Ser Ala Gln Asp Leu Arg Leu Phe Asn Gln Ser Tyr Arg Glu Ser
1105                1110                1115                1120

Leu Gly Val Thr Phe Leu Glu Glu Phe Val Gln Glu Gly Glu Tyr Glu
                1125                1130                1135

Leu Ala Leu Glu Val Arg Glu Gly Glu Ile Asp Phe Ala Leu Asn Leu
            1140                1145                1150

Lys Phe Asn Pro Thr Leu Tyr Arg Met Ala Thr Ile Ala Arg Met Ala
        1155                1160                1165

Glu His Leu Leu Ile Leu Ala Glu His Ala Ile Asp Ala Pro Leu Ser
    1170                1175                1180

Pro Cys Arg Glu Leu Thr Met Leu Ser Glu Arg Glu Arg His Leu Leu
1185                1190                1195                1200

Leu His Glu Trp Asn Ala Thr Thr Glu Pro Tyr Pro Ser Cys Cys Phe
                1205                1210                1215

His Gln Leu Phe Glu Lys Gln Ala Arg Ala Met Pro Gln Ala Ile Ala
            1220                1225                1230

Ala Ile Phe Gln Glu Gln Arg Leu Ser Tyr Ala Glu Leu Asp Glu Arg
        1235                1240                1245

Ser Glu Arg Leu Ala Ile Tyr Leu Gln Gln Cys Gly Val Gln Pro Asn
    1250                1255                1260

Arg Ile Val Ala Val Cys Leu Glu Arg Ser Leu Asp Met Leu Val Ala
1265                1270                1275                1280

Leu Ile Gly Ile Ala Arg Ser Gly Ala Ala Trp Leu Pro Leu Asp Pro
                1285                1290                1295

Asn Tyr Pro Asp Asp Arg Leu Arg Phe Met Leu Ser Asp Ser Gln Ala
            1300                1305                1310

Gln Leu Leu Leu Thr Glu Glu Gly Leu Arg Asp Lys Thr Ala Ala Ile
        1315                1320                1325

Val Ser Gln Ala Val Gly Glu Arg Leu Gln Ile Val Ala Met Asp Gly
    1330                1335                1340

His Trp Pro Glu Ile Glu Arg Gln Ala Arg Thr Ser Glu Leu Gln Met
1345                1350                1355                1360

Arg Asp Asp Pro Arg Asn Leu Ala Tyr Val Ile Tyr Thr Ser Gly Ser
                1365                1370                1375

Thr Gly Ile Pro Lys Gly Val Met Ile Glu His Arg Ser Leu Val Asn
```

1380 1385 1390

Phe Leu Tyr Ser Met Leu Asn Arg Pro Gly Leu Arg Ala Asn Asp Arg
1395 1400 1405

Leu Leu Ala Val Thr Thr Tyr Cys Phe Asp Ile Ala Gly Leu Glu Leu
1410 1415 1420

Leu Val Pro Leu Leu Cys Gly Ala Cys Cys Cys Ile Cys Ala Thr Asp
1425 1430 1435 1440

Lys Leu Asn Asp Ser Glu Ala Leu Gln Gly Glu Ile Glu Arg Leu Gln
1445 1450 1455

Pro Thr Val Met Gln Ala Thr Pro Ser Thr Trp Thr Leu Leu Phe His
1460 1465 1470

Gly Gly Trp Asn Asn Arg Gln Gly Val Lys Ile Leu Cys Gly Gly Glu
1475 1480 1485

Pro Leu Pro Pro Ala Leu Arg Gln Arg Phe Ala Glu Ser Ala Ser Gln
1490 1495 1500

Thr Trp Asn Leu Phe Gly Pro Thr Glu Thr Thr Ile Trp Ser Thr Val
1505 1510 1515 1520

Ser Arg Leu Asp Leu Thr Lys Asp Ser Val Asp Ile Gly Thr Pro Ile
1525 1530 1535

Ala Asn Thr Arg Val Tyr Ile Leu Asn Gly Asp Asp Gln Leu Val Pro
1540 1545 1550

Ile Gly Val Pro Gly Glu Leu Cys Ile Ala Gly Asp Gly Leu Ala Arg
1555 1560 1565

Gly Tyr Leu Gly Asn Pro Gln Leu Thr Ala Gln Lys Phe Ile Ala Asn
1570 1575 1580

Pro Phe Glu Pro Gly Asn Arg Leu Tyr Arg Thr Gly Asp Leu Ala Arg
1585 1590 1595 1600

Trp Arg Glu Asp Gly Val Leu Glu His Leu Gly Arg Leu Asp Gln Gln
1605 1610 1615

Val Lys Val Arg Gly Tyr Arg Ile Glu Leu Ser Asp Ile Glu Thr Trp
1620 1625 1630

Leu Asn Arg His Pro Ser Val Ala Gln Ser Leu Val Val Gly His Glu
1635 1640 1645

Gln Ala Gly Gly Met Leu Leu Val Ala Tyr Tyr Val Lys Asp Ser Glu
1650 1655 1660

Trp Ala Ser Val Ser Ser Thr Glu Leu Arg Asn Tyr Leu Ala Glu His
1665 1670 1675 1680

Leu Pro Glu Tyr Met Val Pro Ala Phe Phe Arg Ala Leu Ser Asn Met
1685 1690 1695

Pro Leu Met Pro Asn Gly Lys Val Asp Arg Lys Ala Leu Ser Ala Arg
1700 1705 1710

Glu Leu Val Ala Glu Glu Ser Glu Ser Gly Gly Arg Leu Pro Cys Ser
1715 1720 1725

Asp Ile Glu Arg Glu Val Leu Asp Ile Trp Arg Ser Leu Leu Ala Val
1730 1735 1740

Glu Gly Ile Gly Val Ser Val Gly Phe Phe Glu Val Gly Gly Asn Ser
1745 1750 1755 1760

Ile Leu Ser Val Met Leu Ala Gln Gln Ile Ser Glu Ala Phe Gly Ile
1765 1770 1775

Arg Phe Ala Ala Thr Asp Leu Phe Lys Tyr Pro Thr Ile Arg Asp Ile
1780 1785 1790

Ser Leu Leu Ile Gly Glu Thr Arg Glu Arg Ser Glu Thr Lys Thr Gly
1795 1800 1805

Thr Met Ala Gly Asp Gly Ser Gly Lys Ala Asp Ser Val Leu Gln Ala
1810 1815 1820

Gln Ala Arg Gly Arg Gln Ser Val Thr Gly Tyr Pro Asp Tyr Tyr Gln
1825 1830 1835 1840

Asp Ser Leu Ala Ile Ile Gly Ile Ser Cys Asn Met Pro Gly Ala Arg
1845 1850 1855

Thr Leu Arg Gln Phe Trp Glu Asn Leu Arg Gln Gly Lys Glu Ser Ser
1860 1865 1870

Thr Arg Leu Ser Glu Arg Glu Leu Arg Arg Ala Gly Val Pro Glu Glu
1875 1880 1885

Leu Ile Arg His Pro Asp Phe Val Pro Met Gln Tyr Ser Met Glu Gly
1890 1895 1900

Lys Glu Leu Phe Asp Pro Asp Phe Phe Asn Leu Ser Ala Lys Asn Ala
1905 1910 1915 1920

Leu Phe Met Asp Pro Gln Tyr Arg Val Leu Leu Gln Gln Ala Trp Gln
1925 1930 1935

Ala Ile Glu Asp Ala Gly Tyr Val Ala Gln Asp Ile Pro Glu Thr Ala
1940 1945 1950

Val Phe Met Ser Ala Ser Asn Asn Phe Tyr Lys Thr Leu Leu His Ser
1955 1960 1965

Ala Gly Ala Val Glu Thr Thr Asp Glu Tyr Ala Ala Trp Ile Ala Gly
1970 1975 1980

Gln Gly Gly Thr Ile Pro Thr Met Ile Ser Tyr Gln Leu Gly Phe Lys
1985 1990 1995 2000

Gly Pro Ser Phe Ala Val His Ser Asn Cys Ser Ser Ser Leu Val Gly
2005 2010 2015

Leu Tyr Leu Ala Ser Gln Cys Leu Arg Leu Lys Glu Ala Lys Tyr Ala
2020 2025 2030

Leu Val Gly Gly Ala Thr Leu Phe Pro Val Ala Gly Thr Gly His Leu
2035 2040 2045

Tyr Thr Pro Asp Met Asn Leu Ser Ser Asp Gly His Cys Lys Ala Phe
2050 2055 2060

Asp Ala Asp Ala Asp Gly Leu Val Gly Gly Glu Gly Ala Val Val Leu
2065 2070 2075 2080

Met Val Arg Lys Ala Leu Asp Ala Ile Arg Asp Gly Asp Pro Ile Tyr
2085 2090 2095

Ala Leu Ile Arg Gly Val Ala Val Asn Asn Asp Gly Ser Asp Lys Val
2100 2105 2110

Gly Phe Tyr Ala Pro Ser Val Asn Gly Gln Ala Ala Val Ile Gln Lys
2115 2120 2125

Ala Leu Asp Ile Thr Gly Val Asp Pro Gln Ser Val Ala Tyr Val Glu
2130 2135 2140

Ala His Gly Thr Gly Thr Arg Leu Gly Asp Pro Val Glu Ile Met Ala
2145 2150 2155 2160

Leu Asn Glu Val Tyr Arg Arg Tyr Thr Glu Lys Arg Gln Phe Cys Arg
2165 2170 2175

Ile Gly Ser Val Lys Pro Asn Ile Gly His Leu Asp Thr Val Ala Gly
2180 2185 2190

Leu Ala Gly Met Leu Lys Val Val Leu Ser Leu Lys His Ala Glu Phe
2195 2200 2205

Phe Pro Ser Ile Asn Tyr Arg Glu Pro Asn Pro Ala Ile Asp Phe Thr
2210 2215 2220

Ser Ser Pro Phe Glu Val Val Thr Gln Leu Thr Pro Trp Pro Ala Gly
2225 2230 2235 2240

Asn Glu Pro Arg Arg Ala Ala Leu Ser Ser Phe Gly Ile Gly Gly Thr
2245 2250 2255

Asn Thr His Ala Ile Leu Glu Glu Tyr Val Ala Arg Thr Asp Ala Asp
2260 2265 2270

Arg Trp Glu Asp Asn Gln Gly Val Pro Leu Pro Glu Gln Val Val Val
2275 2280 2285

Leu Ser Ala Lys Thr Gln Asp Arg Leu Gln Ala Ser Val Val Lys Leu
2290 2295 2300

Tyr Glu Tyr Leu Leu Arg Ala Gln Ala Thr Thr Glu Gln Leu Asp Leu
2305 2310 2315 2320

Gln Asp Leu Ala Tyr Thr Leu Gln Val Gly Arg Gln Ala Met Asp Trp
2325 2330 2335

Arg Val Ala Phe Leu Val Lys Asp Leu His Asp Leu Ser Glu Lys Leu
2340 2345 2350

Glu Arg Phe Leu Gln Gly Asp Ser Leu Val Gln Asp Cys Phe Gln Gly
2355 2360 2365

Arg Val Ala Thr Ser Val Met Asp Ala Ala Ala Thr Pro Leu Pro Val
2370 2375 2380

Ala Gln Asp Arg Glu Gln Ala Ala Ile Ala Lys Ala Trp Val Thr Gly
2385 2390 2395 2400

Arg Leu Val Asp Trp Lys Glu Leu Pro Arg Arg Gly Thr Pro His Arg
2405 2410 2415

Ile Ser Leu Pro Thr Tyr Pro Phe Ala Glu Glu Arg Tyr Trp Val Glu
2420 2425 2430

Met Pro Glu Leu Pro Gly Arg Ser Glu Ser Glu Glu Gln Thr Lys Glu
2435 2440 2445

Trp Ile Glu Gly Gln Ala Glu Arg Thr Leu Leu Val Val His Pro Leu
2450 2455 2460

Trp Gln Ala His Ala Val Val Lys Arg Glu Arg Pro Leu Ile Phe Thr

2465 2470 2475 2480

Glu His Leu Val Trp Leu Cys Gly Phe Asp Val Ser Leu Val Arg Ala
2485 2490 2495

Leu Thr Arg Cys Leu Pro Glu Gly Tyr Arg Ile Val Ser Leu Thr Pro
2500 2505 2510

Glu Gly Arg Gly Val Ala Gln Arg Tyr Gln Ser Leu Cys Leu Gln Met
2515 2520 2525

Leu Glu Arg Leu Gln Lys Cys Ile Gly Asp Ala Thr Lys Leu Thr Leu
2530 2535 2540

Ile Gln Leu Val Leu Pro Asp Glu Gly Glu Tyr Ser Leu Phe Ser Gly
2545 2550 2555 2560

Leu His Ala Leu Leu Lys Thr Val Ser Gln Glu Asn Pro Gln Lys Val
2565 2570 2575

Ala Gln Leu Ile Arg Val Ser Ser Gly Glu Thr Ala Arg Ser Leu Ala
2580 2585 2590

Asp Lys Leu Ile Glu Asn Thr Phe Ala Pro Asp Asp Ser His Leu Arg
2595 2600 2605

Tyr Ala Pro Ser Arg Met Arg Leu Asp Trp Gln Thr Leu Arg Gln Glu
2610 2615 2620

Glu Thr Val Leu Asp Met Pro Trp Lys Glu Gly Gly Val Tyr Leu Leu
2625 2630 2635 2640

Thr Gly Gly Ala Gly Gly Leu Gly Val Leu Phe Ala Glu Glu Ile Ala
2645 2650 2655

Arg Arg Val Arg Lys Ala Thr Leu Val Leu Val Gln Arg Ser Pro Leu
2660 2665 2670

Ser Ala Ala Ala Arg Arg Ala Glu Arg Ile Ala Ala Leu Arg Ser Asp
2675 2680 2685

Ser Ile Thr Val Ile Cys Arg Gln Ala Asp Ile Ser Cys Ala Thr Ser
2690 2695 2700

Cys Ser Gln Leu Ile Ala Asp Ile Ala Glu Gln Cys Gly Thr Ile Asp
2705 2710 2715 2720

Gly Ile Leu His Thr Ala Gly Val Val Arg Asp Ala Phe Ile Leu Asn
2725 2730 2735

Lys Ser Ala Ala Glu Phe Gln Glu Val Leu Ala Ala Lys Val Ala Gly
2740 2745 2750

Thr Val Asn Leu Asp Arg Ala Thr Gln Ala Leu Gly Leu Asp Phe Phe
2755 2760 2765

Leu Leu Phe Ser Ser Ala Ala Ala Ala Phe Gly Asn Ala Gly Gln Ala
2770 2775 2780

Asp Tyr Cys Ala Ala Asn Ala Phe Leu Asp Ala Tyr Ala Tyr Glu Arg
2785 2790 2795 2800

Asn Gln Arg Val Ala Ala Gly Gln Cys Arg Gly His Thr Leu Ser Val
2805 2810 2815

Gly Trp Pro Leu Trp Arg Asp Gly Gly Met Arg Leu Asn Glu Glu Ala
2820 2825 2830

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Gln Gln Ala Met Arg Tyr Thr Thr Gly Leu Val Pro Met Asp Ser Arg
2835 2840 2845

Ser Gly Ile Arg Gly Leu Tyr Arg Ser Leu Ala Ala Arg Leu Gly His
2850 2855 2860

Thr Leu Val Leu Glu Gly Asp Ala Thr Ala Ile Gly Ser Leu Leu Ala
2865 2870 2875 2880

Asn Gly Thr Ala Arg Ser Val Ser Glu Leu Gly Val Pro Ala Ala Asn
2885 2890 2895

Gly Asn Asp Leu Asp Glu Thr Leu Lys Asp Lys Thr Ile Tyr Gln Leu
2900 2905 2910

Lys Arg Leu Leu Ala Gln Val Ile Gly Arg Ala Val Glu Arg Ile Glu
2915 2920 2925

Ser Cys Glu Pro Met Asp Arg Tyr Gly Leu Asp Ser Ile Ala Ile Thr
2930 2935 2940

Gln Leu Asn Arg Lys Leu Glu Glu Gln Phe Gly Gly Leu Ser Lys Thr
2945 2950 2955 2960

Leu Phe Tyr Gln Tyr Gln Thr Val Glu Ala Leu Ala Glu Tyr Leu Val
2965 2970 2975

Leu Asn Lys Thr Val Ser Cys Arg Ala Trp Thr Gly Leu Arg Asp Glu
2980 2985 2990

Ser Val Leu Val Ala Asp Ala Ala Arg Arg Gly Leu Pro Leu Pro Glu
2995 3000 3005

Thr Ala Pro Val Val Glu Arg Asn Val Leu Pro Val Gly Asn Ala Val
3010 3015 3020

Gln Glu Pro Ile Ala Ile Ile Gly Leu Ser Gly Arg Tyr Pro Gln Ala
3025 3030 3035 3040

Glu Thr Leu Glu Glu Phe Trp Glu Asn Leu Gln Ala Gly Lys Asp Cys
3045 3050 3055

Val Ser Glu Ile Pro Glu Asp Arg Trp Arg Leu Glu Asn Phe Phe His
3060 3065 3070

Pro Asp Pro Lys Glu Ala Val Ala Gln Gly Lys Ser Tyr Ser Lys Trp
3075 3080 3085

Gly Gly Phe Ile Glu Gly Phe Ala Glu Phe Asp Pro Leu Phe Phe Asn
3090 3095 3100

Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Glu Arg Leu Phe
3105 3110 3115 3120

Leu Gln Cys Ala Trp His Val Leu Glu Asp Ala Gly Tyr Thr Arg Gln
3125 3130 3135

Ser Leu Gln Gln Gly Gly His Lys Val Gly Val Phe Val Gly Ile Thr
3140 3145 3150

Lys Thr Gly Phe Asp Leu Tyr Gly Pro Glu Leu Trp His Arg Gly Glu
3155 3160 3165

Arg Leu Phe Pro His Thr Ser Phe Ser Ser Val Ala Asn Arg Val Ser
3170 3175 3180

Tyr Cys Leu Asn Leu Lys Gly Pro Ser Met Pro Ile Asp Thr Met Cys
3185 3190 3195 3200

Ser Ser Ser Leu Thr Ala Ile His Glu Ala Cys Gln His Leu Arg Gln
3205 3210 3215

Gly Asp Cys Asp Met Ala Ile Val Gly Gly Val Asn Met Tyr Val His
3220 3225 3230

Pro Ser Thr Tyr Val Gly Leu Cys Ser Ala Tyr Met Leu Ser Arg Asp
3235 3240 3245

Gly Gln Cys Arg Ser Phe Gly Gln Gly Gly Asn Gly Phe Val Pro Gly
3250 3255 3260

Glu Gly Ile Gly Ala Val Leu Leu Lys Pro Leu Ala Arg Ala Gln Glu
3265 3270 3275 3280

Asp Asp Asp Leu Ile His Ala Val Ile Arg Ser Ser Ser Val Asn His
3285 3290 3295

Gly Gly Arg Thr Asn Gly Tyr Thr Val Pro Asn Pro Asn Ala Gln Ala
3300 3305 3310

Glu Leu Ile Gly Asp Cys Leu Lys Lys Ala Gly Val Asp Ala Arg Ser
3315 3320 3325

Ile Gly Tyr Ile Glu Ala His Gly Thr Gly Thr Glu Leu Gly Asp Pro
3330 3335 3340

Ile Glu Val Asn Gly Leu Ala Gln Ala Phe Gly Gln Glu Ala Gly Glu
3345 3350 3355 3360

His Ser Arg Cys Phe Leu Gly Ser Val Lys Ser Asn Leu Gly His Leu
3365 3370 3375

Glu Ala Ala Ala Gly Met Ala Gly Leu Thr Lys Val Ile Leu Gln Met
3380 3385 3390

Arg His Gly Gln Ile Val Pro Ser Leu His Ala Gln Val Leu Asn Pro
3395 3400 3405

Asn Ile Asp Phe Ala Ala Thr Pro Phe Thr Val Pro Gln Gln Leu Val
3410 3415 3420

Glu Trp Arg Arg Thr Ile Leu Gln Glu Ser Gly Arg Ser Arg Glu Leu
3425 3430 3435 3440

Pro Arg Arg Ala Gly Leu Ser Ser Phe Gly Ala Gly Gly Ser Asn Ala
3445 3450 3455

His Leu Ile Leu Glu Glu Tyr Ile Ala Pro Glu Pro Ala Gln Arg Pro
3460 3465 3470

Arg Phe Gly Glu Pro Gly Thr Ala Ala Val Ile Leu Leu Ser Ala Lys
3475 3480 3485

Thr Pro Glu Cys Leu Arg Arg Val Val Ser Asp Leu Leu Ala Phe Ile
3490 3495 3500

Glu Ser Glu Leu Thr Arg Thr Val Asp Pro Asp Gln Thr Leu Phe Asp
3505 3510 3515 3520

Ile Ala Tyr Thr Leu Gln Val Gly Arg Glu Ala Leu Asp Glu Arg Leu
3525 3530 3535

Gly Leu Val Ala Val Ser Leu Gln Glu Leu Ser Arg Gln Leu Ala Ala
3540 3545 3550

Phe Leu Gly Glu Glu Ala Glu Gln Pro Leu Leu Tyr Arg Gly Arg Val

3555 3560 3565

Gln Arg Asn Lys Asp Ala Leu Gln Ala Leu Ala Asn Asp Glu Glu Phe
3570 3575 3580

Gln Glu Thr Val Asp Lys Trp Leu Ala Arg Arg Lys Tyr Ser Lys Leu
3585 3590 3595 3600

Leu Lys Phe Trp Val Thr Gly Leu Ser Val Asp Trp Thr Arg Leu Tyr
3605 3610 3615

Ser Asp Val Leu Pro Arg Arg Ile Arg Leu Pro Val Tyr Pro Phe Val
3620 3625 3630

Arg Gln Arg Tyr Trp Leu Asp Ala Tyr Ser Leu Glu Pro Met Val Pro
3635 3640 3645

Thr Glu Gln Pro Ser Val Val Pro Val Asp Ala Glu Val Ser Gly Ser
3650 3655 3660

Asp Ala Gly Arg Glu Ala Asp Leu Met Met Leu Gly Pro Val Trp Asp
3665 3670 3675 3680

Ala Val Val Glu Gln Gly Thr Glu Asp Phe Pro Pro Ala Gly Ala Arg
3685 3690 3695

Ile Ala Met Val Gly Gly Ser Glu Ala Gln Lys Arg Ala Val Phe Glu
3700 3705 3710

Gln Tyr Pro Lys Ala Leu Glu Leu Ala Ala Gly Ala Val Gly Ala Ala
3715 3720 3725

Ser Ile Ala Arg Leu Gly Arg Leu Asp His Val Val Trp Phe Ala Pro
3730 3735 3740

Ala Ser Gln Thr Gln Gly Met Ala Asp Glu Arg Ile Ile Asp Ala Gln
3745 3750 3755 3760

Arg Asp Gly Val Leu Ala Leu Phe Gln Leu Val Lys Val Leu Leu Ala
3765 3770 3775

Glu Gly Tyr Gly Val Ala Glu Phe Gly Met Thr Val Ile Thr Thr Gln
3780 3785 3790

Ala Leu Ala Thr Cys Asp Thr Glu Arg Ile Asp Pro Thr His Ala Ala
3795 3800 3805

Val His Gly Leu Val Gly Ser Leu Ala Lys Glu Tyr Pro Lys Trp Arg
3810 3815 3820

Leu Arg Ala Leu Asp Ile Asp Ala Arg Ala Glu Trp Pro Val Pro Gly
3825 3830 3835 3840

Leu Trp Arg Leu Leu Pro His Thr Arg Gly Glu Ser Arg Val Trp Arg
3845 3850 3855

Gly Cys Glu Trp Leu Arg Gln Arg Leu Val Ala Leu Asn Gly Met Pro
3860 3865 3870

Val Ala Lys Gly Arg Ala Tyr Arg Arg Gln Gly Val Tyr Val Val Ile
3875 3880 3885

Gly Gly Ala Gly Gly Leu Gly Met Thr Trp Ser Arg Met Met Ile Arg
3890 3895 3900

Asp His Gln Ala Gln Ile Val Trp Leu Gly Arg Ser Ala Lys Asp Ala
3905 3910 3915 3920

Thr Val Arg Ala Lys Leu Asp Glu Val Ala Asp Asp Gly Leu Ala Pro
3925 3930 3935

Asp Tyr Trp Gln Ile Asp Ala Arg Asp Ala Asp Ala Leu Arg Gln Thr
3940 3945 3950

Phe Arg Gln Val Arg Glu Arg Tyr Gly Gln Ile His Gly Val Ile Val
3955 3960 3965

Ser Thr Leu Gly Asp Tyr Asp Gln Ser Val Ala Gln Met Ser Glu Ala
3970 3975 3980

Leu Phe Arg Glu Ile Leu Ser Ser Lys Leu Asp Ile Gly Val Arg Leu
3985 3990 3995 4000

Ser Gln Cys Leu Arg Asp Glu Ala Leu Asp Phe Val Val Phe Phe Ser
4005 4010 4015

Ser Met Val Ala Phe Gly Arg Ser Gly Gly Met Ala Ala Tyr Ser Ala
4020 4025 4030

Ala Cys Ala Phe Asn Asp Thr Phe Ala Arg Gln Leu Gly Asn Glu Leu
4035 4040 4045

Ala Cys Ala Val Lys Val Ile Asn Trp Gly Tyr Trp Asn Leu Gly Gly
4050 4055 4060

Gly Thr Arg Ile Ser Ala Ala Leu Lys Arg Leu Val Glu Gln Arg Gly
4065 4070 4075 4080

Val Arg Pro Ile Glu Ala Arg Glu Gly Leu Cys Ala Leu Ala Val Leu
4085 4090 4095

Leu Asp Gly Pro Leu Arg Gln Leu Ala Val Thr Arg Thr Cys Gln Pro
4100 4105 4110

Ala Ala Ile Glu Thr Phe Glu Ala Gly Gln Trp Leu Thr Val Lys Ala
4115 4120 4125

Gly Thr His Ser Cys Phe Ala Asn Val Glu Ala Tyr Gln Pro Thr Gln
4130 4135 4140

Pro Met Pro Gln Glu Ser Pro Asp Ala Ala Arg Leu Asn Leu Trp Ile
4145 4150 4155 4160

Val Arg Leu Leu Phe Val Gln Leu Gln Ser Leu Gly Leu Phe Gln Glu
4165 4170 4175

Thr Gly Phe Gln Asn Ala Thr Ala Ile Arg Arg Gln Ala Gly Ile Val
4180 4185 4190

Asp Lys Tyr Glu Arg Trp Trp Arg Glu Ser Leu Asn Ile Leu Ala Glu
4195 4200 4205

His Gly Tyr Leu Arg Leu Ala Gly Asp Glu Val Ala Arg Ile Ala Ser
4210 4215 4220

Ala Asp Glu Ile Gly Glu Ser Ser Arg Glu Arg Leu Trp Gln Glu Trp
4225 4230 4235 4240

Arg Glu Cys Lys Thr Arg Phe Leu Glu Gln Pro Gln Thr His Thr Leu
4245 4250 4255

Ala Val Leu Val Glu Asp Cys Leu Ser Gln Leu Pro Glu Val Leu Arg
4260 4265 4270

Gly Thr Arg Leu Val Thr Asp Ile Leu Phe Pro Asn Gly Ser Met Glu
4275 4280 4285

Lys Ile Glu Gly Leu Tyr Lys Asn Asn Leu Ile Cys Asp Tyr Phe Asn
4290 4295 4300

Asp Val Val Ala Gly Val Ala Gln Ala Tyr Ile Gln Arg Arg Leu Glu
4305 4310 4315 4320

Asn Glu Pro Asn Ala Glu Ile Arg Leu Leu Glu Val Gly Ala Gly Thr
4325 4330 4335

Gly Gly Thr Thr Ser Thr Val Leu Pro Gln Leu Asn Leu Trp Arg Ala
4340 4345 4350

Phe Ile Ala Glu Tyr Ala Tyr Thr Asp Leu Ser Lys Ser Phe Phe Asn
4355 4360 4365

His Ala Arg Leu Arg Tyr Gly Thr Asp Tyr Pro Tyr Ile Thr Tyr Arg
4370 4375 4380

Leu Leu Asn Ile Glu Glu Pro Leu Ile Gln Gln Asp Ile Glu Ile Gly
4385 4390 4395 4400

Thr Tyr Asp Ile Leu Ile Ala Thr Asn Val Leu His Ala Thr Arg Asn
4405 4410 4415

Met Arg Asn Thr Leu Arg Asn Ala Lys Ala Ala Leu Arg Gly Asn Gly
4420 4425 4430

Ile Leu Ile Leu Asn Glu Ile Ser Asp Lys Thr Ile Phe Ala Ser Val
4435 4440 4445

Leu Phe Gly Leu Ile Asp Gly Trp Ser Leu Ala Glu Asp Glu His Trp
4450 4455 4460

Arg Ile Pro Gly Ser Pro Gly Leu Phe Ala Glu Asn Trp Gln Ala Leu
4465 4470 4475 4480

Leu Leu Gln Glu Gly Phe Asp Lys Val Ser Phe Pro Ala Gln Val Ala
4485 4490 4495

His Asp Leu Gly Gln Gln Ile Ile Val Ala Gln Thr Asn Gly Val Ile
4500 4505 4510

His Gln His Gly Ala Gly Pro Val Leu Glu Thr Ala Val Ala Asp Lys
4515 4520 4525

Pro Leu Pro Thr Leu Glu Ser Ala Val Ala Ala Glu Arg Leu Val Asp
4530 4535 4540

Arg Ser Ser Val Pro Ala Arg Arg Gln Asp Val Ala Ala Arg Val Arg
4545 4550 4555 4560

Glu Leu Ile Leu Asp Ser Leu Ala Gln Ala Leu Ser Ile Gly Arg Glu
4565 4570 4575

Gln Ile Glu Gln Asp Ile Pro Phe Ser Asp Tyr Gly Ile Asp Ser Ile
4580 4585 4590

Leu Gly Val Gly Phe Val Gln Arg Leu Asn Asp Glu Leu Gly Leu Ser
4595 4600 4605

Leu Asn Thr Thr Leu Leu Phe Asp Tyr Thr Thr Val Gln Arg Leu Ala
4610 4615 4620

Glu His Ile Val Ala Glu Tyr Gly His Thr Leu Asp Val Pro Ala Ala
4625 4630 4635 4640

Leu Pro Gly Pro Glu Leu Ser Val Ser Glu Pro Ala Met Asp Ile Pro

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4645 4650 4655

Leu Pro Ala Val Gln Ala Val Pro Ser Ser Leu Pro Arg Arg Glu Ala
4660 4665 4670

Val Val Gln Thr Asp Gly Ile Ala Val Ile Gly Met Ala Gly Gln Phe
4675 4680 4685

Pro Gly Ala Asp Ser Val Asp Ala Leu Trp Gln Asn Met Val Ala Gly
4690 4695 4700

Val Asn Pro Val Thr Glu Leu Ser Glu Leu Tyr Leu Pro Tyr His Ala
4705 4710 4715 4720

Tyr Ser Pro Glu Lys Gln Pro Gly Lys Ser Tyr Cys Lys Trp Gly Gly
4725 4730 4735

Ala Leu Gln Gly Arg Asp Cys Phe Asp Pro Leu Phe Phe Asn Ile Ser
4740 4745 4750

Pro Arg Glu Ala Glu Ser Met Asn Pro His Gln Arg Leu Ile Leu Gln
4755 4760 4765

Glu Ser Trp Lys Ala Leu Glu Asp Ala Gly Tyr Ala Pro Arg Ser Leu
4770 4775 4780

Ser Asp Ser Arg Thr Gly Ile Phe Val Gly Ala Glu Pro Ser Ala Tyr
4785 4790 4795 4800

Val His Glu Ser Phe Val Gly Ala Ser Asp Ala Ile Val Ala Ser Arg
4805 4810 4815

Leu Ser Tyr Phe Leu Asp Leu Lys Gly Pro Ala Phe Val Val Asn Thr
4820 4825 4830

Gly Cys Ser Ser Ser Gly Val Ala Leu His Leu Ala Cys Glu Ser Leu
4835 4840 4845

Arg Asn Gly Glu Thr Glu Val Ala Leu Ala Gly Gly Val Phe Ala Val
4850 4855 4860

Met Gly Gln Thr Ile Leu Val Gly Leu Ala Gln Thr Asp Met Leu Ser
4865 4870 4875 4880

Arg Thr Gly Cys Cys Cys Thr Phe Asp Ala Asp Ala Asp Gly Met Val
4885 4890 4895

Met Ser Glu Gly Val Gly Met Val Val Leu Lys Arg Leu Asp Gln Ala
4900 4905 4910

Leu Ser Asp Gly Asp Thr Ile Tyr Gly Val Ile Arg Ala Ser Gly Ile
4915 4920 4925

Asn Gln Asp Gly Ala Ser Asn Gly Ile Thr Ala Pro Ser Gly Ile Ala
4930 4935 4940

Gln Gln Gln Leu Ile Thr Asp Val Tyr Arg Arg Tyr Ala Ile Asp Pro
4945 4950 4955 4960

Arg Arg Ile Thr Tyr Val Glu Ala His Gly Thr Gly Thr Arg Leu Gly
4965 4970 4975

Asp Pro Val Glu Ala Asn Ala Leu Val Arg Ala Phe Arg Ser Phe Thr
4980 4985 4990

Glu Ser Thr Gly Tyr Cys Ala Val Gly Ser Ile Lys Ser His Ile Gly
4995 5000 5005

His Thr Ser Ser Ser Ser Gly Val Ile Gly Leu Ile Ser Ile Leu Leu
5010 5015 5020

Cys Leu Lys His His Gln Leu Pro Gly Met Arg His Phe Lys Arg Leu
5025 5030 5035 5040

Asn Pro Leu Ile Glu Phe Glu Arg Ser Pro Phe Tyr Val Asn Ala Arg
5045 5050 5055

Met Met Pro Trp Arg Ser Gly Ser Gly Glu Pro Leu Met Ala Ala Leu
5060 5065 5070

Asn Ser Phe Gly His Ser Gly Thr Asn Val His Leu Val Val Glu Glu
5075 5080 5085

Phe Val Arg Ser Asn Ser Glu Asp Pro Arg Val Leu Asp Asp Val Ser
5090 5095 5100

Ser Thr Ala Gln Pro Glu Leu Ile Leu Leu Ser Thr Lys Asp Ala Glu
5105 5110 5115 5120

Arg Leu Ser Glu Val Leu Asn Asn Leu Ala His Phe Val Arg Gln Ala
5125 5130 5135

Gln Asn Gln Pro Ala Asp Leu Glu Arg Leu Ser Leu Ala Asp Leu Ala
5140 5145 5150

Tyr Thr Leu Gln Thr Gly Arg Glu Ala Met Glu Gln Arg Val Ala Leu
5155 5160 5165

Leu Val Gly Asp Leu Ala Gly Leu Leu Glu Ala Leu Ser Ala Leu Arg
5170 5175 5180

Glu Glu Arg Pro Cys Pro Val Ser Val Trp Ser Gly Arg Val Glu Pro
5185 5190 5195 5200

Gly Pro Ser Arg Gly Ala Glu Thr Val Asn Ala Asp Gln Pro Ala Ala
5205 5210 5215

Glu Leu Leu Gln Arg Ile Pro Gln Trp Leu Ala Glu Gly Ala Leu Asp
5220 5225 5230

Glu Leu Ala Gln Ala Trp Val Ala Gly Ala Pro Ile Asp Trp Cys Gln
5235 5240 5245

Leu Arg Arg Arg Arg Pro Pro Arg Arg Val His Leu Pro Ser Tyr Pro
5250 5255 5260

Phe Ala Arg Glu Arg Tyr Trp Arg Ser Glu Pro Ala Val His Ser Pro
5265 5270 5275 5280

Val Val Ala Ala Gly Leu His Pro Leu Val Gln Arg Asn Thr Ser Thr
5285 5290 5295

Leu Asp Arg His Cys Phe Glu Ser Ser Phe Asp Gly Ser Glu Phe Phe
5300 5305 5310

Phe Arg Asp His Arg Val Gln Gly Gln Pro Leu Leu Pro Ala Val Ala
5315 5320 5325

Tyr Leu Glu Trp Ala Arg Ala Ala Ala Gln Ile Ala Leu Gly Asn Ala
5330 5335 5340

Cys Pro Asp Val Ala Leu Lys Leu Ser Asn Val Val Trp Ile Gly Pro
5345 5350 5355 5360

Leu Leu Ala Glu Gln Pro Ile Val Gly Thr Ile Thr Leu Gln Ala Arg
5365 5370 5375

Glu Asp Arg Gly Ile Asp Tyr Gln Ile Ser Ser Val Ser Ala Ala Gly
5380 5385 5390

Gln Gln Pro Val Val His Cys Gln Gly Ile Ala Thr Thr Glu Thr Glu
5395 5400 5405

Lys Glu Ala Ala Pro Val Leu Asp Leu Asp Ala Leu Arg Ser Arg Leu
5410 5415 5420

Thr Gln Lys Glu Ile Gly Val Glu Arg Cys Tyr Ala Ala Leu Glu Ala
5425 5430 5435 5440

Ala Gly Val Asn His Gly Pro Ala Met Arg Gly Leu Gln Ala Val Ser
5445 5450 5455

Arg Asn Ala Glu Glu Val Leu Ala Thr Leu Arg Leu Pro Ala Glu Thr
5460 5465 5470

Val Gly Glu Ala Ser Ala Tyr Val Leu His Pro Ala Ile Leu Asp Ala
5475 5480 5485

Ala Leu Gln Ala Ser Ile Ala Leu Thr Leu Arg Asp Asp Glu Val Glu
5490 5495 5500

Pro Ser Pro Glu Thr Ser Pro Arg Pro Val Leu Leu Pro Phe Ala Leu
5505 5510 5515 5520

Glu Ser Leu Arg Val Tyr Ala Pro Cys Cys Ala Ser Met Trp Ala Trp
5525 5530 5535

Ile Arg Leu Val Ala Val Glu His Ala Gly Gln Ala Leu Gln Arg Leu
5540 5545 5550

Asp Val Asp Ile Cys Thr Lys Glu Gly Glu Val Cys Val Ala Leu Arg
5555 5560 5565

Gly Phe Thr Ser Arg Ser Leu Pro Pro Ser Gly Ala Thr Glu Ser Arg
5570 5575 5580

Ala Ser Ala Ser Ala Ala Ser Ser Thr Leu Val Ser Thr Glu Gly Val
5585 5590 5595 5600

Ser Arg Phe Lys Gly Glu Glu Phe Phe Leu Arg Asp His Ser Gly Met
5605 5610 5615

Leu Pro Ala Ala Val Tyr Leu Glu Met Val Arg Ala Phe Ala Glu Gly
5620 5625 5630

Lys His Glu Arg Lys Ile Thr Gly Leu Ser His Val Val Trp Pro Lys
5635 5640 5645

Val Leu Leu Val Ser Gly Glu Gly Arg Glu Val Arg Thr Cys Leu Thr
5650 5655 5660

Asn Val Asp Arg Ser Ala Phe Leu Ile Ser Ala Cys Glu Gln Ser Ser
5665 5670 5675 5680

Glu Gly Pro Gln Glu Val Thr Tyr Cys Gln Gly Asn Leu Leu Leu Pro
5685 5690 5695

Glu Val Met Glu Glu Pro Gly Ala Ala Leu Ala Ile Glu Ala Ile Ala
5700 5705 5710

Tyr Arg Cys Pro Ser Val Leu Glu Ala Lys Gln Cys Asp Arg Leu Leu
5715 5720 5725

Gln Ser Thr His Gly Pro Ala Leu Met Ser Val Gln Gln Leu Arg Tyr

5730 5735 5740

Ser Asp Arg Glu Ala Leu Ala Leu Leu Gln Leu Pro Asp Glu Leu Gln
5745 5750 5755 5760

Met Gly Trp Asp Asp Tyr Gly Trp His Pro Ser Leu Leu Asn Gly Ala
5765 5770 5775

Ile Leu Ala Ser Val Val Trp Cys Leu Ala Arg Ala Pro Arg Ser Arg
5780 5785 5790

Ala Gly Leu Pro Met Pro Phe Ser Leu Asp Arg Leu Arg Val Phe Gln
5795 5800 5805

Pro Phe Glu Arg Gln Met Gln Ala Tyr Val Arg Arg His Gly Ser Ala
5810 5815 5820

Arg Ser Leu Gly Glu Asn Leu Glu Lys Val Asp Ile Asp Leu Leu Asp
5825 5830 5835 5840

Ser Gln Gly Arg Cys Leu Ala Ser Leu Glu Gly Phe Thr Leu Val Phe
5845 5850 5855

Ala Pro Asp Ala Asn Arg Leu Val Tyr Ala Ile Pro Gln Trp Val Glu
5860 5865 5870

Gln Ala Leu Pro Ala Arg Val Ala Ala Ser Ala Pro Leu Ala Val Gln
5875 5880 5885

Ala Pro Val Phe Ile Leu Ala Gly Ala Gly Glu Pro Leu Arg Arg Ala
5890 5895 5900

Leu His Asp Ser Trp Pro Asp Ala Leu Leu His Glu Leu Pro Glu Ser
5905 5910 5915 5920

Ala Phe Glu Val Gly Asp Gly Leu Arg Gln Ala Val Val Glu Val Phe
5925 5930 5935

Gly Trp Cys Arg Arg Leu Leu Pro Tyr Lys Gly Ala Ala Leu Gln Pro
5940 5945 5950

Leu Leu Val Leu Leu Pro Glu Ala Glu Arg Glu Val Thr Pro Gln Ala
5955 5960 5965

Leu Leu Gly Gly Ala Leu Ser Gly Leu Leu Lys Thr Val Arg Leu Glu
5970 5975 5980

His Pro Arg Ile Thr Ala Arg Ile Ile Ser Tyr Pro Val Asp Asp Thr
5985 5990 5995 6000

Val Thr Ala Gly Trp Met Lys Val Leu Ala Ala Glu Ile Ala Ser Pro
6005 6010 6015

Glu Gly Asp Val Glu Ile Arg Tyr Asp Arg Gln Ala Arg Arg His Ile
6020 6025 6030

Lys Val Leu His Glu Ile Thr Leu Ser Ala Gly Glu His Gly Asp Ser
6035 6040 6045

Leu Phe Arg Pro Asp Asp Val Val Trp Leu Thr Gly Gly Leu Gly Gly
6050 6055 6060

Ile Gly Arg Gln Ile Ala Arg Tyr Leu Gly Val Glu Arg Arg Val Arg
6065 6070 6075 6080

Leu Ala Leu Ser Gly Arg Ser Ala Ile Asp Asp Lys Gly Glu Arg Phe
6085 6090 6095

Leu Gln Glu Leu Arg Arg Glu Gly Ala Val Val Ser Tyr Leu Arg Val
6100 6105 6110

Asp Val Ala Asp Ala Asp Ala Val Gly Arg Ala Leu Leu Ala Ile Glu
6115 6120 6125

Gln Glu His Gly Gly Leu Thr Gly Ile Ile His Ser Ala Gly Ile Ile
6130 6135 6140

Ala Asp Asp Tyr Leu Asn Ser Lys Thr Thr Ala Gln Phe Glu Gln Val
6145 6150 6155 6160

Leu Lys Pro Lys Val Ser Gly Val Val Asn Leu Asp Ala Ala Thr Ala
6165 6170 6175

Asn Arg Ser Leu Arg Tyr Leu Leu Val Phe Ser Ser Ile Ala Gly Val
6180 6185 6190

Leu Gly Asn Met Gly Gln Ala Asp Tyr Ala Ala Ala Asn Gly Phe Leu
6195 6200 6205

Asp Ser Phe Ala His Tyr Arg Glu Ala Leu Val Arg Gln Gly Leu Arg
6210 6215 6220

Ser Gly Lys Ser Leu Ser Leu Asn Trp Pro Leu Trp Arg Glu Gly Gly
6225 6230 6235 6240

Met Gln Met Gly Arg His Gly Glu Ala Leu Met Gln Gln Ala Thr Gly
6245 6250 6255

Met Leu Ala Met Glu Ser Ala Gln Gly Phe Glu Ala Leu Glu Ala Gly
6260 6265 6270

Leu Arg Ser Ala Gln Ala Gln Ile Leu Val Ala Phe Gly Glu Pro Val
6275 6280 6285

Ser Ile Arg Asn Arg Leu Leu Thr Phe Arg Met Asp Ala Pro Glu Pro
6290 6295 6300

Pro Ala Pro Ser Val Val Glu Met Asp Arg Ala Pro Gly Glu Glu Val
6305 6310 6315 6320

Gly Glu Gln Glu Thr Gln Gln Leu Val Arg Ser Val Glu Ala Glu Leu
6325 6330 6335

Ile Arg Ile Val Ala Phe Val Gln Arg Ile Pro Ala Glu Lys Ile Asn
6340 6345 6350

Val Arg Arg Asp Ile Ser Ala Tyr Gly Phe Asp Ser Ile Ser Phe Thr
6355 6360 6365

Glu Phe Ala Asn Ala Leu Asn Lys Ala Tyr Lys Leu Ser Leu Met Pro
6370 6375 6380

Thr Leu Phe Phe Glu Ile Ala Ser Leu Ala Asp Leu Ala Gly His Leu
6385 6390 6395 6400

Leu Thr Gln His Arg Pro Ala Leu Leu Glu Lys His Ala Val Asp Val
6405 6410 6415

Glu Lys Pro Ser Glu Cys His Ser Gly Val Ala Ala Gln Ile Pro Ile
6420 6425 6430

Pro Thr Met Pro Lys Ser Glu Cys Ile Ala Thr Leu Pro Leu Leu Pro
6435 6440 6445

Val Gly Ser Ile Glu Pro Glu Pro Gln Ala Asp Leu Glu Ala Val Ala
6450 6455 6460

Val Ile Gly Met Ala Gly Lys Phe Pro Gly Cys Glu Asp Leu Glu Asp
6465 6470 6475 6480

Phe Trp Thr Cys Leu Gln Ser Cys Gln Asp Leu Ile Ser Glu Val Pro
6485 6490 6495

Glu Gln Arg Trp Asp Trp Arg Arg Phe Tyr Gly Asp Pro His Gln Glu
6500 6505 6510

Pro Gly Lys Thr Lys Ile Lys Trp Gly Gly Phe Val Ala Asp Ala Asp
6515 6520 6525

Cys Phe Asp Ala Arg Phe Phe Gly Ile Ser Pro Val Glu Ala Glu Val
6530 6535 6540

Met Asp Pro Gln Leu Arg Leu Phe Leu Glu Thr Val Trp Ala Ala Leu
6545 6550 6555 6560

Glu Asp Ala Gly Tyr Pro Ala Gly Arg Leu Ala Gly Ser Arg Thr Gly
6565 6570 6575

Val Phe Ala Gly Val Ala Thr Ala Asp Tyr Lys Asp Leu Leu Ile Glu
6580 6585 6590

Ala Arg Ala Arg Gly Leu Val Gln Thr Pro Ser Glu Pro Phe Pro Phe
6595 6600 6605

Met Ile Ala Asn Arg Ile Ser Tyr Trp Phe Asn Phe Asn Gly Pro Ser
6610 6615 6620

Glu Ala Ile Asp Thr Ala Cys Ser Ser Ser Leu Ile Ala Val His Lys
6625 6630 6635 6640

Ala Ile Glu Ser Leu Arg Leu Gly Ser Cys Glu Met Ala Leu Ala Gly
6645 6650 6655

Gly Val Asn Val Leu Gly Ser Pro Arg Ile Thr Ile Ala Ser Ser Gln
6660 6665 6670

Ala Gly Met Leu Ser Glu Asp Gly Arg Cys Met Thr Phe Asp Glu Arg
6675 6680 6685

Ala Asn Gly Tyr Val Arg Ser Glu Gly Val Ala Ile Leu Leu Leu Lys
6690 6695 6700

Pro Leu Arg Lys Ala Ile Ala Asp Asn Asp Arg Ile His Gly Leu Ile
6705 6710 6715 6720

Arg Gly Ser Gly Glu Asn His Gly Gly Arg Ser Ala Ser Pro Thr Ala
6725 6730 6735

Pro Asn Gly Asn Ala Gln Lys Arg Leu Leu Val Asp Ile Tyr Ser Arg
6740 6745 6750

Ala Asp Ile Asp Pro Arg Thr Ile Ser Tyr Ile Glu Ala His Gly Thr
6755 6760 6765

Gly Thr Val Leu Gly Asp Pro Val Glu Val Asn Gly Leu Lys Ala Ala
6770 6775 6780

Phe Gln Glu Leu Tyr Gln Ser Arg Gly Leu Asp Val Pro Glu Gln Pro
6785 6790 6795 6800

His Cys Gly Leu Asn Ser Val Lys Ala Asn Val Gly His Leu Glu Ala
6805 6810 6815

Ala Ala Gly Ala Val Gly Ile Val Lys Val Leu Leu Met Leu Lys His

6820 6825 6830

Arg Lys Ile Pro Gly Asn Pro His Leu Arg Arg Pro Asn Pro Tyr Leu
6835 6840 6845

Gln Leu Glu Gly Thr Pro Phe Tyr Leu Val Arg Glu Thr Leu Asp Trp
6850 6855 6860

Pro Gln Pro Thr Asp Val Arg Gly Asn Pro Leu Ala Arg Arg Ala Gly
6865 6870 6875 6880

Val Ser Ser Phe Gly Val Gly Gly Ser Asn Ala His Val Ile Leu Glu
6885 6890 6895

Glu Tyr Gln Glu Pro Glu Arg Gln Gly Trp Gly Ser Glu Pro Ala Tyr
6900 6905 6910

Pro Ala Leu Ile Val Leu Ser Ala Lys Asp Glu Glu Arg Leu Val Cys
6915 6920 6925

Val Ala Gln Arg Leu Leu Arg Phe Ile Arg Asp Tyr Gly Ser Glu Leu
6930 6935 6940

Tyr Leu His Asp Ile Ala Tyr Thr Leu Gln Val Gly Arg Glu Ala Met
6945 6950 6955 6960

Pro Arg Arg Leu Ala Leu Ala Val Thr Ser Leu Ala Gln Leu Ala Asp
6965 6970 6975

Arg Leu Gln Thr Trp Leu Glu Gln Pro Thr Gln Thr Glu Gly Val Gln
6980 6985 6990

Gln Gly Leu Val Thr Gln Glu Ala Glu Glu Gln Phe Asp Thr Val Leu
6995 7000 7005

Gly Asp Glu Asp Arg Ala Ala Ala Val Glu Arg Trp Val Glu Lys Gly
7010 7015 7020

Gln Tyr Glu Lys Leu Leu Asp Ala Trp Thr Arg Gly Trp Ala Ile Asp
7025 7030 7035 7040

Trp Asn Val Leu Tyr Cys Thr Asp Thr Arg Pro Arg Arg Ile Gly Leu
7045 7050 7055

Pro Thr Tyr Pro Phe Ala Arg Arg Arg Tyr Trp Val Ala Ser Val Pro
7060 7065 7070

Gln Ala Glu Asp Arg Gly Asn Ser Thr Leu Ser Glu Pro Glu Pro Glu
7075 7080 7085

Gln Arg Ser Ala Lys Ser Asp Leu Leu Thr Phe Glu Glu Tyr Trp Ala
7090 7095 7100

Glu Val Pro Leu Ala Ala Pro Ala Thr Asp Arg Val Lys Thr Leu Leu
7105 7110 7115 7120

Cys Leu Cys Ser Asp Pro Glu His Gln Arg Arg Ile Ala Glu Gln Xaa
7125 7130 7135

Asp Ser Arg Asp Pro Gly Val Gln Leu Ile Phe Ile Glu Gln Gly Asp
7140 7145 7150

Ala Pro Ala Glu Pro Asp Glu Ala Arg Gln Arg Ile Asp Pro Leu Gln
7155 7160 7165

Pro Ser Ser Tyr Ser Arg Ala Leu Thr Thr Ile Ala Lys Ala Leu Gly
7170 7175 7180

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Arg Val Asp Ala Leu Leu Tyr Leu Trp Pro Cys Glu Asp Arg Arg Trp
7185 7190 7195 7200

Ile Ser Asn Val Leu Pro Val Leu His Leu Leu Gln Ala Leu Tyr Glu
7205 7210 7215

Thr Gly Leu Arg Pro Arg Lys Leu Leu Leu Ser Gly Glu Tyr Ala Asp
7220 7225 7230

Ala Leu Glu Arg Cys His Leu Asp Ser Trp Val Ala Phe Glu Arg Ser
7235 7240 7245

Leu Gly Val Val Met Pro Glu Thr Gln Val Ala Val Val Phe Arg Glu
7250 7255 7260

Arg Ala Ala Asp Thr Gly Glu Ser Ser Pro Thr Trp Asp Trp Leu Glu
7265 7270 7275 7280

Val Leu Val Ala Glu Leu Phe Ala Glu Lys Leu Arg Ser Ala Cys Tyr
7285 7290 7295

Arg Gln Gly Val Arg His Val Pro Leu Ile Arg Pro Leu Ala Trp Gln
7300 7305 7310

Pro Gly Ser Ala Ser Pro Phe Lys Gln Gly Gly Val Tyr Leu Ile Thr
7315 7320 7325

Gly Gly Gly Gly Gly Leu Gly Met Ile Val Ala Glu His Leu Ala Thr
7330 7335 7340

Val Tyr Ala Ala Arg Leu Val Leu Ser Gly Arg Ser Ser Ser Leu Ala
7345 7350 7355 7360

Ala Glu Lys Tyr Glu Leu Leu Gln Ala Arg Gly Ala Gln Val Leu Tyr
7365 7370 7375

Val Gly Ala Asp Val Thr Asp Val His Ala Met Gln Glu Val Val Asp
7380 7385 7390

Gln Ala Arg Arg His Phe Ser Pro Leu Asn Gly Val Leu His Ile Ala
7395 7400 7405

Gly Leu Asn Gly Thr Ala Glu Val Leu Lys Ala Glu Ala Asp Ala Phe
7410 7415 7420

Gln Arg Val Leu Asp Ala Lys Ile Thr Gly Ser Gln Val Leu Asp Gln
7425 7430 7435 7440

Val Leu Arg Arg Glu Ser Leu Asp Phe Ile Cys Tyr Phe Cys Ser Ser
7445 7450 7455

Ser Ala Ile Ile Gly Asp Phe Gly Ser Cys Asp Tyr Ala Leu Gly Asn
7460 7465 7470

Arg Phe Gln Ser Ala Tyr Ala Leu Tyr Arg Ala Gln Met Val Glu Ser
7475 7480 7485

Ser Ala Leu Ser Gly Lys Thr Leu Ala Ile Asn Trp Pro Leu Trp Gln
7490 7495 7500

Asp Gly Gly Leu Gly Val Gly Asp Ala Glu Gln Thr Arg Phe Tyr Leu
7505 7510 7515 7520

Gln Ser Ser Gly Gln Arg Ser Leu Cys Ser Gln Glu Ala Leu Ala Leu
7525 7530 7535

Leu Glu Gln Leu Leu Thr Gln Asp Arg Ala Gln Cys Leu Val Trp Ala
7540 7545 7550

Gly Gln Pro Asp Arg Leu Leu Arg Trp Val Asn Gln Glu Pro Leu Glu
7555 7560 7565

Ala Ala Thr Val Thr Val Pro Glu Pro Val Arg Ala Ala Lys Ala Val
7570 7575 7580

Ala Glu Arg Ala Glu Leu Gly Gly Gly Leu Asp Leu Gln Gln Cys Leu
7585 7590 7595 7600

Leu Arg Asp Leu Lys Thr Lys Ile Cys Glu Leu Leu Gly Thr Gln Tyr
7605 7610 7615

Asn Glu Leu Glu Asn His Ala Asn Leu Val Asp Phe Gly Phe Asp Ser
7620 7625 7630

Ile Ser Leu Ala Glu Phe Ser Arg Val Leu Ser Arg Phe Tyr Ser Leu
7635 7640 7645

Asp Ile Ser Pro Ser Val Phe Phe Ser His Ser Thr Leu Asn Arg Leu
7650 7655 7660

Thr Ala Tyr Phe Leu Ala Glu His Arg Gln Thr Leu Glu Gly Phe Tyr
7665 7670 7675 7680

Gln Gln Pro Gln Pro Ala Gly Pro Glu His Ala Pro Val Pro Thr Glu
7685 7690 7695

Val Ala Gln Val Ser Val Pro Val Pro Val Thr Ala Leu Leu Pro Thr
7700 7705 7710

Gly Thr Ser Ile Gly Ser Ala Ser Gln Gly Gln Asp Glu Pro Ile Ala
7715 7720 7725

Ile Ile Gly Leu Ser Gly Arg Phe Pro Gln Ala Arg Thr Ile Glu Glu
7730 7735 7740

Leu Trp Arg Ile Leu Glu Gln Gly Arg Asp Ala Ile Gln Glu Val Pro
7745 7750 7755 7760

Ile Asp Arg Phe Asp Trp Arg Ser Tyr Tyr Ser Pro Ser Gln Glu Met
7765 7770 7775

Ser Lys Ser Asn Ser Lys Trp Gly Gly Cys Ile Pro Gly Ile Ala Glu
7780 7785 7790

Phe Asp Pro Leu Phe Phe Glu Ile Ser Pro Leu Glu Ala Glu Arg Met
7795 7800 7805

Asp Pro Arg Gln Arg His Leu Met Gln Glu Ala Trp Leu Ala Leu Glu
7810 7815 7820

Asp Ala Gly Tyr Gly Pro Glu Gln Leu Glu Cys Asn Lys Ile Ser Met
7825 7830 7835 7840

Phe Val Gly Val Glu Glu Gly Cys Asp Tyr Gln Arg Arg Leu Thr Gln
7845 7850 7855

Gln Thr Ser Leu Thr Ser Met His Asn Gly Ile Leu Ala Ser Arg Leu
7860 7865 7870

Ala Tyr Phe Leu Asn Leu Lys Gly Pro Val Met Ala Ile Asn Thr Ala
7875 7880 7885

Cys Ser Ser Ala Leu Val Ala Val His Gln Ala Cys Gln Ser Leu Arg
7890 7895 7900

His Gly Glu Cys Asp Thr Ala Ile Ala Ala Gly Val Asn Leu Leu Val

7905 7910 7915 7920

Ala Pro Glu Ala Tyr Val Gly Met Thr Gln Ala Gly Met Leu Ser Pro
7925 7930 7935

Asp Gly Lys Cys Tyr Val Phe Asp Lys Arg Ala Asn Gly Leu Val Pro
7940 7945 7950

Gly Glu Ala Val Ala Val Val Val Leu Lys Arg Leu Ser Lys Ala Leu
7955 7960 7965

Ala Asp Gly Asp Pro Ile Lys Ala Leu Ile Arg Gly Ser Gly Ile Asn
7970 7975 7980

Tyr Asp Gly Lys Thr Asn Gly Ile Thr Ala Pro Ser Gly Ala Ser Gln
7985 7990 7995 8000

Thr Glu Leu Leu Glu Gly Ile Tyr Arg Gln Cys Ala Leu Gln Pro Gln
8005 8010 8015

Asp Ile Ser Tyr Ile Val Thr His Gly Thr Gly Thr Gln Leu Gly Asp
8020 8025 8030

Pro Ile Glu Ile Asn Ala Leu Tyr Asp Val Phe Lys Gly Lys Thr Asp
8035 8040 8045

Lys Gln Gly Phe Cys Ala Leu Thr Ser Ile Lys Ser Asn Leu Gly His
8050 8055 8060

Thr Phe Ala Ala Ser Gly Leu Val Ser Leu Ile Ser Leu Val Leu Ala
8065 8070 8075 8080

Ile Arg His Arg Thr Ile Pro Ser Ser Leu His Cys Glu Gln Lys Asn
8085 8090 8095

Asp Tyr Ile Arg Trp Gln Glu Ser Pro Phe Tyr Val Asn Thr Arg Lys
8100 8105 8110

Lys His Trp Glu Cys Ala Leu Gly Gln Pro Arg Ile Gly Ala Val Ser
8115 8120 8125

Ala Phe Gly Met Ser Gly Thr Asn Ala His Val Val Val Gln Glu His
8130 8135 8140

Gln Pro Ala Glu Pro Ser Arg Trp Ser Thr Ala Ala Pro Tyr Tyr Leu
8145 8150 8155 8160

Trp Val Val Ser Ala Lys Thr Glu Thr Thr Leu Gln Glu Gln Ile Arg
8165 8170 8175

Gln Trp Glu Asp Tyr Leu Ser Arg His Pro Asp Leu Asp Phe Glu Ala
8180 8185 8190

Val Ser Tyr Thr Leu Leu Lys Gly Arg His His Phe Lys Tyr Arg Cys
8195 8200 8205

Ala Ile Val Ala Lys Asp Leu Ser Gln Val Leu Gln Ala Leu Arg Gln
8210 8215 8220

Ala Leu Asp Arg Gln Thr Gln Ala Asn Leu Cys Met Gly Cys Val Asp
8225 8230 8235 8240

Arg Asp Phe Ser Gly Gln Lys Ala Ile Arg Asp Phe Ile Ala Ser Leu
8245 8250 8255

Ala Ala Gln Gly Glu Ala Leu Arg Asp Lys Pro Asp Asp Tyr Arg Asp
8260 8265 8270

Asn Leu Ile Ala Leu Ala Asp Phe Tyr Cys Gln Gly Tyr Glu Val Ala
8275 8280 8285

Asp Val His Leu Phe Ala Gly Arg Pro Gln Arg Leu Ser Leu Pro Gly
8290 8295 8300

Tyr Pro Phe Ala Arg Glu His Tyr Trp Ile Asp Glu Pro Ser Ala Ala
8305 8310 8315 8320

His Arg Ala Glu Leu Ser Glu Arg Ser Phe Asp Thr Gln Leu Asn Pro
8325 8330 8335

Leu Leu Gln Arg Asn Leu Ser Thr Leu Ser Glu Gln Arg Tyr Ala Ser
8340 8345 8350

Ala Phe Lys Gly Asp Glu Arg Phe Met Leu Arg Ile Ala His Gly Gln
8355 8360 8365

Glu Leu Leu Ile Pro Thr Leu Phe Tyr Leu Glu Met Ala Arg Leu Ala
8370 8375 8380

Ala Gln Gln Ser Leu Asp Met Pro Val Arg Ala Leu Lys Asn Met Val
8385 8390 8395 8400

Trp Ala Cys Pro Leu Tyr Tyr Gln Gln Gly Ser Asp Tyr Glu Leu Phe
8405 8410 8415

Leu Ser Leu His Glu Lys Asp Ser Asp Leu Leu Tyr Thr Val Glu Met
8420 8425 8430

Gln Gly Glu Pro Val Val Cys Gly His Phe Gly Glu Ile Asp Ser Thr
8435 8440 8445

Glu Ala Ala Leu Gln Leu Pro Val Val Pro Asp Ile Ala Arg Leu Arg
8450 8455 8460

Ala Ser Leu Pro Val Val Pro Asp Val Ala Leu Gly Ala Pro Glu Met
8465 8470 8475 8480

Gly Val Ala Arg Ile Ser Asp Val Gln Ala Asp Ala Thr Thr Leu Leu
8485 8490 8495

Ala Thr Leu Asn Val Pro Ala Asp Gly Glu Asp Arg Ser Met Trp Phe
8500 8505 8510

His Pro Leu Leu Ile Asn Ala Gly Trp Trp Leu Leu Gln Gln Phe Val
8515 8520 8525

Gly Asp Arg Ala Glu Gly Gly Pro Leu Leu Pro Phe Ser Leu Lys Gln
8530 8535 8540

Ile Thr Ala Pro Ala Ala Pro Pro Asp Gln Ser Leu Leu Leu Leu Arg
8545 8550 8555 8560

Arg His Val Arg Asp Val Glu Gln Gly Leu Thr Cys Asp Met Ile Phe
8565 8570 8575

Tyr Asn Ser Lys Gly Glu Thr Cys Leu Tyr Leu Gln Glu Leu Asn Val
8580 8585 8590

Thr Thr Leu Asp Arg Leu Phe Asp Leu
8595 8600

<210> 8
<211> 433
<212> PRT

<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedG putative flavin-binding monooxygenase

<400> 8

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Met Asn Gln Lys Phe Arg Leu Cys Ile Ile Gly Gly Gly Pro Leu Gly
  1               5                  10                  15

Ile Gly Leu Gly Arg Glu Leu Ser Glu Gly Ala Ile Asp Tyr Asp Leu
            20                  25                  30

Tyr Glu Ala Glu Ser Asp Leu Gly Gly Val Trp Asn Arg Glu Gly Lys
        35                  40                  45

Cys Gly Arg Val Tyr Pro Ser Leu His Leu Ile Ser Pro Lys Phe Asn
    50                  55                  60

Thr Gln Val Pro Asp Tyr Pro Met Pro Asp His Tyr Pro Val Tyr Pro
65                  70                  75                  80

Asn His Lys Met Met Leu Ala Tyr Met Arg Ser Tyr Ala Arg Asp Phe
                85                  90                  95

Gly Val Tyr Glu His Ala Ile Phe Asn Thr Ser Val Thr Arg Leu Glu
            100                 105                 110

Pro Asp Gly Glu Gly Trp Glu Val Glu Leu Ser Ser Gly Glu Arg Lys
        115                 120                 125

Arg Tyr Glu Val Val Ala Val Cys Asn Gly Ala Gln Arg Val Ala Arg
    130                 135                 140

Phe Pro Asp Pro Pro His Pro Gly Thr Phe Gln Gly Lys Val Leu His
145                 150                 155                 160

Ser Met Asp Tyr Lys Ser Pro Asp Leu Val Arg Asp Lys Arg Val Leu
                165                 170                 175

Val Val Gly Ala Gly Asn Ser Gly Cys Asp Ile Ala Val Asp Ala Ser
            180                 185                 190

His His Ala Glu Gln Val Tyr His Ser Thr Arg Arg Gly Tyr His Tyr
        195                 200                 205

Phe Pro Lys Phe Ile Asp Gly Lys Pro Thr Pro Gln Trp Met Leu Gln
    210                 215                 220

Leu Gly Asn Lys Phe Glu Thr Lys Glu Gln Thr Leu Ala Tyr Met Gln
225                 230                 235                 240

Gln Val Phe Lys Val Ala Gly Phe Asp Gly Met Asp Tyr Gly Leu Lys
                245                 250                 255

Lys Pro Asp His Pro Leu Asp Gly Ala His Pro Ile Met Asn Ser Gln
            260                 265                 270

Ile Leu Tyr His Ile Gly His Gly Asp Ile Leu Pro Lys Asp Asn Ile
        275                 280                 285

Glu Tyr Phe Glu Gly Asn Thr Val Phe Phe Ile Asp Gly Thr Lys Ala
    290                 295                 300

Asp Val Asp Leu Ile Ile Tyr Ala Thr Gly Tyr Asp Arg Asp Phe Pro
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305 310 315 320

Phe Ile Asp His Ala Leu Leu Glu Trp Lys Asp Gly Leu Pro Asp Leu
325 330 335

Phe Ile His Ile Val Pro Arg Asn Leu Asp Asn Ile Phe Phe Phe Gly
340 345 350

Phe Val Asn Ala Ala Ala Gly Leu Gly Asp Gly Leu Arg Leu Gln Gly
355 360 365

Gln Phe Val Arg Ser Tyr Val Arg Ala Leu Gln Gln Lys Ser Lys Gly
370 375 380

Tyr Phe Lys Phe Ile Gln Thr Lys Gln Asn Asp Asn Pro Asp Leu Gly
385 390 395 400

Gln Asp Tyr Phe Leu Asp Ser His Arg His Arg Trp Glu Val Asp Phe
405 410 415

Trp Lys Phe Ile Lys Cys Ala Arg Arg Tyr Arg Glu Met Leu Asp Glu
420 425 430

Ile

<210> 9
<211> 6266
<212> PRT
<213> Unknown Organism

<220>
<223> Description of Unknown Organism: Bacterial Symbiont of Paederus fuscipes

<220>
<223> PedH mixed type I polyketide synthase/nonribosomal peptide synthetase

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Met Thr Phe Asn Thr Ser Asn Asp Gln Asp Ala Ala Ala Arg Glu Phe
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Leu Glu His Glu Leu Ala Lys Ala Val Leu Asp Gln Phe Thr Glu Thr
20 25 30

Gln Ser Ser Pro Ser Val Ala Gln Ile Ile Asp Val Ala Thr Asn Ser
35 40 45

Val Lys Asn Ile Ser Pro Ala Ala Asp Glu Thr Leu Val Lys Phe Lys
50 55 60

Glu Glu Ile Ala Gln Ile Ala Ser Thr Val Leu Lys Ile Pro Ala Glu
65 70 75 80

Arg Leu Asp Val Arg Glu Asn Met Ser Arg Tyr Gly Val Asp Ser Ile
85 90 95

Val Val Thr Glu Ile Met Arg Cys Ile Ser Asp His Leu Asp Leu Pro
100 105 110

Ile Ala Pro Thr Val Phe Phe Glu Ala Gly Asn Phe Glu Glu Leu Ala
115 120 125

Thr Ile Leu Tyr Gln Arg Tyr His Lys Arg Ile Asp Glu Arg Tyr Gln
130 135 140

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Thr Gln Ala Arg Ala Gln Glu Arg Glu Ser Ala Lys Val Ala Pro Leu
145                 150                 155                 160

His Glu Arg Gly Arg Ala Val Gln Lys Asn Gly Glu Leu Gly Val Met
                165                 170                 175

Glu Ala Leu Gly Ser Asp Ala Leu Ala Trp Ile Gln Arg Phe Arg Ser
            180                 185                 190

Val Thr Ser Ser Glu Val Ala Arg Pro Gln Ala Gln Val Arg Arg Val
        195                 200                 205

Thr Lys Ala Ala Arg Ala Asp Gly Glu Ile Leu Tyr Glu Pro Ile Ala
    210                 215                 220

Ile Ile Ala Met Asp Gly Val Phe Pro Gln Ser Ala Asp Leu Leu Glu
225                 230                 235                 240

Phe Glu Arg His Leu Arg Gln Gly Asp Asp Cys Ile Ser Glu Ile Pro
                245                 250                 255

Ala Asp Arg Trp Asp Trp Arg Glu Val Tyr Gly Asp Pro Lys Glu Gly
            260                 265                 270

Glu Phe Thr Arg Val Lys Tyr Gly Gly Phe Ala Pro Asp Ile Asp Lys
        275                 280                 285

Phe Asp Pro Leu Phe Phe Gly Met Ser Pro Arg Glu Ala Gln Leu Met
    290                 295                 300

Asp Pro Gln His Arg Gln Phe Ile Gln Cys Val Trp Arg Leu Ile Glu
305                 310                 315                 320

Ser Ala Gly Tyr Ala Pro Lys Ala Leu Ser Gly Ser Lys Val Gly Leu
                325                 330                 335

Phe Ile Gly Ile Asn Leu Gln Asp Tyr Ala His Leu Val Asp Arg Ala
            340                 345                 350

Asp Ala Met Asp Ala Leu His Leu Thr Ser Leu Gly His Met Phe Cys
        355                 360                 365

Pro Asn Arg Leu Ser Phe Leu Leu Asn Leu His Gly Pro Ser Gln Val
    370                 375                 380

Ile Asp Thr Ala Cys Ser Ser Ser Ser Val Ala Leu His Arg Ala Val
385                 390                 395                 400

Leu Ser Ile Gln Tyr Glu Gly Cys Glu Met Ala Ile Ala Gly Gly Ala
                405                 410                 415

Asn Leu Leu Ile Ser Pro Asp Met His Ile Met Tyr Ser Lys Val Gly
            420                 425                 430

Met Ile Cys Glu Asp Gly Arg Cys Lys Thr Phe Ser Lys Glu Ala Asn
        435                 440                 445

Gly Tyr Val Arg Ser Asp Gly Ile Gly Ala Val Leu Leu Lys Ser Leu
    450                 455                 460

His Arg Ala Glu Glu Asp Gly Asp Ile Ile Leu Ala Val Ile Arg Gly
465                 470                 475                 480

Ser Ala Glu Asn His Gly Gly Met Ser Thr Ser Leu Thr Ala Pro Asn
                485                 490                 495

Pro Lys Ala Gln Ala Ser Leu Ile Val Glu Ala His Arg Lys Ala Lys
            500                 505                 510
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Val Asp Pro Arg Ser Ile Gly Tyr Ile Glu Cys His Gly Thr Gly Thr
        515                 520                 525

Ser Leu Gly Asp Pro Ile Glu Ile Asn Gly Leu Lys Leu Ala Phe Glu
    530                 535                 540

Gln Leu Tyr Arg Glu Ala Gly His Glu Leu Pro Met Arg Pro Ser Cys
545                 550                 555                 560

Gly Leu Gly Ser Val Lys Ser Asn Ile Gly His Ala Glu Thr Ser Ala
                565                 570                 575

Gly Ile Ala Gly Val Ile Lys Thr Val Leu Ser Leu Arg Asn Lys Arg
            580                 585                 590

Leu Tyr Gln Ser Leu His Ser Ala Asp Ile Asn Pro Met Ile Asp Leu
        595                 600                 605

Glu Gln Ser Pro Phe Phe Ile Leu Gln Gln Gly Arg Asp Trp Gln Arg
    610                 615                 620

Pro Leu Ile Glu Gly Gln Glu Gln Pro Arg Arg Ala Gly Ile Ser Ser
625                 630                 635                 640

Phe Gly Ala Gly Gly Ser Asn Ala His Ile Val Ile Glu Glu Tyr Leu
                645                 650                 655

Val Pro Pro Leu Pro Glu Pro Val Leu Gln Gly Pro Leu Ile Ile Leu
            660                 665                 670

Leu Ser Ala Lys Asn Ala Ala Arg Leu Asp Asp Met Thr Arg Gln Leu
        675                 680                 685

Leu His Trp Leu Glu Ser Thr Glu Arg Val Pro Ser Ile Val Asp Ile
    690                 695                 700

Ala Tyr Thr Leu Gln Val Gly Arg Glu Ala Leu Ser Gln Arg Leu Ala
705                 710                 715                 720

Leu Ile Val Thr Asp Leu Val Asp Leu Lys Thr Arg Leu Arg Ser Leu
                725                 730                 735

Leu Glu Gly Gly Glu Glu Pro Ser Gly Val Tyr Arg Gly Asp Thr Lys
            740                 745                 750

Ala Asn Lys Ala Ala Leu Gln Glu Ile Asp Asp Asp Asp Arg Ser Leu
        755                 760                 765

Glu Lys Leu Ile Ala Tyr Phe Ser Gln Asp Asp Val His Lys Leu Ala
    770                 775                 780

Lys Leu Trp Thr Gln Gly Val Glu Val Asp Trp Pro Ser Leu Tyr Ala
785                 790                 795                 800

Arg Met Pro Phe Ala Gly Arg Ser Pro Arg Arg Val Ala Leu Pro Thr
                805                 810                 815

Tyr Pro Phe Ala Arg Gln Arg His Trp Ile Asp Lys Ile Ala Gly Ser
            820                 825                 830

Pro Gln Asn Arg Arg Glu Ala Ala Ala Thr Ser Pro Ile Val Ala Ser
        835                 840                 845

Arg Pro Ala Gly Tyr Pro Leu Leu Gln Arg Thr Val Ala Asp Pro Ala
    850                 855                 860

Lys Arg Cys Tyr Gly Cys Val Leu Thr Gly Glu Glu Phe Phe Leu Thr
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865 870 875 880

Asp His Gln Val Lys Gly Asn Lys Val Leu Pro Gly Val Ala Tyr Leu
885 890 895

Glu Met Ala Arg Ala Ala Val Glu Arg Ile Ser Ala His Asp Ala Arg
900 905 910

Asp Lys Ala Pro Leu Tyr Leu Lys Asn Val Val Trp Ala Arg Pro Leu
915 920 925

Met Val Asn Gly Ala Thr Ser Leu Tyr Ile Ser Leu Ala Pro Glu Gln
930 935 940

Asp Gly Arg Val Ala Tyr Arg Ile Tyr Ser Glu Gly Glu Gly Glu Ser
945 950 955 960

Thr Glu Ile Leu His Ser Gln Gly Ser Ala Ile Leu Arg Gly Ser Glu
965 970 975

Ser Gly Ser Glu Val Ala Thr Ala Arg Leu Asp Leu Asp Glu Leu Arg
980 985 990

Glu Arg Ile Thr Gly Gly Ala Pro Asn Ala Gln Arg Leu Glu Ser Ala
995 1000 1005

Arg Cys Tyr Glu Ala Phe Arg Ala Met Gly Ile Asp Tyr Gly Pro Ala
1010 1015 1020

His Arg Cys Leu Glu Ser Val Tyr Phe Ser Ala Lys Glu Ala Leu Pro
1025 1030 1035 1040

Ala Pro Glu Val Leu Ala Lys Leu Val Leu Pro Ala Trp Ala Gln Glu
1045 1050 1055

Gly Ala Ala Ala Phe Val Leu His Pro Gly Leu Ile Asp Ser Gly Leu
1060 1065 1070

Gln Ala Cys Ile Gly Leu Ile Val Gly Ala Gly His Glu Leu Pro Thr
1075 1080 1085

Glu Ala Glu Ser Glu Ile Ser Gly Met Thr Ala Thr Leu Pro Phe Ala
1090 1095 1100

Leu Asp Ser Leu Thr Leu Leu Ala Pro Pro Ser Asp Ile Leu Trp Val
1105 1110 1115 1120

Trp Val Arg Tyr Ala Asp Gly Ser Ser Thr Ser Asp Lys Val Gln Lys
1125 1130 1135

Leu Asp Ile Asp Phe Cys Asp Val His Gly Arg Val Cys Ile Arg Leu
1140 1145 1150

Arg Gly Phe Ser Ser Arg Ala Leu Glu Ala Glu Gln Ala Pro Asp Ser
1155 1160 1165

Ala Thr Thr Val Leu Cys Glu Pro Leu Trp Asn Glu Arg Ser Val Asp
1170 1175 1180

Ser Ser Ala Gln Val Leu Trp Ala Arg His Glu Val Leu Leu Cys Asp
1185 1190 1195 1200

Val Gln Asp Asp Phe Asp Ala Val Phe Glu Gln Asn Leu Gly Val Thr
1205 1210 1215

Leu Gly Val Pro Cys Ser Arg Leu Ala Leu Asp Gly Pro Leu Glu Asn
1220 1225 1230

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Arg Tyr Gln Lys Ala Ala Leu Gly Val Phe Glu Trp Ile Arg Gln Ala
1235 1240 1245

Ile Gly Asp Lys Ile Gly Gly Ser Leu Leu Leu Gln Ile Val Ile Pro
1250 1255 1260

Ala Thr Asp Arg Gly Cys Leu Leu Ala Gly Leu Ser Gly Leu Leu Lys
1265 1270 1275 1280

Thr Ala Asn Arg Glu Asn Asn Arg Phe Arg Gly Gln Leu Ile Glu Leu
1285 1290 1295

Glu Leu Arg Glu Thr Ala Glu Gly Val Ala Ala Lys Leu Gln Ala Asp
1300 1305 1310

Ser Arg Ala Ala Gln Asp Thr His Ile Arg His Arg Asp Ser Leu Arg
1315 1320 1325

Glu Val Arg His Trp Gln Val Val Pro Ala Gly Ala Val Ser Thr Val
1330 1335 1340

Leu Pro Trp Lys Asp Asn Gly Val Tyr Leu Ile Thr Gly Gly Asn Gly
1345 1350 1355 1360

Gly Leu Ala Trp Leu Phe Ala Glu His Ile Ala Gln His Ala Pro His
1365 1370 1375

Ala Ser Leu Val Met Cys Gly Arg Ser Ala Leu Thr Ser Glu Arg His
1380 1385 1390

Gln Ala Leu Glu His Leu Arg Gly Met Gly Pro Arg Leu Asp Tyr Arg
1395 1400 1405

Arg Val Asp Val Thr Gln Ala Ala Gln Val Glu Ala Leu Ile Arg Asp
1410 1415 1420

Leu Thr Thr Val Tyr Glu Arg Ile Asp Gly Val Leu His Cys Ala Gly
1425 1430 1435 1440

Leu Leu Arg Asp Asn Phe Ile Gln Lys Lys Thr Pro Gln Glu Phe Ala
1445 1450 1455

Glu Val Leu Ala Pro Lys Val Ala Gly Thr Leu His Leu Asp His Ala
1460 1465 1470

Thr Gln Ala Leu Asp Leu Asp Phe Phe Ile Leu Phe Ser Ser Ala Ala
1475 1480 1485

Gly Val Trp Gly Ser Ala Gly Gln Thr Asp Tyr Ala Ala Ala Asn Gly
1490 1495 1500

Phe Leu Asp Ala Phe Ala Ser Tyr Arg Gln Ala Leu Thr Ala Ala Gly
1505 1510 1515 1520

Arg Arg His Gly Arg Thr Leu Ser Ile Asp Trp Pro Leu Trp Ala Glu
1525 1530 1535

Gly Gly Met Arg Met Glu Ala Asn Ala Gln Ile Met Met Gln Arg Ala
1540 1545 1550

Thr Gly Leu Thr Ala Leu Pro Ser Ala Ala Gly Ile Glu Ala Phe Cys
1555 1560 1565

Arg Ile Met Gly Ser Gly Ala Thr Gln Met Met Val Met His Gly Ala
1570 1575 1580

Ala Val Arg Ile Gln Arg Met Leu Asp Glu Ser Ala Glu Pro Leu Arg
1585 1590 1595 1600

Ala Ala Leu Pro Val Arg Ser Ala Thr Ala Thr Glu Glu Pro Ala Ala
1605 1610 1615

Arg Gly Arg Phe Asp Thr Gln Ala Leu Lys Ala Gly Ile Glu Gln Leu
1620 1625 1630

Leu Leu Gln Arg Ile Ala Glu Leu Met Lys Phe Glu Leu Glu Asp Leu
1635 1640 1645

Asp Val Glu Thr Gln Leu Thr Asp Tyr Gly Phe Asn Ser Ile Thr Leu
1650 1655 1660

Thr Asp Phe Ser Asn Arg Leu Asn Gln Gln Tyr Ser Leu Glu Met Thr
1665 1670 1675 1680

Pro Thr Val Phe Phe Glu Tyr Pro Thr Val Ser Glu Phe Ala Gly Trp
1685 1690 1695

Leu Ser Thr Glu Tyr Pro Asp Val Phe Ala Gln Ala Leu Gly Leu Ser
1700 1705 1710

Ile Glu Thr Pro Ala Glu Phe Arg Pro Glu Val Arg Thr Asp Asp Gly
1715 1720 1725

Ala Arg Glu Pro Ser Ser Val Leu Ser Ser Val Gln Ala Glu Arg Met
1730 1735 1740

Leu Gly Gly Ile Ala Met Met Ala Ser Gln Ala Val Ser Val Asp Asp
1745 1750 1755 1760

Ala Ala Val Ala Ile Ile Gly Met Ser Gly Arg Phe Pro Met Ala Glu
1765 1770 1775

Asp Ile Gln Ala Phe Trp Ser Asn Leu Leu Glu Gly Lys Asp Cys Ile
1780 1785 1790

Ser Glu Ile Pro Glu Asp Arg Trp Asp Trp Arg Ala Ile Tyr Gly Asp
1795 1800 1805

Pro Thr Lys Glu Ala Asn Lys Ser Asp Val Lys Trp Gly Gly Phe Ile
1810 1815 1820

Asp Gly Val Ala His Phe Asp Ala Arg Phe Phe Gly Ile Ser Pro Arg
1825 1830 1835 1840

Glu Ala Glu Leu Met Asp Pro Gln Gln Arg Leu Leu Met Gln Tyr Val
1845 1850 1855

Trp Lys Ala Val Glu Asp Ala Gly Tyr Ala Pro Ala Ser Leu Ser Gly
1860 1865 1870

Ser Arg Thr Ala Ile Phe Val Gly Thr Ala Ser Ser Gly Tyr Gly Glu
1875 1880 1885

Leu Met Ala Gln Glu Gly Leu Ala Ile Glu Ser Tyr Ser Ser Thr Gly
1890 1895 1900

Val Val Gly Ser Val Gly Pro Asn Arg Met Ser Tyr Phe Leu Asn Leu
1905 1910 1915 1920

His Gly Pro Ser Glu Pro Val Glu Thr Ala Cys Ser Ser Ser Leu Val
1925 1930 1935

Ala Ile His Arg Ala Leu Ser Ala Met Ala Ile Gly Asp Cys Asp Gln
1940 1945 1950

Ala Ile Val Gly Gly Val Asn Leu Leu Ile Ser Pro Gln Thr His Ile

1955 1960 1965

Ser Phe Asn Lys Ala Gly Met Leu Cys Ser Asp Gly Arg Cys Lys Thr
1970 1975 1980

Phe Ser Ser Lys Ala Asn Gly Tyr Val Arg Gly Glu Gly Val Gly Met
1985 1990 1995 2000

Leu Met Leu Lys Lys Leu Lys Ala Ala Glu Gln Ala Gly Asn His Ile
2005 2010 2015

Tyr Ala Val Ile Arg Gly Ser Ala Glu Asn His Gly Gly Arg Gly Ser
2020 2025 2030

Ser Leu Thr Ala Pro Asn Pro Lys Ala Gln Thr Gln Leu Ile Lys Ala
2035 2040 2045

Ala Tyr Glu Arg Ala Gly Ile Asp Pro Arg Ser Val Ser Tyr Ile Glu
2050 2055 2060

Ala His Gly Thr Gly Thr Glu Leu Gly Asp Pro Ile Glu Ile Asn Ala
2065 2070 2075 2080

Leu Lys Ala Ala Phe Lys Asp Leu Tyr Gln Ala Thr Gly Ser Val Glu
2085 2090 2095

Val Thr Ala Pro His Cys Ala Leu Gly Ala Val Lys Thr Asn Ile Gly
2100 2105 2110

His Leu Glu Leu Ala Ala Gly Val Ala Gly Val Ile Lys Val Leu Leu
2115 2120 2125

Gln Leu Lys His Lys Thr Leu Val Lys Ser Leu His Cys Asp Glu Val
2130 2135 2140

Asn Pro Tyr Ile Gln Leu Gln Gly Ser Pro Phe Tyr Leu Leu Ser Glu
2145 2150 2155 2160

Thr Gln Pro Trp Ser Thr Leu Arg Asp Ala Gln Gly Arg Glu Leu Pro
2165 2170 2175

Arg Arg Ala Gly Ile Ser Ser Phe Gly Phe Gly Gly Val Asn Ala His
2180 2185 2190

Leu Val Leu Glu Glu Tyr Pro Gln Ala Glu Tyr Ile Ala Glu Ser Ser
2195 2200 2205

Met Glu Ser Leu Gln Ala Ser Ser Thr Cys Val Val Pro Leu Ser Ala
2210 2215 2220

Lys Thr Pro Glu Arg Leu Lys Val Tyr Ala Ser Ser Leu Leu Asp Phe
2225 2230 2235 2240

Ile Thr Ala Pro Val Ala Val Ser Gly Pro Glu Gly Glu Gly Ala His
2245 2250 2255

Gln Leu Leu Thr Arg Trp Met Gln Ala Met Val Ala Glu Ile Leu Glu
2260 2265 2270

Ile Ala Val Glu Glu Ile Glu Leu Thr Gln Pro Leu Gln Glu Tyr Gly
2275 2280 2285

Phe Asp Thr Val His Gly Val Ile Leu Leu Ala Arg Phe Arg Asp Ala
2290 2295 2300

Trp Gly Val Asp Val Gly Ser Ala Val Leu Leu Gly His Gln Thr Ser
2305 2310 2315 2320

Ile Thr Ser Phe Val Thr Thr Val Leu Arg Glu Gln Pro Ser Leu Arg
2325 2330 2335

Glu Arg Leu Ser Gly Glu Pro Ala Ala Val Ala Ala Ser Pro Glu Pro
2340 2345 2350

Gly His Arg Val Arg Arg Asp Ile Arg Leu Ala Asp Leu Ala Tyr Thr
2355 2360 2365

Leu Gln Val Gly Arg Asp Ala Met Ala Glu Arg Leu Ala Met Thr Ala
2370 2375 2380

Asp Ser Met Glu Glu Leu Glu His Lys Leu Arg Ala Phe Val Glu Gly
2385 2390 2395 2400

Arg Ser Gly Glu Val Lys Asp Leu Tyr Gln Gly Ser Val Lys Gln Asn
2405 2410 2415

Lys Arg Ile Leu Ser Ala Phe Ala Gly Asp Glu Glu Met Gln Glu Ala
2420 2425 2430

Leu Asp Lys Trp Ile Gln Arg Gly Lys Leu Ala Lys Leu Leu Glu Ile
2435 2440 2445

Trp Val Ala Gly Leu Asn Ile Asp Trp Gln Gln Leu Tyr Gly Ser Asp
2450 2455 2460

Arg Ser Gly Thr Pro Pro His Arg Ile Ser Ala Pro Gly Tyr Pro Phe
2465 2470 2475 2480

Ala Glu Gln Arg His Trp Ile Gln Thr Pro Ser Met Ser Pro Ala Pro
2485 2490 2495

Val Pro Val Ser Ala Pro Val Ala Ala Pro Glu Val Leu His Pro Leu
2500 2505 2510

Val His Glu Ser Leu Cys Gly Pro Gly Leu Thr Arg Phe Lys Ser Arg
2515 2520 2525

Phe Glu Gly Thr Glu Phe Phe Leu Asp Asp His Arg Val Lys Gly Arg
2530 2535 2540

Lys Val Met Pro Gly Val Ala Tyr Leu Glu Met Ala His Ala Ala Ala
2545 2550 2555 2560

His Leu Ala Gln Ala Ile Ala Pro Ser Ser Arg Val Cys Leu Gln Asp
2565 2570 2575

Val Ala Trp Ile Ser Pro Leu Leu Val Asp Gln Pro Gln Glu Val Leu
2580 2585 2590

Ile Asp Ile Glu Pro Gly Gln Gly Glu Arg Arg Ser Phe Ser Val Tyr
2595 2600 2605

Cys Met Ala Gly Asp Gly Arg Arg Leu His Ser Gln Gly Gly Leu Leu
2610 2615 2620

Tyr Val Pro Gln Asp Ser Ala Gln Ser Arg Pro Cys Leu Glu Leu Gln
2625 2630 2635 2640

Ala Leu Leu Ala Gln Ser Gly Met Arg Leu Ile Asn Ala Asp His Cys
2645 2650 2655

Tyr Glu Arg Leu Ala Ala Gly Gly Leu Glu Tyr Gly Pro Gly His Arg
2660 2665 2670

Gly Ile His Gln Leu Tyr Ala Gly Asn Asp Gln Val Leu Ala His Leu
2675 2680 2685

Val Leu Pro Glu Ser Leu Gln Ala Thr Ala Gly His Tyr Val Leu His
2690 2695 2700

Pro Cys Leu Val Asp Ser Ala Leu Gln Ala Ser Ile Gly Leu Val Leu
2705 2710 2715 2720

Thr Ala Ser Glu Thr Ala Ser Gly Gly Arg Glu Ala Pro Leu Met Leu
2725 2730 2735

Pro Phe Ala Val Gln Ser Val Asp Val Phe Ala Ser Cys Glu Ser Val
2740 2745 2750

Thr Trp Ala Trp Leu Arg His Gln Ala Gly Ile Pro Val Ser Gly Arg
2755 2760 2765

Val Gln Lys Leu Asp Ile Asp Leu Cys Asp Glu Arg Gly Lys Val Cys
2770 2775 2780

Ile Gln Ile Lys Gly Phe Ser Ser Arg Val Leu Ala Pro Glu Gly Gly
2785 2790 2795 2800

Arg Ser Glu Ala Val Thr Ala His Glu Arg Arg Glu Pro Leu Gly Val
2805 2810 2815

Phe Ala Ala Arg Ala Thr Thr Pro Ser Pro Ala Pro Ala Pro Ala Leu
2820 2825 2830

Ser Ala Val Ala Glu Val Asp Asp Asp Glu Leu Ser Lys Arg Ala Ile
2835 2840 2845

Asp Tyr Phe Lys Ala Leu Leu Ser Ser Thr Leu Lys Phe Pro Val Glu
2850 2855 2860

Glu Ile Ala Pro Asp Glu Thr Met Asp Ala Tyr Gly Ile Asp Ser Ile
2865 2870 2875 2880

Met Val Ala Glu Leu Thr Ser Thr Leu Glu Ser His Phe Gly Pro Leu
2885 2890 2895

Ser Lys Thr Leu Phe Phe Glu Tyr Gln Thr Leu Gly Glu Leu Val Asp
2900 2905 2910

Tyr Phe Leu Asp Ala His Arg Ala Arg Leu Leu Gln Leu Cys Val Thr
2915 2920 2925

Gly Gly Ala Gly Thr Ser Leu Ala Ala Asp Ala Val Leu Asp Ser Pro
2930 2935 2940

Pro Ser Thr Lys Pro Ala Val Leu Val Glu His Leu Pro Gln Pro Val
2945 2950 2955 2960

Pro Met Ala Ala Ala Ser Asn Thr Ala Leu Asp Ile Ala Val Ile Gly
2965 2970 2975

Ile Ser Gly Arg Tyr Pro Met Ala Asn Asp Leu Asp Glu Phe Trp Leu
2980 2985 2990

Asn Leu Arg Glu Gly Lys Asp Cys Val Ser Glu Val Pro Ser Gln Arg
2995 3000 3005

Trp Asn Trp Arg Asp His Tyr Ser Glu Glu His Ser Arg Ala Gly Gly
3010 3015 3020

His Phe Cys Lys Trp Gly Gly Phe Ile Asp Asp Ile Asp Lys Phe Asp
3025 3030 3035 3040

Pro Leu Phe Phe Asn Ile Ser Pro Ser Ala Ala Glu Tyr Met Asp Pro

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                3045                3050                3055

Gln Glu Arg Leu Phe Leu Glu His Ala Trp Met Ala Met Glu Asp Ala
            3060                3065                3070

Gly Tyr Arg Arg Glu Asp Leu Arg Lys Leu Ala Arg Gly Ser Ala Ala
        3075                3080                3085

Glu Asp Leu Pro Gly Gln Val Gly Val Tyr Ala Gly Val Met Tyr Ser
    3090                3095                3100

Glu Tyr Gln Leu Leu Gly Ile Glu Ala Ala Arg Gln Gly Lys Gly Ala
3105                3110                3115                3120

Thr Val Ala Asn Phe His Ala Ser Val Ala Asn Arg Val Ser Tyr Val
                3125                3130                3135

Leu Asp Leu His Gly Pro Ser Met Thr Val Asp Thr Met Cys Ser Ser
            3140                3145                3150

Ser Leu Thr Ala Leu His Leu Ala Cys Gln Asp Leu Lys Thr Gly Arg
        3155                3160                3165

Thr Asp Met Ala Leu Ala Gly Gly Val Asn Leu Ser Val His Pro Asn
    3170                3175                3180

Lys Tyr Ser Val Leu Ser Leu Asn Glu Phe Ile Ser Ser Gln Gly Arg
3185                3190                3195                3200

Cys Thr Ser Phe Gly Glu Gly Gly Asp Gly Tyr Val Pro Ser Glu Gly
                3205                3210                3215

Val Gly Val Val Leu Leu Lys Arg Leu Val Asp Ala Glu Arg Asp Arg
            3220                3225                3230

Asp His Ile His Ala Val Ile Lys Ser Ser Val Leu Asn His Gly Gly
        3235                3240                3245

Lys Thr His Gly Phe Ser Val Pro Asn Pro Lys Ala Gln Gln His Leu
    3250                3255                3260

Ile Ser Arg Ala Leu Arg Glu Ala Glu Val Asp Pro Arg Ala Ile Thr
3265                3270                3275                3280

Tyr Val Glu Ala His Gly Thr Gly Thr Pro Leu Gly Asp Pro Ile Glu
                3285                3290                3295

Val Thr Ala Leu Ser Lys Ala Phe Ala Gln Tyr Ser Leu Gly Gly Gln
            3300                3305                3310

Pro Tyr Trp Ile Gly Ser Val Lys Ser Asn Ile Gly His Thr Glu Ser
        3315                3320                3325

Thr Ala Gly Ile Ala Gly Leu Ser Lys Val Ile Leu Gln Met Arg Glu
    3330                3335                3340

Gly Gln Leu Ala Pro Ser Leu His Ser Gln Thr Leu Asn Pro Asn Ile
3345                3350                3355                3360

Asp Phe Ala Ser Ser Pro Phe Gln Val Asn Arg Gln Leu Arg Glu Trp
                3365                3370                3375

Pro Arg Pro Val Leu Asp Gly Arg Leu Gln Pro Arg Val Ala Ser Leu
            3380                3385                3390

Ser Ser Phe Gly Ala Gly Gly Ser Asn Ala His Leu Val Ile Ser Glu
        3395                3400                3405
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Tyr Ile Glu Pro Val Glu Arg Arg Ala Pro Asp Thr Thr Asp Ser Arg
3410 3415 3420

Pro Cys Leu Ile Val Leu Ser Ala Lys Ser Glu Glu Arg Leu Lys Ala
3425 3430 3435 3440

Tyr Ala Gly Lys Leu Cys Ala Phe Leu Glu Ser Ala Gly Thr Arg Leu
3445 3450 3455

Glu Leu Ser Leu Arg Asn Val Ala Tyr Thr Leu Gln Val Gly Arg Glu
3460 3465 3470

Ala Met Gln His Arg Leu Ala Phe Ser Ala Arg Ser Ile Glu Asp Ala
3475 3480 3485

Arg Arg Ile Leu Glu Ala Phe Ala Gln Gly Arg Glu Val Ala Arg Leu
3490 3495 3500

Tyr Arg Gly Tyr Val Lys Thr Ala Arg Asp Ser Arg Ser Gly Arg Arg
3505 3510 3515 3520

Asp Glu Ser Val Ala Glu Pro Ile Arg Gly Lys Asp His Asp Ala Val
3525 3530 3535

Leu Ala Leu Trp Val Lys Gly Val Asp Val Asn Trp Gln Glu Leu Tyr
3540 3545 3550

Ala Ala Glu Ser Asp Leu Pro Tyr Arg Ile Ser Leu Pro Thr Tyr Pro
3555 3560 3565

Phe Ala Arg Glu Arg Tyr Trp Leu Thr Leu Pro Glu Pro Pro Pro Pro
3570 3575 3580

Gly Gly Glu Arg Arg Leu Pro Asn Ala Pro Ile Ala Leu Ala Val Leu
3585 3590 3595 3600

Ser Asp Ala Leu Leu Gly Ser Pro Ala Trp Lys Ala Arg Ala Ala Glu
3605 3610 3615

Pro Ala Ala Val Leu Gly Asp Tyr Val Glu Arg Arg Leu Tyr Val Val
3620 3625 3630

Gly Ser Ser Met Glu Val Pro Gly Ile Ala Cys Val Ala Leu Asp Ser
3635 3640 3645

Asp Gly Gln Thr Val Asp Gln Arg Ile Thr Asp Tyr Ala Thr Gln Leu
3650 3655 3660

Phe Gly Asp Ile Lys Thr Leu Phe Gln Arg Lys Pro Lys Pro Lys Gly
3665 3670 3675 3680

Glu Val Leu Phe Gln Ile Leu Leu Ala Gln Asp Thr Pro Met Ala Gly
3685 3690 3695

Ala Leu Ala Ala Leu Leu Lys Thr Ala Ala Met Glu Asn Pro Gln Phe
3700 3705 3710

Phe Gly Gln Val Leu Glu Leu Gly Ala Asp Ile Leu Pro Asp Pro Ser
3715 3720 3725

Lys Leu Gly Ala Leu Leu Asp Glu Asn Ala Gln Asp Arg Arg His Pro
3730 3735 3740

His Ile Arg Tyr Ser Arg Ser Gly Arg Gln Val Pro Ser Trp Ser Val
3745 3750 3755 3760

Leu Ser Met Ala Ser Glu Gly Glu Ala Val Trp Lys Gln Gly Gly Val
3765 3770 3775

Tyr Leu Val Ser Gly Gly Val Gly Gly Leu Gly Leu Ile Phe Ala Arg
3780 3785 3790

Glu Ile Ile Arg Arg Val Ser Asp Val Thr Leu Ile Leu Thr Gly Arg
3795 3800 3805

Ser Pro Leu Glu Gly Ala Arg Ala Ala Ala Val Gln Ala Leu Arg Ala
3810 3815 3820

Ser Gly Thr Asn Val Glu Tyr Arg Arg Val Asp Val Gly Asp Arg His
3825 3830 3835 3840

Ala Val Thr Asp Leu Ile Gly Glu Ile Glu Arg Phe Cys Arg Asp Arg
3845 3850 3855

Gly Tyr Gly Glu Leu Asn Gly Val Ile His Ala Ala Gly Val Leu Arg
3860 3865 3870

Asp Asn Phe Ile Leu Arg Lys Thr His Ala Gln Phe Ser Glu Val Met
3875 3880 3885

Ala Ala Lys Val Ala Gly Val Val Asn Leu Asp Leu Ala Thr Arg Ser
3890 3895 3900

Ala Asn Leu Asp Phe Phe Val Met Phe Ser Ser Leu Ala Gly Val Val
3905 3910 3915 3920

Gly Asn Pro Gly Gln Cys Asp Tyr Ser Thr Ala Asn Ala Phe Leu Asp
3925 3930 3935

His Tyr Thr Val Tyr Arg Asn Gln Leu Val Ala Lys Gly Gly Thr Ser
3940 3945 3950

Ala Pro Lys Gly His Thr Leu Ser Ile Asp Trp Pro Leu Trp Gln Glu
3955 3960 3965

Gly Gly Met Asp Leu Ala Pro Glu His Lys Glu Glu Leu Trp Arg Ser
3970 3975 3980

Ala Gly Ile Lys Pro Met Arg Ser Glu Ile Gly Ile Ala Ala Phe Tyr
3985 3990 3995 4000

Ala Cys Leu Gln Ala Gly Val Glu Gln Ala Leu Val Leu Glu Gly Asp
4005 4010 4015

Leu Pro Arg Leu Arg Gln Leu Phe Phe Asp Asp His Ser Gln Pro Val
4020 4025 4030

Val Asp Glu Ala Ala Gln Gly Ala Glu Thr Cys Thr Ser Glu His Ser
4035 4040 4045

Pro Asp Ser Leu Val Arg Ala Val Glu Gly Leu Leu Val Arg His Leu
4050 4055 4060

Ser Glu Leu Leu Lys Leu Pro Glu His Arg Ile Glu Thr Asp Val Pro
4065 4070 4075 4080

Val Glu His Tyr Gly Ile Asp Ser Val Gly Met Met Arg Leu Thr Val
4085 4090 4095

Glu Leu Glu Glu Thr Phe Gly Ser Leu Ser Lys Thr Leu Phe Phe Glu
4100 4105 4110

Tyr Gln Asp Val Gln Ser Leu Ala Ala Tyr Leu Ala Gln Thr Phe Pro
4115 4120 4125

Asp Gln Ala Arg Ala Leu Cys Gly Glu Pro Ser Ala Gln Ala Ala Pro

4130 4135 4140

Met Glu Val Pro Ile Ser Ser Ala Pro Glu Pro Gly Ser Leu Pro Ala
4145 4150 4155 4160

Gly Leu Val Glu Ala Val Val Thr Ala Gly Glu Ala Ala Glu Trp Gln
4165 4170 4175

Met Gly Glu Arg Asp Ile Ala Ile Ile Gly Met Ser Gly Arg Phe Pro
4180 4185 4190

Phe Ala Pro Asp Leu Glu Ala Phe Trp Glu Asn Leu Ser Gln Gly Cys
4195 4200 4205

Asp Cys Ile Thr Glu Ile Pro Pro Thr Arg Trp Lys His Gln Glu Tyr
4210 4215 4220

Phe Asp Pro Glu Lys Gly Lys Pro Gly Lys Thr Tyr Cys Lys Trp Gly
4225 4230 4235 4240

Gly Phe Leu Glu Ser Ile Asp Gln Phe Asp Pro Leu Phe Phe Lys Ile
4245 4250 4255

Pro Pro Ala Gln Ala Glu Val Leu Asp Pro Gln Glu Arg Leu Phe Leu
4260 4265 4270

Glu Thr Val Trp Asn Leu Leu Glu Ser Ser Gly Tyr Leu Gly Glu Thr
4275 4280 4285

Leu Gln Arg Ile Ala Gln Ser Arg Val Gly Val Phe Val Gly Ser Met
4290 4295 4300

Ser Gln Gln Tyr His Ala Phe Gln Ala Asp Leu Thr Arg Glu Ser Leu
4305 4310 4315 4320

Val Thr Met Ser Ser His Ser Ser Ile Ala Asn Arg Val Ser Tyr Phe
4325 4330 4335

Phe Asp Phe Gln Gly Pro Ser Val Ala Val Asp Thr Met Cys Ser Ser
4340 4345 4350

Ala Leu Val Ala Val His Met Ala Cys Glu Ser Leu Leu Arg Asp Asp
4355 4360 4365

Cys Lys Ala Ala Val Ala Gly Gly Val Asn Leu Ser Ile His Pro Lys
4370 4375 4380

Lys Tyr Ile Gly Leu Ser Ala Ser Gln Ile Leu Gly Ser His Pro Asp
4385 4390 4395 4400

Ser Ser Ser Phe Gly Gln Gly Asp Gly Tyr Leu Pro Ser Glu Gly Val
4405 4410 4415

Gly Ala Val Leu Leu Lys Pro Leu Arg Glu Ala Val Ala Asp Asn Asp
4420 4425 4430

Thr Ile Leu Gly Val Ile Lys Ser Thr Thr Ile Asn His Ser Gly Gln
4435 4440 4445

Ser Asn Gly Tyr Phe Val Pro Asn Gly Ala Ala Gln Thr Glu Leu Met
4450 4455 4460

Val Ser Asn Phe Thr Lys Ala Gly Ile Asp Pro Arg Thr Leu Ser Tyr
4465 4470 4475 4480

Val Glu Ser Ala Ala Asn Gly Ser Ser Leu Gly Asp Ala Ile Glu Ile
4485 4490 4495

Asn Ala Leu Thr Ala Gly Phe Gly Arg Tyr Thr Ala Asp Lys Gln Phe
4500 4505 4510

Cys Ala Leu Gly Ser Val Lys Ser Asn Ile Gly His Gly Glu Ala Ala
4515 4520 4525

Ser Gly Ile Ala Gln Leu Ile Lys Val Leu Leu Gln Leu Lys His Arg
4530 4535 4540

Gln Leu Val Pro Thr Ile Lys Ala Gln Pro Leu Asn Ser Asn Ile Asp
4545 4550 4555 4560

Phe Thr His Thr Pro Phe Cys Leu Gln Arg Arg Leu Glu Pro Trp Arg
4565 4570 4575

Arg Pro Ser Leu Ala Leu Gly Asp Gly Pro Met Arg Glu Tyr Pro Leu
4580 4585 4590

Arg Ala Thr Val Ser Ser Phe Gly Ala Gly Gly Ser Asn Ala His Leu
4595 4600 4605

Ile Leu Glu Glu Phe Pro Leu Asp Arg Gln Glu Ser Asp Asn Leu Glu
4610 4615 4620

His Glu Arg Leu Pro Asp Ser Glu Glu His Leu Leu Val Phe Ser Ala
4625 4630 4635 4640

Arg Thr Glu Ala Gln Leu Gln Ala Val Val Gln Gln Met Leu Ala Glu
4645 4650 4655

Leu Glu Lys Glu Arg Ser Leu Ser Leu Ala Asp Ile Ala Phe Thr Leu
4660 4665 4670

Gln Thr Gly Arg Lys Ala Met Asp Phe Arg Leu Ala Val Val Val Glu
4675 4680 4685

Gly Val Glu Ala Arg Leu Arg Ala Val Glu Ser Leu Arg Ala Tyr Leu
4690 4695 4700

Arg Asn Glu Thr Pro Gly Pro Thr Val Phe Val Asp Asn Val Leu Glu
4705 4710 4715 4720

Asp His Ser Arg Val Arg Glu Gln Leu Val Gly Ser Ala Gly Gln Ala
4725 4730 4735

Ile Leu Gln Arg Ala Leu Met Glu Pro Asp Leu Arg Ala Leu Ala Gly
4740 4745 4750

Tyr Trp Val Lys Gly Ile Lys Leu Pro Trp His Gln Leu His Ala Gly
4755 4760 4765

Trp Lys Arg Lys Arg Val Val Leu Pro Thr Tyr Pro Phe Glu Arg Lys
4770 4775 4780

Ser Tyr Trp Leu Gly Gly Asn Ala Gly Arg Val Val Leu Lys Ala Ser
4785 4790 4795 4800

Glu His Ser Glu Arg Asp Ala Val Glu Pro Glu Val Glu Arg Asn Gly
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Ser Ala Ser Ile Glu Arg Val Ile Ala Gln Arg Leu Gly Ser Met Leu
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Gly Met Asp Glu Gly Glu Ile Glu Met Gly Arg Ser Phe Gln Asp Tyr
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Gly Val Asp Ser Ile Ala Ser Ser Glu Leu Cys Arg Ala Leu Glu Gln
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Thr Phe Lys Val Gln Ile Ser Ser Leu Glu Leu Phe Ser Leu Ser Ser
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Leu Ala Glu Leu Ala Glu Leu Ile Ala Gly Arg Leu Pro Glu Gln Pro
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Leu Lys Lys Leu Lys Lys Leu Glu Thr Pro Glu Thr Val Ser Val Ser
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Ser Val Ser Met Pro Val Ser Glu Gly Gln Lys Gly Leu Trp Leu Leu
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His Gln Arg Ser Pro Asn Met Ser Ala Tyr Asn Val Pro Leu Val Phe
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Cys Phe Lys Gly Glu Leu Asp Val Ser Leu Phe Arg Lys Ala Cys Glu
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Leu Met Leu Glu Arg His Pro Ile Leu Gly Ser Val Phe Arg Leu Thr
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Arg Glu Asp Ile Gln Arg Ile Glu Leu Arg Glu Ala His Met Gly Phe
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Glu His Val Ser Val Glu Leu His Gln Arg Ser Glu Ile Leu Glu Arg
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Leu Arg Asp Tyr Ser Lys Gln Pro Phe Asp Leu Glu Gln Gly Pro Leu
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Tyr Arg Val Tyr Leu Leu Thr Ser Arg Thr Asp Asn Asp Ala Tyr Val
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Leu Ile Cys Val His His Ile Val Phe Asp Gly Ser Ser Ala Met Leu
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Leu Leu Lys Asp Leu Leu Ala Thr Tyr Arg Asn Leu Leu His Gly Gly
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Gln Pro Ala Asn Ile Arg Pro Ala Ala Gly Tyr Gln Ser Phe Val His
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Trp Gln Arg Gln Leu Leu Asn Ser Glu Lys Gly Gln Thr Gln Leu Asp
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Tyr Trp Lys Thr Gln Leu Ser Gly Glu Gln Pro Val Leu Ser Leu Pro
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Tyr Asp Phe Pro Arg Pro Ala Met Pro Gly Phe His Gly Ala Ser Glu
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Glu Leu Thr Leu Ser Gln Ala Leu Ser Ser Arg Leu Gln Ala Leu Thr
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Lys Thr Leu Gln Val Asn Pro Ser Val Val Phe Leu Gly Ala Phe Lys
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Leu Leu Leu Asn Arg Tyr Ser Gly Tyr Asp Asp Ile Arg Val Gly Met
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Pro Thr Ser Gly Arg Ser Leu Pro Ala Phe Gln Asp Gln Ile Gly Tyr
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Phe Val Asn Met Leu Val Ile Arg Ser Arg Val Ile Gly Gln Gln Ser
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Val Ala Asp Phe Leu Lys Val Leu Gln Leu Thr Val Ala Thr Ala Leu

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Asp Asn Ala Asp Cys Pro Phe Pro Val Val Leu Glu Ala Leu Arg Gly
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Asp Gly Glu Pro Gln Ser Ser Ser Trp Phe Gln Val Val Phe Ser Tyr
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Gln Gly Thr Thr Ala Val Glu Leu Val Ser Gly Ile Asn Gln Glu Gly
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Gly Asn Asp Ile Ala Leu Asp Val Tyr His Gly Gly Glu Gln Phe Leu
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Leu Lys Met Ala Tyr Asp Lys Asp Leu Phe Glu Ala Ala Thr Ile Arg
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Arg Ile Met Thr His Tyr Val Asn Leu Leu Glu Ser Ile Ala Thr His
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Gln Lys Ile Leu Gly Asp Trp Ser Asn Thr Gly Ala Ser Leu Ser Met
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Pro His Lys Thr Ala Leu Val Phe Glu Gln Gln Ser Leu Thr Phe Ala
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Glu Leu Asp Asp Gln Ser Ser Arg Leu Ser Leu Cys Leu Ala Asn Tyr
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Lys Val Ala Pro Gly Asp Leu Val Gly Ala Cys Leu Gly Arg Gly Val
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Arg Met Val Val Ala Leu Leu Ala Ile Leu Lys Ala Asp Ala Val Tyr
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Val Pro Ile Ala Pro Asp Ser Pro Val Gln Arg Ile Cys Arg Leu Leu
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Val Asp Ser Gly Ile Ser Leu Leu Leu Ser Glu Leu Glu Leu Cys Asn
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Ser Phe Leu Ser Asp Leu Gly Thr Ile Glu Cys Val Cys Leu Ala Ile
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Asp Ala Pro Gly Trp Glu Pro Glu Glu Gly Glu Leu Pro Val Pro Pro
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Val Ile Glu Gly Arg Gln Pro Ala Tyr Val Ile Tyr Thr Ser Gly Ser
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Thr Gly Gln Pro Lys Gly Val Ile Ile Ser His Asp Ser Ile Ser His
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His Cys Gln Val Ile Arg Asp Tyr Tyr Arg Ile Thr Ala Gln Asp Val
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Ile Leu Gln Phe Ala Pro Met Asn Val Asp Ala Ala Leu Glu Gln Leu
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Leu Pro Gly Leu Ile Ser Gly Ala Thr Val Val Ile Arg Ser Glu Pro
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Leu Trp Ser Pro Asp Ile Leu Cys Arg Lys Val Val Glu Leu Gly Ile
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Ser Val Leu Asp Leu Pro Pro Ser Tyr Leu Tyr Glu Leu Leu Leu Glu
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Gly Cys Ala Leu Ser Glu Cys Arg Leu Val Asn Ala Tyr Gly Pro Thr
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Glu Thr Thr Ile Thr Ser Thr Val Tyr Glu Ile Glu Ser Arg Ala Arg
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Gly Glu Ser Ala Tyr Ile Leu Asp Thr Gln Arg Arg Pro Leu Pro Val
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Gly Val Pro Gly Glu Leu Tyr Ile Gly Gly Ala Gly Val Ala Ile Gly
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Tyr Leu Asn Arg Pro Glu Leu Thr Ala Ser Thr Phe Val Glu Asn Pro
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Phe Met Ala Gly Thr Arg Leu Tyr Lys Thr Gly Asp Ala Ala Arg Trp
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Leu Ala Asp Gly Asn Ile Ala Leu Leu Gly Arg Leu Asp Gln Gln Val
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Lys Ile Arg Gly Phe Arg Val Glu Cys Gly Glu Ile Glu Ala Ala Leu
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Gln Ala Leu Asp Val Val Lys His Val Ala Val Leu Ala Gln Pro Thr
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Gln Gly Ser His Arg Leu Val Ala Phe Leu Glu Leu Val Gln Pro Ala
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Leu Pro Glu Trp Lys Gln His Leu Lys Gln Ala Leu Ile Lys Lys Leu
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Pro Glu His Met Ile Pro Ser Val Phe Val Ser Leu Pro Arg Ile Pro
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Leu Ser Val Ser Gly Lys Val Asp Arg Asn Ala Leu Lys His Leu Glu
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Leu Ala Asn Thr Glu Ser Glu Val Phe Val Ala Pro Arg Thr Ser Met
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Glu Ile Arg Leu Ala Glu Ile Trp Arg Arg Val Leu Asp Ile Asp Arg
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Val Gly Val His Asp Ser Phe Phe Asp Leu Gly Gly His Ser Leu Leu
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Ala Leu Arg Leu Met Ser Ala Ile Lys Gln Gly Leu Gly Tyr Glu Leu
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Pro Ile Ser Ser Leu Phe Gln Ala Pro Thr Leu Thr Ala Gln Ala Glu
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Leu Leu Gly Gln Asp Ala Ala Val Trp Ser Pro Leu Val Cys Leu Gln
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Ala Ser Gly Glu Leu Ser Pro Trp Phe Cys Ile His Ala Ala Ala Gly
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Asn Val Leu Cys Tyr Arg Glu Leu Ala Glu Cys Leu Gly Ile Glu Arg
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Pro Phe Tyr Ala Leu Gln Ala Pro Asp Ala Val Gly Gly Gly His Pro
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Gly Ser Ile Val Gly Leu Ala Ala Leu Tyr Val Arg Ala Ile Arg Ile
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Phe Gln Pro Trp Gly Pro Tyr Phe Leu Ala Gly Trp Ser Met Gly Gly
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Val Val Ala Tyr Glu Met Ala Gln Gln Leu Leu Gln Ala Gly Glu Gln
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Val Glu Val Leu Ala Leu Leu Glu Ser Tyr Thr Pro Glu Ala Ile Arg
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Ser Leu Glu Arg Lys Ala Leu Gly Leu Ser Ala Glu Ser Asp Asp Arg
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Thr Pro Trp Glu Leu Ser Ala Val Asp Leu Ala Gln Gly Leu Glu Trp
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Ile Leu Lys Arg Leu Glu Gly Ser Asn Leu Ser Thr Ala Ser Phe Asp
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Leu Glu Gln Leu His Lys Leu Phe Arg Leu Tyr Glu Ala Asn Leu Asn
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Ala Leu Asp Arg Tyr Arg Leu Gln Pro Tyr Ser Gly Arg Val Val Leu
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Ile Tyr Ala Asp Gln Thr Gln Gln Ile Asp Ala Asp Glu Ala Gln His
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Leu Gly Gly Trp Gln Pro Trp Leu Arg Ser Gly His Cys Arg Ser Ala
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Thr Ile Val Gly Asp His Tyr Ser Ile Leu Gln Arg Pro Gln Val Val
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