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(54) **MULTIPLE DRUG RESISTANCE GENE**  
**ATRD OF ASPERGILLUS NIDULANS**

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(57) **ABSTRACT**

The invention provides isolated nucleic acid compounds encoding a multiple drug resistance protein of *Aspergillus nidulans*. Vectors and transformed host cells comprising the multiple drug resistance-encoding DNA of *Aspergillus nidulans* atrD are also provided. The invention further provides assays which utilize these transformed host cells.

**3 Claims, No Drawings**

## MULTIPLE DRUG RESISTANCE GENE ATR D OF ASPERGILLUS NIDULANS

This application is a divisional of, and claims the benefit of priority of, U.S. application Ser. No. 09/328,320 filed Jun. 8, 1999, now U.S. Pat. No. 6,228,615, which is a divisional of U.S. application Ser. No. 08/996,545 filed Dec. 23, 1997, now U.S. Pat. No. 5,928,898, the contents of each of which are herein incorporated by reference in their entirety.

### TECHNICAL FIELD OF THE INVENTION

This invention relates to recombinant DNA technology. In particular, the invention concerns the cloning of nucleic acid encoding a multiple drug resistance protein of *Aspergillus nidulans*.

### BACKGROUND OF THE INVENTION

Multiple drug resistance (MDR) mediated by the human *mdr-1* gene product was initially recognized during the course of developing regimens for cancer chemotherapy (Fojo et al., 1987, *Journal of Clinical Oncology* 5:1922-1927). A multiple drug resistant cancer cell line exhibits resistance to high levels of a large variety of cytotoxic compounds. Frequently these cytotoxic compounds will have no common structural features nor will they interact with a common target within the cell. Resistance to these cytotoxic agents is mediated by an outward directed, ATP-dependent pump encoded by the *mdr-1* gene. By this mechanism, toxic levels of a particular cytotoxic compound are not allowed to accumulate within the cell.

MDR-like genes have been identified in a number of divergent organisms including numerous bacterial species, the fruit fly *Drosophila melanogaster*, *Plasmodium falciparum*, the yeast *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Leishmania donovani*, marine sponges, the plant *Arabidopsis thaliana*, as well as *Homo sapiens*. Extensive searches have revealed several classes of compounds that are able to reverse the MDR phenotype of multiple drug resistant human cancer cell lines rendering them susceptible to the effects of cytotoxic compounds. These compounds, referred to herein as "MDR inhibitors", include for example, calcium channel blockers, antiarrhythmics, antihypertensives, antibiotics, antihistamines, immuno-suppressants, steroid hormones, modified steroids, lipophilic cations, diterpenes, detergents, antidepressants, and antipsychotics (Gottesman and Pastan, 1993, *Annual Review of Biochemistry* 62:385-427). Clinical application of human MDR inhibitors to cancer chemotherapy has become an area of intensive focus for research.

On another front, the discovery and development of antifungal compounds for specific fungal species has also met with some degree of success. *Candida* species represent the majority of fungal infections, and screens for new antifungal compounds have been designed to discover anti-*Candida* compounds. During development of antifungal agents, activity has generally been optimized based on activity against *Candida albicans*. As a consequence, these anti-*Candida* compounds frequently do not possess clinically significant activity against other fungal species such as *Aspergillus nidulans*. However, it is interesting to note that at higher concentrations some anti-*Candida* compounds are able to kill other fungal species such as *A. nidulans* and *A. fumigatus*. This type of observation suggests that the antifungal target(s) of these anti-*Candida* compounds is present in *A. nidulans* as well. Such results indicate that *A. nidulans* may possess a natural mechanism of resistance that permits

them to survive in clinically relevant concentrations of antifungal compounds. Until the present invention, such a general mechanism of resistance to antifungal compounds in *A. nidulans* has remained undescribed.

### SUMMARY OF THE INVENTION

The invention provides, inter alia, isolated nucleic acid molecules that comprise nucleic acid encoding a multiple drug resistance protein from *Aspergillus nidulans*, herein referred to as *atrD*, vectors encoding *atrD*, and host cells transformed with these vectors.

In another embodiment, the invention provides a method for determining the fungal MDR inhibition activity of a compound which comprises:

- a) placing a culture of fungal cells, transformed with a vector capable of expressing *atrD*, in the presence of:
  - (i) an antifungal agent to which said fungal cell is resistant, but to which said fungal cell is sensitive in its untransformed state;
  - (ii) a compound suspected of possessing fungal MDR inhibition activity; and
- b) determining the fungal MDR inhibition activity of said compound by measuring the ability of the antifungal agent to inhibit the growth of said fungal cell.

In still another embodiment the present invention relates to strains of *A. nidulans* in which the *atrD* gene is disrupted or otherwise mutated such that the *atrD* protein is not produced in said strains.

In yet another embodiment, the present invention relates to a method for identifying new antifungal compounds comprising the use of *atrD* gene disruption or gene replacement strains of *A. nidulans*.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides isolated nucleic acid molecules that comprise a nucleic acid sequence encoding *atrD*. The cDNA (complementary deoxyribonucleic acid) sequence encoding *atrD* is provided in the Sequence Listing as SEQ ID NO: 1. The amino acid sequence of the protein encoded by *atrD* is provided in the Sequence Listing as SEQ ID NO: 2.

Those skilled in the art will recognize that the degenerate nature of the genetic code enables one to construct many different nucleic acid sequences that encode the amino acid sequence of SEQ ID NO: 2. The cDNA sequence depicted by SEQ ID NO: 1 is only one of many possible *atrD*-encoding sequences. Consequently, the constructions described below and in the accompanying examples for the preferred nucleic acid molecules, vectors, and transformants of the invention are illustrative and are not intended to limit the scope of the invention.

All nucleotide and amino acid abbreviations used in this disclosure are those accepted by the United States Patent and Trademark Office as set forth in 37 C.F.R. §1.822(b)(1994).

The term "vector" refers to any autonomously replicating or integrating agent, including but not limited to plasmids, cosmids, and viruses (including phage), comprising a nucleic acid molecule to which one or more additional nucleic acid molecules can be added. Included in the definition of "vector" is the term "expression vector". Vectors are used either to amplify and/or to express deoxyribonucleic acid (DNA), either genomic or cDNA, or RNA (ribonucleic acid) which encodes *atrD*, or to amplify DNA or RNA that hybridizes with DNA or RNA encoding *atrD*.

The term "expression vector" refers to vectors which comprise a transcriptional promoter (hereinafter "promoter") and other regulatory sequences positioned to drive expression of a DNA segment that encodes atrD. Expression vectors of the present invention are replicable DNA constructs in which a DNA sequence encoding atrD is operably linked to suitable control sequences capable of effecting the expression of atrD in a suitable host. Such control sequences include a promoter, an optional operator sequence to control transcription, a sequence encoding suitable MRNA ribosomal binding sites, and sequences which control termination of transcription and translation. DNA regions are operably linked when they are functionally related to each other. For example, a promoter is operably linked to a DNA coding sequence if it controls the transcription of the sequence, or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation.

The term "MDR inhibition activity" refers to the ability of a compound to inhibit the MDR activity of a host cell, thereby increasing the antifungal activity of an antifungal compound against said host cell.

In the present invention, atrD may be synthesized by host cells transformed with vectors that provide for the expression of DNA encoding atrD. The DNA encoding atrD may be the natural sequence or a synthetic sequence or a combination of both ("semi-synthetic sequence"). The in vitro or in vivo transcription and translation of these sequences results in the production of atrD. Synthetic and semi-synthetic sequences encoding atrD may be constructed by techniques well known in the art. See Brown et al. (1979) *Methods in Enzymology*, Academic Press, N.Y., 68:109-151. atrD-encoding DNA, or portions thereof, may be generated using a conventional DNA synthesizing apparatus such as the Applied Biosystems Model 380A,380B, 394 or 3948 DNA synthesizers (commercially available from Applied Biosystems, Inc., 850 Lincoln Center Drive, Foster City, Calif. 94404).

Owing to the natural degeneracy of the genetic code, the skilled artisan will recognize that a sizable yet definite number of nucleic acid sequences may be constructed which encode atrD. All such nucleic acid sequences are provided by the present invention. These sequences can be prepared by a variety of methods and, therefore, the invention is not limited to any particular preparation means. The nucleic acid sequences of the invention can be produced by a number of procedures, including DNA synthesis, cDNA cloning, genomic cloning, polymerase chain reaction (PCR) technology, or a combination of these approaches. These and other techniques are described by Maniatis, et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1989), or *Current Protocols in Molecular Biology* (F. M. Ausubel et al., 1989 and supplements). The contents of both of these references are incorporated herein by reference.

In another aspect, this invention provides the cDNA encoding atrD, which may be obtained by synthesizing the desired portion of SEQ ID NO:1 or by following the procedure carried out by Applicants. This procedure involved construction of a cosmid genomic DNA library from *Aspergillus nidulans* strain OC-1, a mutant derived from A42355. This library was screened for genes related to MDRs using a homologous probe generated by PCR. Degenerate PCR primers directed towards amplification of DNA sequences encoding highly conserved regions found in the ATP-binding domain of several MDR genes were synthesized. PCR using these primers and *Aspergillus nidulans*

genomic DNA as template produced an approximately 400 base pair DNA fragment. The DNA sequence of this fragment was highly homologous to the ATP-binding region of several MDRs as predicted. This fragment was used as a hybridization probe to identify cosmid clones containing the entire atrD gene. A subclone from one such cosmid containing the entire atrD gene was sequenced to ascertain the entire sequence of atrD.

To effect the translation of atrD-encoding mRNA, one inserts the natural, synthetic, or semi-synthetic atrD-encoding DNA sequence into any of a large number of appropriate expression vectors through the use of appropriate restriction endonucleases and DNA ligases. Synthetic and semi-synthetic atrD-encoding DNA sequences can be designed, and natural atrD-encoding nucleic acid can be modified, to possess restriction endonuclease cleavage sites to facilitate isolation from and integration into these vectors. Particular restriction endonucleases employed will be dictated by the restriction endonuclease cleavage pattern of the expression vector utilized. Restriction enzyme sites are chosen so as to properly orient the atrD-encoding DNA with the control sequences to achieve proper in-frame transcription and translation of the atrD molecule. The atrD-encoding DNA must be positioned so as to be in proper reading frame with the promoter and ribosome binding site of the expression vector, both of which are functional in the host cell in which atrD is to be expressed.

Expression of atrD in fungal cells, such as *Saccharomyces cerevisiae* is preferred. Suitable promoter sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase (found on plasmid pAP12BD (ATCC 53231) and described in U.S. Pat. No. 4,935,350, Jun. 19, 1990) or other glycolytic enzymes such as enolase (found on plasmid pAC1 (ATCC 39532)), glyceraldehyde-3-phosphate dehydrogenase (derived from plasmid pHe-GAPC1 (ATCC 57090, 57091)), hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase. Inducible yeast promoters have the additional advantage of transcription controlled by growth conditions. Such promoters include the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein (contained on plasmid vector pCL28XhoLHBPV (ATCC 39475), U.S. Pat. No. 4,840, 896), glyceraldehyde 3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization (GAL1 found on plasmid pRY121 (ATCC 37658) and on plasmid pPST5, described below). Suitable vectors and promoters for use in yeast expression are further described by R. Hitzeman et al., in European Patent Publication No. 73,657A. Yeast enhancers such as the UAS Gal enhancer from *Saccharomyces cerevisiae* (found in conjunction with the CYCI promoter on plasmid YEpsc—hI1beta, ATCC 67024), also are advantageously used with yeast promoters.

A variety of expression vectors useful in the present invention are well known in the art. For expression in *Saccharomyces*, the plasmid YRp7, for example, (ATCC-40053, Stinchcomb et al., 1979, *Nature* 282:39; Kingsman et al., 1979, *Gene* 7:141; Tschemper et al., 1980, *Gene* 10:157) is commonly used. This plasmid contains the trp gene which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example ATCC 44076 or PEP4-1 (Jones, 1977, *Genetics* 85:12).

Expression vectors useful in the expression of atrD can be constructed by a number of methods. For example, the

cDNA sequence encoding atrD can be synthesized using DNA synthesis techniques such as those described above. Such synthetic DNA can be synthesized to contain cohesive ends that allow facile cloning into an appropriately digested expression vector. For example, the cDNA encoding atrD can be synthesized to contain NotI cohesive ends. Such a synthetic DNA fragment can be ligated into a NotI-digested expression vector such as pYES-2 (Invitrogen Corp., San Diego Calif. 92121).

An expression vector can also be constructed in the following manner. Logarithmic phase *Aspergillus nidulans* cells are disrupted by grinding under liquid nitrogen according to the procedure of Minuth et al., 1982 (*Current Genetics* 5:227-231). *Aspergillus nidulans* mRNA is preferably isolated from the disrupted cells using the QuickPrep® mRNA Purification Kit (Pharmacia Biotech) according to the instructions of the manufacturer. cDNA is produced from the isolated mRNA using the TimeSaver® cDNA Synthesis Kit (Pharmacia Biotech) using oligo (dT) according to the procedure described by the manufacturer. In this process an EcoRI/NotI adapter (Stratagene, Inc.) is ligated to each end of the double stranded cDNA. The adapter modified cDNA is ligated into the vector Lambda Zap®II using the Predigested Lambda Zap®II/EcoRI/CIAP Cloning Kit (Stratagene, Inc.) according to the instructions of the manufacturer to create a cDNA library.

The library is screened for full-length cDNA encoding atrD using a <sup>32</sup>P-radiolabeled fragment of the atrD gene. In this manner, a full-length cDNA clone is recovered from the *Aspergillus nidulans* cDNA library. A full-length cDNA clone recovered from the library is removed from the Lambda Zap®II vector by digestion with the restriction endonuclease NotI which produces a DNA fragment encoding atrD. The atrD encoding fragment is subcloned into plasmid pYES2 for expression studies. In this plasmid the atrD gene is operably linked to the *Saccharomyces cerevisiae* GAL1 promoter at the 5' end, and the yeast *cycl1* transcription terminator at the 3' end. This plasmid further comprises the ColE1 origin of replication (ColE1) which allows replication in *Escherichia coli* host cells, and the ampicillin resistance gene (Amp) for selection of *E. coli* cells transformed with the plasmid grown in the presence of ampicillin. The expression plasmid further comprises the yeast *2μ* origin of replication (*2μ ori*) allowing replication in yeast host cells, the yeast URA3 gene for selection of *S. cerevisiae* cells transformed with the plasmid grown in a medium lacking uracil, and the origin of replication from the *f1* filamentous phage.

In a preferred embodiment of the invention *Saccharomyces cerevisiae* INVSc1 or INVSc2 cells (Invitrogen Corp., Sorrento Valley Blvd., San Diego Calif. 92121) are employed as host cells, but numerous other cell lines are available for this use. The transformed host cells are plated on an appropriate medium under selective pressure (minimal medium lacking uracil). The cultures are then incubated for a time and temperature appropriate to the host cell line employed.

The techniques involved in the transformation of yeast cells such as *Saccharomyces cerevisiae* cells are well known in the art and may be found in such general references as Ausubel et al., *Current Protocols in Molecular Biology* (1989), John Wiley & Sons, New York, N.Y. and supplements. The precise conditions under which the transformed yeast cells are cultured is dependent upon the nature of the yeast host cell line and the vectors employed.

Nucleic acid, either RNA or DNA, which encodes atrD, or a portion thereof, is also useful in producing nucleic acid

molecules useful in diagnostic assays for the detection of atrD mRNA, atrD cDNA, or atrD genomic DNA. Further, nucleic acid, either RNA or DNA, which does not encode atrD, but which nonetheless is capable of hybridizing with atrD-encoding DNA or RNA is also useful in such diagnostic assays. These nucleic acid molecules may be covalently labeled by known methods with a detectable moiety such as a fluorescent group, a radioactive atom or a chemiluminescent group. The labeled nucleic acid is then used in conventional hybridization assays, such as Southern or Northern hybridization assays, or polymerase chain reaction assays (PCR), to identify hybridizing DNA, cDNA, or RNA molecules. PCR assays may also be performed using unlabeled nucleic acid molecules. Such assays may be employed to identify atrD vectors and transformants and in in vitro diagnosis to detect atrD-like mRNA, cDNA, or genomic DNA from other organisms.

U.S. patent application Ser. No. 08/111,680 (now abandoned), the entire contents of which are hereby incorporated herein by reference, describes the use of combination therapy involving an antifungal agent possessing a proven spectrum of activity, with a fungal MDR inhibitor to treat fungal infections. This combination therapy approach enables an extension of the spectrum of antifungal activity for a given antifungal compound which previously had only demonstrated limited clinically relevant antifungal activity. Similarly, compounds with demonstrated antifungal activity can also be potentiated by a fungal MDR inhibitor such that the antifungal activity of these compounds is extended to previously resistant species. To identify compounds useful in such combination therapy the present invention provides an assay method for identifying compounds with *Aspergillus nidulans* MDR inhibition activity. Host cells that express atrD provide an excellent means for the identification of compounds useful as inhibitors of *Aspergillus nidulans* MDR activity. Generally, the assay utilizes a culture of a yeast cell transformed with a vector which provides expression of atrD. The expression of atrD by the host cell enables the host cell to grow in the presence of an antifungal compound to which the yeast cell is sensitive to in the untransformed state. Thus, the transformed yeast cell culture is grown in the presence of i) an antifungal agent to which the untransformed yeast cell is sensitive, but to which the transformed host cell is resistant, and ii) a compound that is suspected of being an MDR inhibitor. The effect of the suspected MDR inhibitor is measured by testing for the ability of the antifungal compound to inhibit the growth of the transformed yeast cell. Such inhibition will occur if the suspected *Aspergillus nidulans* MDR inhibitor blocks the ability of atrD to prevent the antifungal compound from acting on the yeast cell. An illustrative example of such an assay is provided in Example 3.

In order to illustrate more fully the operation of this invention, the following examples are provided, but are not to be construed as a limitation on the scope of the invention.

#### EXAMPLE 1

##### Source of the atrD-Encoding Genomic DNA and cDNA of *Aspergillus nidulans*

Genomic DNA encoding atrD, or the corresponding cDNA sequence (presented in SEQ ID NO:1), may be from a natural sequence, a synthetic source or a combination of both ("semi-synthetic sequence"). The in vitro or in vivo transcription and translation of these sequences results in the production of atrD. Synthetic and semi-synthetic sequences encoding atrD may be constructed by techniques well

known in the art. See Brown et al. (1979) *Methods in Enzymology*, Academic Press, N.Y., 68:109–151. atrD-encoding DNA, or portions thereof, may be generated using a conventional DNA synthesizing apparatus such as the Applied Biosystems Model 380A, 380B, 384 or 3848 DNA synthesizers (commercially available from Applied Biosystems, Inc., 850 Lincoln Center Drive, Foster City, Calif. 94404). The polymerase chain reaction is especially useful in generating these DNA sequences. PCR primers are constructed which include the translational start (ATG) and translational stop codon (TAG) of atrD. Restriction enzyme sites may be included on these PCR primers outside of the atrD coding region to facilitate rapid cloning into expression vectors. *Aspergillus nidulans* genomic DNA is used as the PCR template for synthesis of atrD including introns which is useful for expression studies in closely related fungi. In contrast, cDNA is used as the PCR template for synthesis of atrD devoid of introns which is useful for expression in foreign hosts such as *Saccharomyces cerevisiae* or bacterial hosts such as *Escherichia coli*.

#### EXAMPLE 2

##### Expression of the atrD Protein

*Saccharomyces cerevisiae* INVSc1 cells (Invitrogen Corp., San Diego Calif. 92191) are transformed with the plasmid containing atrD by the technique described by J. D. Beggs, 1988, *Nature* 275:104–109). The transformed yeast cells are grown in a broth medium containing YNB/CSM-Ura/raf (YNB/CSM-Ura [Yeast Nitrogen Base (Difco Laboratories, Detroit, Mich.) supplemented with CSM-URA (Bio 101, Inc.)] supplemented with 4% raffinose) at 28° C. in a shaker incubator until the culture is saturated. To induce expression of atrD, a portion of the culture is used to inoculate a flask containing YNB/CSM-Ura medium supplemented with 2% galactose (YNB/CSM-Ura/gal) rather than raffinose as the sole carbon source. The inoculated flask is incubated at 28° C. for about 16 hours.

#### EXAMPLE 3

##### Antifungal Potentiator Assay

Approximately  $1 \times 10^6$  cells of a *Saccharomyces cerevisiae* INVSc1 culture expressing atrD are delivered to each of several agar plates containing YNB/CSM-Ura/gal. The agar surface is allowed to dry in a biohazard hood.

An antifungal compound that the untransformed yeast cell is typically sensitive to is dissolved in an appropriate solvent at a concentration that is biologically effective. Twenty  $\mu$ l of the solution is delivered to an antibiotic susceptibility test disc (Difco Laboratories, Detroit, Mich.). After addition of the antifungal solution the disc is allowed to air dry in a biohazard hood. When dry, the disc is placed on the surface of the petri plates containing the transformed *Saccharomyces cerevisiae* INVSc1 cells.

Compounds to be tested for the ability to inhibit atrD are dissolved in dimethylsulfoxide (DMSO). The amount of compound added to the DMSO depends on the solubility of the individual compound to be tested. Twenty  $\mu$ l of the suspensions containing a compound to be tested are delivered to an antibiotic susceptibility test disc (Difco Laboratories, Detroit, Mich.). The disc is then placed on the surface of the dried petri plates containing the transformed *Saccharomyces cerevisiae* INVSc1 cells approximately 2 cm from the antifungal-containing disc. Petri plates containing the two discs are incubated at 28° C. for about 16–48 hours.

Following this incubation period, the petri plates are examined for zones of growth inhibition around the discs. A zone of growth inhibition near the antifungal disc on the test plate indicates that the compound being tested for MDR inhibition activity blocks the activity of atrD and allows the antifungal compound to inhibit the growth of the yeast host cell. Such compounds are said to possess MDR inhibition activity. Little or no zone of growth inhibition indicates that the test compound does not block MDR activity and, thus, atrD is allowed to act upon the antifungal compound to prevent its activity upon the host cell.

#### EXAMPLE 4

##### Screen For Novel Antifungal Compounds

A plasmid molecule is constructed which contains DNA sequence information required for replication and genetic transformation in *E. coli* (e.g. ampicillin resistance). The plasmid also comprises DNA sequences encoding a marker for selection in fungal cells (e.g. hygromycin B phosphotransferase, phleomycin resistance, G418 resistance) under the control of an *A. nidulans* promoter. Additionally, the plasmid contains an internal portion of the atrD gene (e.g. about 3000 base pairs which lack 500 base pairs at the N-terminal end, and about 500 base pairs at the C-terminal end of the coding region specified by SEQ ID NO:1). The atrD gene fragment enables a single crossover gene disruption when transformed or otherwise introduced into *A. nidulans*.

Alternatively, a 5 kilobase pair to 6 kilobase pair region of *A. nidulans* genomic DNA containing the atrD gene is subcloned into the aforementioned plasmid. Then, a central portion of the atrD gene is removed and replaced with a selectable marker, such as hygromycin B phosphotransferase, for a double crossover gene replacement.

Gene disruption and gene replacement procedures for *A. nidulans* are well known in the art (See e.g. May et al, *J. Cell Biol.* 101, 712, 1985; Jones and Sealy-Lewis, *Curr. Genet.* 17, 81, 1990). Transformants are recovered on an appropriate selection medium, for example, hygromycin (if hygromycin B gene is used in the construction of disruption cassette). Gene replacement, or gene disruption, is verified by any suitable method, for example, by Southern blot hybridization.

Gene disruption or gene replacement strains are rendered hypersensitive to antifungal compounds, and are useful in screens for new antifungal compounds in whole cell growth inhibition studies.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 3

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 4002 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..4002

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

ATG TCC CCG CTA GAG ACA AAT CCC CTT TCG CCA GAG ACT GCT ATG CGC	48
Met Ser Pro Leu Glu Thr Asn Pro Leu Ser Pro Glu Thr Ala Met Arg	
1 5 10 15	
GAA CCT GCT GAG ACT TCA ACG ACG GAG GAG CAA GCT TCT ACA CCA CAC	96
Glu Pro Ala Glu Thr Ser Thr Thr Glu Glu Gln Ala Ser Thr Pro His	
20 25 30	
GCT GCG GAC GAG AAG AAA ATC CTC AGC GAC CTC TCG GCT CCA TCT AGT	144
Ala Ala Asp Glu Lys Lys Ile Leu Ser Asp Leu Ser Ala Pro Ser Ser	
35 40 45	
ACT ACA GCA ACC CCC GCA GAC AAG GAG CAC CGT CCT AAA TCG TCG TCC	192
Thr Thr Ala Thr Pro Ala Asp Lys Glu His Arg Pro Lys Ser Ser Ser	
50 55 60	
AGC AAT AAT GCG GTC TCG GTC AAC GAA GTC GAT GCG CTT ATT GCG CAC	240
Ser Asn Asn Ala Val Ser Val Asn Glu Val Asp Ala Leu Ile Ala His	
65 70 75 80	
CTG CCA GAA GAC GAG AGG CAG GTC TTG AAG ACG CAG CTG GAG GAG ATC	288
Leu Pro Glu Asp Glu Arg Gln Val Leu Lys Thr Gln Leu Glu Glu Ile	
85 90 95	
AAA GTA AAC ATC TCC TTC TTC GGT CTC TGG CGG TAT GCA ACA AAG ATG	336
Lys Val Asn Ile Ser Phe Phe Gly Leu Trp Arg Tyr Ala Thr Lys Met	
100 105 110	
GAT ATA CTT ATC ATG GTA ATC AGT ACA ATC TGT GCC ATT GCT GCC GCG	384
Asp Ile Leu Ile Met Val Ile Ser Thr Ile Cys Ala Ile Ala Ala Ala	
115 120 125	
TCG ACT TTC CAG AGG ATA ATG TTA TAT CAA ATC TCG TAC GAC GAG TTC	432
Ser Thr Phe Gln Arg Ile Met Leu Tyr Gln Ile Ser Tyr Asp Glu Phe	
130 135 140	
TAT GAT GAA TTG ACC AAG AAC GTA CTG TAC TTC GTA TAC CTC GGT ATC	480
Tyr Asp Glu Leu Thr Lys Asn Val Leu Tyr Phe Val Tyr Leu Gly Ile	
145 150 155 160	
GGC GAG TTT GTC ACT GTC TAT GTT AGT ACT GTT GGC TTC ATC TAT ACC	528
Gly Glu Phe Val Thr Val Tyr Val Ser Thr Val Gly Phe Ile Tyr Thr	
165 170 175	
GGA GAA CAC GCC ACG CAG AAG ATC CGC GAG TAT TAC CTT GAG TCT ATC	576
Gly Glu His Ala Thr Gln Lys Ile Arg Glu Tyr Tyr Leu Glu Ser Ile	
180 185 190	
CTG CGC CAG AAC ATT GGC TAT TTT GAT AAA CTC GGT GCC GGG GAA GTG	624
Leu Arg Gln Asn Ile Gly Tyr Phe Asp Lys Leu Gly Ala Gly Glu Val	
195 200 205	

-continued

ACC ACC CGT ATA ACA GCC GAT ACA AAC CTT ATC CAG GAT GGC ATT TCG	672
Thr Thr Arg Ile Thr Ala Asp Thr Asn Leu Ile Gln Asp Gly Ile Ser	
210 215 220	
GAG AAG GTC GGT CTC ACT TTG ACT GCC CTG GCG ACA TTC GTG ACA GCA	720
Glu Lys Val Gly Leu Thr Leu Thr Ala Leu Ala Thr Phe Val Thr Ala	
225 230 235 240	
TTC ATT ATC GCC TAC GTC AAA TAC TGG AAG TTG GCT CTA ATT TGC AGC	768
Phe Ile Ile Ala Tyr Val Lys Tyr Trp Lys Leu Ala Leu Ile Cys Ser	
245 250 255	
TCA ACA ATT GTG GCC CTC GTT CTC ACC ATG GGC GGT GGT TCT CAG TTT	816
Ser Thr Ile Val Ala Leu Val Leu Thr Met Gly Gly Gly Ser Gln Phe	
260 265 270	
ATC ATC AAG TAC AGC AAA AAG TCG CTT GAC AGC TAC GGT GCA GGC GGC	864
Ile Ile Lys Tyr Ser Lys Lys Ser Leu Asp Ser Tyr Gly Ala Gly Gly	
275 280 285	
ACT GTT GCG GAA GAG GTC ATC AGC TCC ATC AGA AAT GCC ACA GCG TTT	912
Thr Val Ala Glu Glu Val Ile Ser Ser Ile Arg Asn Ala Thr Ala Phe	
290 295 300	
GGC ACC CAA GAC AAG CTT GCG AAG CAG TAT GAG GTC CAC TTA GAC GAA	960
Gly Thr Gln Asp Lys Leu Ala Lys Gln Tyr Glu Val His Leu Asp Glu	
305 310 315 320	
GCT GAG AAA TGG GGA ACA AAG AAC CAG ATT GTC ATG GGT TTC ATG ATT	1008
Ala Glu Lys Trp Gly Thr Lys Asn Gln Ile Val Met Gly Phe Met Ile	
325 330 335	
GGC GCC ATG TTT GGC CTT ATG TAC TCG AAC TAC GGT CTT GGC TTC TGG	1056
Gly Ala Met Phe Gly Leu Met Tyr Ser Asn Tyr Gly Leu Gly Phe Trp	
340 345 350	
ATG GGT TCT CGT TTC CTG GTA GAT GGT GCA GTC GAT GTG GGT GAT ATT	1104
Met Gly Ser Arg Phe Leu Val Asp Gly Ala Val Asp Val Gly Asp Ile	
355 360 365	
CTC ACA GTT CTC ATG GCC ATC TTG ATC GGA TCG TTC TCC TTG GGG AAC	1152
Leu Thr Val Leu Met Ala Ile Leu Ile Gly Ser Phe Ser Leu Gly Asn	
370 375 380	
GTT AGT CCA AAT GCT CAA GCA TTT ACA AAC GCT GTG GCC GCG GCC GCA	1200
Val Ser Pro Asn Ala Gln Ala Phe Thr Asn Ala Val Ala Ala Ala Ala	
385 390 395 400	
AAG ATA TTT GGA ACG ATC GAT CGC CAG TCC CCA TTA GAT CCA TAT TCG	1248
Lys Ile Phe Gly Thr Ile Asp Arg Gln Ser Pro Leu Asp Pro Tyr Ser	
405 410 415	
AAC GAA GGG AAG ACG CTC GAC CAT TTT GAG GGC CAC ATT GAG TTA CGC	1296
Asn Glu Gly Lys Thr Leu Asp His Phe Glu Gly His Ile Glu Leu Arg	
420 425 430	
AAT GTC AAG CAT ATT TAC CCA TCT AGA CCC GAG GTC ACC GTC ATG GAG	1344
Asn Val Lys His Ile Tyr Pro Ser Arg Pro Glu Val Thr Val Met Glu	
435 440 445	
GAT GTT TCT CTG TCA ATG CCC GCT GGA AAA ACA ACC GCT TTA GTC GGC	1392
Asp Val Ser Leu Ser Met Pro Ala Gly Lys Thr Thr Ala Leu Val Gly	
450 455 460	
CCC TCT GGC TCT GGA AAA AGT ACG GTG GTC GGC TTG GTT GAG CGA TTC	1440
Pro Ser Gly Ser Gly Lys Ser Thr Val Val Gly Leu Val Glu Arg Phe	
465 470 475 480	
TAC ATG CCT GTT CGC GGT ACG GTT TTG CTG GAT GGC CAT GAC ATC AAG	1488
Tyr Met Pro Val Arg Gly Thr Val Leu Leu Asp Gly His Asp Ile Lys	
485 490 495	
GAC CTC AAT CTC CGC TGG CTT CGC CAA CAG ATC TCT TTG GTT AGC CAG	1536
Asp Leu Asn Leu Arg Trp Leu Arg Gln Gln Ile Ser Leu Val Ser Gln	
500 505 510	
GAG CCT GTT CTT TTT GGC ACG ACG ATT TAT AAG AAT ATT AGG CAC GGT	1584
Glu Pro Val Leu Phe Gly Thr Thr Ile Tyr Lys Asn Ile Arg His Gly	

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515					520					525						
CTC	ATC	GGC	ACA	AAG	TAC	GAG	AAT	GAA	TCC	GAG	GAT	AAG	GTC	CGG	GAA	1632
Leu	Ile	Gly	Thr	Lys	Tyr	Glu	Asn	Glu	Ser	Glu	Asp	Lys	Val	Arg	Glu	
	530					535					540					
CTC	ATC	GAG	AAC	GCG	GCA	AAA	ATG	GCG	AAT	GCT	CAT	GAC	TTT	ATT	ACT	1680
Leu	Ile	Glu	Asn	Ala	Ala	Lys	Met	Ala	Asn	Ala	His	Asp	Phe	Ile	Thr	
	545					550					555				560	
GCC	TTG	CCT	GAA	GGT	TAT	GAG	ACC	AAT	GTT	GGG	CAG	CGT	GGC	TTT	CTC	1728
Ala	Leu	Pro	Glu	Gly	Tyr	Glu	Thr	Asn	Val	Gly	Gln	Arg	Gly	Phe	Leu	
				565					570					575		
CTT	TCA	GGT	GGC	CAG	AAA	CAG	CGC	ATT	GCA	ATC	GCC	CGT	GCC	GTT	GTT	1776
Leu	Ser	Gly	Gly	Gln	Lys	Gln	Arg	Ile	Ala	Ile	Ala	Arg	Ala	Val	Val	
				580					585					590		
AGT	GAC	CCA	AAA	ATC	CTG	CTC	CTG	GAT	GAA	GCT	ACT	TCG	GCC	TTG	GAC	1824
Ser	Asp	Pro	Lys	Ile	Leu	Leu	Leu	Asp	Glu	Ala	Thr	Ser	Ala	Leu	Asp	
		595					600					605				
ACA	AAA	TCC	GAA	GGC	GTG	GTT	CAA	GCA	GCT	TTG	GAG	AGG	GCA	GCT	GAA	1872
Thr	Lys	Ser	Glu	Gly	Val	Val	Gln	Ala	Ala	Leu	Glu	Arg	Ala	Ala	Glu	
		610					615					620				
GGC	CGA	ACT	ACT	ATT	GTG	ATC	GCT	CAT	CGC	CTT	TCC	ACG	ATC	AAA	ACG	1920
Gly	Arg	Thr	Thr	Ile	Val	Ile	Ala	His	Arg	Leu	Ser	Thr	Ile	Lys	Thr	
	625					630					635				640	
GCG	CAC	AAC	ATT	GTG	GTT	CTG	GTC	AAT	GGC	AAA	ATT	GCT	GAA	CAA	GGA	1968
Ala	His	Asn	Ile	Val	Val	Leu	Val	Asn	Gly	Lys	Ile	Ala	Glu	Gln	Gly	
				645					650					655		
ACT	CAC	GAT	GAA	TTG	GTT	GAC	CGC	GGA	GGC	GCT	TAT	CGC	AAA	CTT	GTG	2016
Thr	His	Asp	Glu	Leu	Val	Asp	Arg	Gly	Gly	Ala	Tyr	Arg	Lys	Leu	Val	
			660					665					670			
GAG	GCT	CAA	CGT	ATC	AAT	GAA	CAG	AAG	GAA	GCT	GAC	GCC	TTG	GAG	GAC	2064
Glu	Ala	Gln	Arg	Ile	Asn	Glu	Gln	Lys	Glu	Ala	Asp	Ala	Leu	Glu	Asp	
		675					680					685				
GCC	GAC	GCT	GAG	GAT	CTC	ACG	AAT	GCA	GAT	ATT	GCC	AAA	ATC	AAA	ACT	2112
Ala	Asp	Ala	Glu	Asp	Leu	Thr	Asn	Ala	Asp	Ile	Ala	Lys	Ile	Lys	Thr	
	690					695					700					
GCG	TCA	AGC	GCA	TCA	TCC	GAT	CTC	GAC	GGA	AAA	CCC	ACA	ACC	ATT	GAC	2160
Ala	Ser	Ser	Ala	Ser	Ser	Asp	Leu	Asp	Gly	Lys	Pro	Thr	Thr	Ile	Asp	
	705					710					715				720	
CGC	ACG	GGC	ACC	CAC	AAG	TCT	GTT	TCC	AGC	GCG	ATT	CTT	TCT	AAA	AGA	2208
Arg	Thr	Gly	Thr	His	Lys	Ser	Val	Ser	Ser	Ala	Ile	Leu	Ser	Lys	Arg	
				725					730					735		
CCC	CCC	GAA	ACA	ACT	CCG	AAA	TAC	TCA	TTA	TGG	ACG	CTG	CTC	AAA	TTT	2256
Pro	Pro	Glu	Thr	Thr	Pro	Lys	Tyr	Leu	Leu	Trp	Thr	Leu	Leu	Lys	Phe	
			740					745						750		
GTT	GCT	TCC	TTC	AAC	CGC	CCT	GAA	ATC	CCG	TAC	ATG	CTC	ATC	GGT	CTT	2304
Val	Ala	Ser	Phe	Asn	Arg	Pro	Glu	Ile	Pro	Tyr	Met	Leu	Ile	Gly	Leu	
		755					760					765				
GTC	TTC	TCA	GTG	TTA	GCT	GGT	GGT	GGC	CAA	CCC	ACG	CAA	GCA	GTG	CTA	2352
Val	Phe	Ser	Val	Leu	Ala	Gly	Gly	Gly	Gln	Pro	Thr	Gln	Ala	Val	Leu	
	770					775					780					
TAT	GCT	AAA	GCC	ATC	AGC	ACA	CTC	TCG	CTC	CCA	GAA	TCA	CAA	TAT	AGC	2400
Tyr	Ala	Lys	Ala	Ile	Ser	Thr	Leu	Ser	Leu	Pro	Glu	Ser	Gln	Tyr	Ser	
				790					795					800		
AAG	CTT	CGA	CAT	GAT	GCG	GAT	TTC	TGG	TCA	TTG	ATG	TTC	TTC	GTG	GTT	2448
Lys	Leu	Arg	His	Asp	Ala	Asp	Phe	Trp	Ser	Leu	Met	Phe	Phe	Val	Val	
				805					810					815		
GGT	ATC	ATT	CAG	TTT	ATC	ACG	CAG	TCA	ACC	AAT	GGT	GCT	GCA	TTT	GCC	2496
Gly	Ile	Ile	Gln	Phe	Ile	Thr	Gln	Ser	Thr	Asn	Gly	Ala	Ala	Phe	Ala	
			820						825					830		
GTA	TGC	TCC	GAG	AGA	CTT	ATT	CGT	CGC	GCG	AGA	AGC	ACT	GCC	TTT	CGG	2544



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Val	Cys	Ser	Glu	Arg	Leu	Ile	Arg	Arg	Ala	Arg	Ser	Thr	Ala	Phe	Arg	
		835					840					845				
ACG	ATA	CTC	CGT	CAA	GAC	ATT	GCT	TTC	TTT	GAC	AAG	GAA	GAG	AAT	AGC	2592
Thr	Ile	Leu	Arg	Gln	Asp	Ile	Ala	Phe	Phe	Asp	Lys	Glu	Glu	Asn	Ser	
	850					855				860						
ACC	GGC	GCT	CTG	ACC	TCT	TTC	CTG	TCC	ACC	GAG	ACG	AAG	CAT	CTC	TCC	2640
Thr	Gly	Ala	Leu	Thr	Ser	Phe	Leu	Ser	Thr	Glu	Thr	Lys	His	Leu	Ser	
	865				870					875				880		
GGT	GTT	AGC	GGT	GTG	ACT	CTA	GGC	ACG	ATC	TTG	ATG	ACC	TCC	ACG	ACC	2688
Gly	Val	Ser	Gly	Val	Thr	Leu	Gly	Thr	Ile	Leu	Met	Thr	Ser	Thr	Thr	
					885				890					895		
CTA	GGA	GCG	GCT	ATC	ATT	ATT	GCC	CTG	GCG	ATT	GGG	TGG	AAA	TTG	GCC	2736
Leu	Gly	Ala	Ala	Ile	Ile	Ile	Ala	Leu	Ala	Ile	Gly	Trp	Lys	Leu	Ala	
			900					905					910			
TTA	GTT	TGT	ATC	TCG	GTT	GTG	CCG	GTT	CTC	CTG	GCA	TGC	GGT	TTC	TAC	2784
Leu	Val	Cys	Ile	Ser	Val	Val	Pro	Val	Leu	Leu	Ala	Cys	Gly	Phe	Tyr	
		915					920					925				
CGA	TTC	TAT	ATG	CTA	GCC	CAG	TTT	CAA	TCA	CGC	TCC	AAG	CTT	GCT	TAT	2832
Arg	Phe	Tyr	Met	Leu	Ala	Gln	Phe	Gln	Ser	Arg	Ser	Lys	Leu	Ala	Tyr	
	930					935					940					
GAG	GGA	TCT	GCA	AAC	TTT	GCT	TGC	GAG	GCT	ACA	TCG	TCT	ATC	CGC	ACA	2880
Glu	Gly	Ser	Ala	Asn	Phe	Ala	Cys	Glu	Ala	Thr	Ser	Ser	Ile	Arg	Thr	
	945				950					955					960	
GTT	GCG	TCA	TTA	ACC	CGG	GAA	AGG	GAT	GTC	TGG	GAG	ATT	TAC	CAT	GCC	2928
Val	Ala	Ser	Leu	Thr	Arg	Glu	Arg	Asp	Val	Trp	Glu	Ile	Tyr	His	Ala	
				965					970					975		
CAG	CTT	GAC	GCA	CAA	GGC	AGG	ACC	AGT	CTA	ATC	TCT	GTC	TTG	AGG	TCA	2976
Gln	Leu	Asp	Ala	Gln	Gly	Arg	Thr	Ser	Leu	Ile	Ser	Val	Leu	Arg	Ser	
			980					985					990			
TCC	CTG	TTA	TAT	GCG	TCG	TCG	CAG	GCA	CTT	GTT	TTC	TTC	TGC	GTT	GCG	3024
Ser	Leu	Leu	Tyr	Ala	Ser	Ser	Gln	Ala	Leu	Val	Phe	Phe	Cys	Val	Ala	
		995					1000						1005			
CTC	GGG	TTT	TGG	TAC	GGA	GGG	ACA	CTT	CTT	GGT	CAC	CAC	GAG	TAT	GAC	3072
Leu	Gly	Phe	Trp	Tyr	Gly	Gly	Thr	Leu	Leu	Gly	His	His	Glu	Tyr	Asp	
	1010					1015						1020				
ATT	TTC	CGC	TTC	TTT	GTT	TGT	TTC	TCC	GAG	ATT	CTC	TTT	GGT	GCT	CAA	3120
Ile	Phe	Arg	Phe	Phe	Val	Cys	Phe	Ser	Glu	Ile	Leu	Phe	Gly	Ala	Gln	
	1025				1030					1035					1040	
TCC	GCG	GGC	ACC	GTC	TTT	TCC	TTT	GCA	CCA	GAC	ATG	GGC	AAG	GCG	AAG	3168
Ser	Ala	Gly	Thr	Val	Phe	Ser	Phe	Ala	Pro	Asp	Met	Gly	Lys	Ala	Lys	
				1045					1050					1055		
AAT	GCG	GCC	GCC	GAA	TTC	CGA	CGA	CTG	TTC	GAC	CGA	AAG	CCA	CAA	ATT	3216
Asn	Ala	Ala	Ala	Glu	Phe	Arg	Arg	Leu	Phe	Asp	Arg	Lys	Pro	Gln	Ile	
			1060					1065					1070			
GAT	AAC	TGG	TCT	GAA	GAG	GGC	GAG	AAG	CTC	GAA	ACG	GTG	GAA	GGT	GAA	3264
Asp	Asn	Trp	Ser	Glu	Glu	Gly	Glu	Lys	Leu	Glu	Thr	Val	Glu	Gly	Glu	
		1075					1080					1085				
ATC	GAA	TTT	AGG	AAC	GTG	CAC	TTC	AGA	TAC	CCG	ACC	CGC	CCA	GAA	CAG	3312
Ile	Glu	Phe	Arg	Asn	Val	His	Phe	Arg	Tyr	Pro	Thr	Arg	Pro	Glu	Gln	
	1090					1095						1100				
CCT	GTC	CTG	CGC	GGC	TTG	GAC	CTG	ACC	GTG	AAG	CCT	GGA	CAA	TAT	GTT	3360
Pro	Val	Leu	Arg	Gly	Leu	Asp	Leu	Thr	Val	Lys	Pro	Gly	Gln	Tyr	Val	
	1105				1110					1115					1120	
GCG	CTT	GTC	GGA	CCC	AGC	GGT	TGT	GGC	AAG	AGT	ACC	ACC	ATT	GCA	TTG	3408
Ala	Leu	Val	Gly	Pro	Ser	Gly	Cys	Gly	Lys	Ser	Thr	Thr	Ile	Ala	Leu	
				1125					1130					1135		
CTT	GAG	CGC	TTT	TAC	GAT	GCG	ATT	GCC	GGG	TCC	ATC	CTT	GTT	GAT	GGG	3456
Leu	Glu	Arg	Phe	Tyr	Asp	Ala	Ile	Ala	Gly	Ser	Ile	Leu	Val	Asp	Gly	
			1140					1145						1150		

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AAG GAC ATA AGT AAA CTA AAT ATC AAC TCC TAC CGC AGC TTT CTG TCA	3504
Lys Asp Ile Ser Lys Leu Asn Ile Asn Ser Tyr Arg Ser Phe Leu Ser	
1155 1160 1165	
CTG GTC AGC CAG GAG CCG ACA CTG TAC CAG GGC ACC ATC AAG GAA AAC	3552
Leu Val Ser Gln Glu Pro Thr Leu Tyr Gln Gly Thr Ile Lys Glu Asn	
1170 1175 1180	
ATC TTA CTT GGT ATT GTC GAA GAT GAC GTA CCG GAA GAA TTC TTG ATT	3600
Ile Leu Leu Gly Ile Val Glu Asp Asp Val Pro Glu Glu Phe Leu Ile	
1185 1190 1195 1200	
AAG GCT TGC AAG GAC GCT AAT ATC TAC GAC TTC ATC ATG TCG CTC CCG	3648
Lys Ala Cys Lys Asp Ala Asn Ile Tyr Asp Phe Ile Met Ser Leu Pro	
1205 1210 1215	
GAG GGC TTT AAT ACA GTT GTT GGC AGC AAG GGA GGC ATG TTG TCT GGC	3696
Glu Gly Phe Asn Thr Val Val Gly Ser Lys Gly Gly Met Leu Ser Gly	
1220 1225 1230	
GGC CAA AAG CAA CGT GTG GCC ATT GCC CGA GCC CTT CTT CGG GAT CCC	3744
Gly Gln Lys Gln Arg Val Ala Ile Ala Arg Ala Leu Leu Arg Asp Pro	
1235 1240 1245	
AAA ATC CTT CTT CTC GAT GAA GCG ACG TCA GCC CTC GAC TCC GAG TCA	3792
Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ser Glu Ser	
1250 1255 1260	
GAA AAG GTC GTC CAG GCG GCT TTG GAT GCC GCT GCC CGA GGC CGA ACC	3840
Glu Lys Val Val Gln Ala Ala Leu Asp Ala Ala Arg Gly Arg Thr	
1265 1270 1275 1280	
ACA ATC GCC GTT GCA CAC CGA CTC AGC ACG ATT CAA AAG GCG GAC GTT	3888
Thr Ile Ala Val Ala His Arg Leu Ser Thr Ile Gln Lys Ala Asp Val	
1285 1290 1295	
ATC TAT GTT TTC GAC CAA GGC AAG ATC GTC GAA AGC GGA ACG CAC AGC	3936
Ile Tyr Val Phe Asp Gln Gly Lys Ile Val Glu Ser Gly Thr His Ser	
1300 1305 1310	
GAA CTG GTC CAG AAA AAG GGC CGG TAC TAC GAG CTG GTC AAC TTG CAG	3984
Glu Leu Val Gln Lys Lys Gly Arg Tyr Tyr Glu Leu Val Asn Leu Gln	
1315 1320 1325	
AGC TTG GGC AAG GGC CAT	4002
Ser Leu Gly Lys Gly His	
1330	

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1334 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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

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100					105					110					
Asp	Ile	Leu	Ile	Met	Val	Ile	Ser	Thr	Ile	Cys	Ala	Ile	Ala	Ala	Ala
		115					120					125			
Ser	Thr	Phe	Gln	Arg	Ile	Met	Leu	Tyr	Gln	Ile	Ser	Tyr	Asp	Glu	Phe
		130					135					140			
Tyr	Asp	Glu	Leu	Thr	Lys	Asn	Val	Leu	Tyr	Phe	Val	Tyr	Leu	Gly	Ile
		145					150					155			160
Gly	Glu	Phe	Val	Thr	Val	Tyr	Val	Ser	Thr	Val	Gly	Phe	Ile	Tyr	Thr
				165					170					175	
Gly	Glu	His	Ala	Thr	Gln	Lys	Ile	Arg	Glu	Tyr	Tyr	Leu	Glu	Ser	Ile
			180						185					190	
Leu	Arg	Gln	Asn	Ile	Gly	Tyr	Phe	Asp	Lys	Leu	Gly	Ala	Gly	Glu	Val
			195						200					205	
Thr	Thr	Arg	Ile	Thr	Ala	Asp	Thr	Asn	Leu	Ile	Gln	Asp	Gly	Ile	Ser
							215							220	
Glu	Lys	Val	Gly	Leu	Thr	Leu	Thr	Ala	Leu	Ala	Thr	Phe	Val	Thr	Ala
				225					230					235	240
Phe	Ile	Ile	Ala	Tyr	Val	Lys	Tyr	Trp	Lys	Leu	Ala	Leu	Ile	Cys	Ser
				245					250					255	
Ser	Thr	Ile	Val	Ala	Leu	Val	Leu	Thr	Met	Gly	Gly	Gly	Ser	Gln	Phe
				260					265					270	
Ile	Ile	Lys	Tyr	Ser	Lys	Lys	Ser	Leu	Asp	Ser	Tyr	Gly	Ala	Gly	Gly
				275					280					285	
Thr	Val	Ala	Glu	Glu	Val	Ile	Ser	Ser	Ile	Arg	Asn	Ala	Thr	Ala	Phe
				290					295					300	
Gly	Thr	Gln	Asp	Lys	Leu	Ala	Lys	Gln	Tyr	Glu	Val	His	Leu	Asp	Glu
				305					310					315	320
Ala	Glu	Lys	Trp	Gly	Thr	Lys	Asn	Gln	Ile	Val	Met	Gly	Phe	Met	Ile
				325					330					335	
Gly	Ala	Met	Phe	Gly	Leu	Met	Tyr	Ser	Asn	Tyr	Gly	Leu	Gly	Phe	Trp
				340					345					350	
Met	Gly	Ser	Arg	Phe	Leu	Val	Asp	Gly	Ala	Val	Asp	Val	Gly	Asp	Ile
				355					360					365	
Leu	Thr	Val	Leu	Met	Ala	Ile	Leu	Ile	Gly	Ser	Phe	Ser	Leu	Gly	Asn
				370					375					380	
Val	Ser	Pro	Asn	Ala	Gln	Ala	Phe	Thr	Asn	Ala	Val	Ala	Ala	Ala	Ala
				385					390					395	400
Lys	Ile	Phe	Gly	Thr	Ile	Asp	Arg	Gln	Ser	Pro	Leu	Asp	Pro	Tyr	Ser
				405					410					415	
Asn	Glu	Gly	Lys	Thr	Leu	Asp	His	Phe	Glu	Gly	His	Ile	Glu	Leu	Arg
				420					425					430	
Asn	Val	Lys	His	Ile	Tyr	Pro	Ser	Arg	Pro	Glu	Val	Thr	Val	Met	Glu
				435					440					445	
Asp	Val	Ser	Leu	Ser	Met	Pro	Ala	Gly	Lys	Thr	Thr	Ala	Leu	Val	Gly
				450					455					460	
Pro	Ser	Gly	Ser	Gly	Lys	Ser	Thr	Val	Val	Gly	Leu	Val	Glu	Arg	Phe
				465					470					475	480
Tyr	Met	Pro	Val	Arg	Gly	Thr	Val	Leu	Leu	Asp	Gly	His	Asp	Ile	Lys
				485					490					495	
Asp	Leu	Asn	Leu	Arg	Trp	Leu	Arg	Gln	Gln	Ile	Ser	Leu	Val	Ser	Gln
				500					505					510	
Glu	Pro	Val	Leu	Phe	Gly	Thr	Thr	Ile	Tyr	Lys	Asn	Ile	Arg	His	Gly
				515					520					525	

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Leu Ile Gly Thr Lys Tyr Glu Asn Glu Ser Glu Asp Lys Val Arg Glu  
 530 535 540

Leu Ile Glu Asn Ala Ala Lys Met Ala Asn Ala His Asp Phe Ile Thr  
 545 550 555 560

Ala Leu Pro Glu Gly Tyr Glu Thr Asn Val Gly Gln Arg Gly Phe Leu  
 565 570 575

Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Val Val  
 580 585 590

Ser Asp Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp  
 595 600 605

Thr Lys Ser Glu Gly Val Val Gln Ala Ala Leu Glu Arg Ala Ala Glu  
 610 615 620

Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Ile Lys Thr  
 625 630 635 640

Ala His Asn Ile Val Val Leu Val Asn Gly Lys Ile Ala Glu Gln Gly  
 645 650 655

Thr His Asp Glu Leu Val Asp Arg Gly Gly Ala Tyr Arg Lys Leu Val  
 660 665 670

Glu Ala Gln Arg Ile Asn Glu Gln Lys Glu Ala Asp Ala Leu Glu Asp  
 675 680 685

Ala Asp Ala Glu Asp Leu Thr Asn Ala Asp Ile Ala Lys Ile Lys Thr  
 690 695 700

Ala Ser Ser Ala Ser Ser Asp Leu Asp Gly Lys Pro Thr Thr Ile Asp  
 705 710 715 720

Arg Thr Gly Thr His Lys Ser Val Ser Ser Ala Ile Leu Ser Lys Arg  
 725 730 735

Pro Pro Glu Thr Thr Pro Lys Tyr Ser Leu Trp Thr Leu Leu Lys Phe  
 740 745 750

Val Ala Ser Phe Asn Arg Pro Glu Ile Pro Tyr Met Leu Ile Gly Leu  
 755 760 765

Val Phe Ser Val Leu Ala Gly Gly Gly Gln Pro Thr Gln Ala Val Leu  
 770 775 780

Tyr Ala Lys Ala Ile Ser Thr Leu Ser Leu Pro Glu Ser Gln Tyr Ser  
 785 790 795 800

Lys Leu Arg His Asp Ala Asp Phe Trp Ser Leu Met Phe Phe Val Val  
 805 810 815

Gly Ile Ile Gln Phe Ile Thr Gln Ser Thr Asn Gly Ala Ala Phe Ala  
 820 825 830

Val Cys Ser Glu Arg Leu Ile Arg Arg Ala Arg Ser Thr Ala Phe Arg  
 835 840 845

Thr Ile Leu Arg Gln Asp Ile Ala Phe Phe Asp Lys Glu Glu Asn Ser  
 850 855 860

Thr Gly Ala Leu Thr Ser Phe Leu Ser Thr Glu Thr Lys His Leu Ser  
 865 870 875 880

Gly Val Ser Gly Val Thr Leu Gly Thr Ile Leu Met Thr Ser Thr Thr  
 885 890 895

Leu Gly Ala Ala Ile Ile Ile Ala Leu Ala Ile Gly Trp Lys Leu Ala  
 900 905 910

Leu Val Cys Ile Ser Val Val Pro Val Leu Leu Ala Cys Gly Phe Tyr  
 915 920 925

Arg Phe Tyr Met Leu Ala Gln Phe Gln Ser Arg Ser Lys Leu Ala Tyr  
 930 935 940

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Glu Gly Ser Ala Asn Phe Ala Cys Glu Ala Thr Ser Ser Ile Arg Thr  
 945 950 955 960

Val Ala Ser Leu Thr Arg Glu Arg Asp Val Trp Glu Ile Tyr His Ala  
 965 970 975

Gln Leu Asp Ala Gln Gly Arg Thr Ser Leu Ile Ser Val Leu Arg Ser  
 980 985 990

Ser Leu Leu Tyr Ala Ser Ser Gln Ala Leu Val Phe Phe Cys Val Ala  
 995 1000 1005

Leu Gly Phe Trp Tyr Gly Gly Thr Leu Leu Gly His His Glu Tyr Asp  
 1010 1015 1020

Ile Phe Arg Phe Phe Val Cys Phe Ser Glu Ile Leu Phe Gly Ala Gln  
 1025 1030 1035 1040

Ser Ala Gly Thr Val Phe Ser Phe Ala Pro Asp Met Gly Lys Ala Lys  
 1045 1050 1055

Asn Ala Ala Ala Glu Phe Arg Arg Leu Phe Asp Arg Lys Pro Gln Ile  
 1060 1065 1070

Asp Asn Trp Ser Glu Glu Gly Glu Lys Leu Glu Thr Val Glu Gly Glu  
 1075 1080 1085

Ile Glu Phe Arg Asn Val His Phe Arg Tyr Pro Thr Arg Pro Glu Gln  
 1090 1095 1100

Pro Val Leu Arg Gly Leu Asp Leu Thr Val Lys Pro Gly Gln Tyr Val  
 1105 1110 1115 1120

Ala Leu Val Gly Pro Ser Gly Cys Gly Lys Ser Thr Thr Ile Ala Leu  
 1125 1130 1135

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

Lys Asp Ile Ser Lys Leu Asn Ile Asn Ser Tyr Arg Ser Phe Leu Ser  
 1155 1160 1165

Leu Val Ser Gln Glu Pro Thr Leu Tyr Gln Gly Thr Ile Lys Glu Asn  
 1170 1175 1180

Ile Leu Leu Gly Ile Val Glu Asp Asp Val Pro Glu Glu Phe Leu Ile  
 1185 1190 1195 1200

Lys Ala Cys Lys Asp Ala Asn Ile Tyr Asp Phe Ile Met Ser Leu Pro  
 1205 1210 1215

Glu Gly Phe Asn Thr Val Val Gly Ser Lys Gly Gly Met Leu Ser Gly  
 1220 1225 1230

Gly Gln Lys Gln Arg Val Ala Ile Ala Arg Ala Leu Leu Arg Asp Pro  
 1235 1240 1245

Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ser Glu Ser  
 1250 1255 1260

Glu Lys Val Val Gln Ala Ala Leu Asp Ala Ala Ala Arg Gly Arg Thr  
 1265 1270 1275 1280

Thr Ile Ala Val Ala His Arg Leu Ser Thr Ile Gln Lys Ala Asp Val  
 1285 1290 1295

Ile Tyr Val Phe Asp Gln Gly Lys Ile Val Glu Ser Gly Thr His Ser  
 1300 1305 1310

Glu Leu Val Gln Lys Lys Gly Arg Tyr Tyr Glu Leu Val Asn Leu Gln  
 1315 1320 1325

Ser Leu Gly Lys Gly His  
 1330

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 4002 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

AUGUCCCCG	UAGAGACAAA	UCCCCUUUCG	CCAGAGACUG	CUAUGCGCGA	ACCUGCUGAG	60
ACUUCAACGA	CGGAGGAGCA	AGCUUCUACA	CCACACGCUG	CGGACGAGAA	GAAAAUCCUC	120
AGCGACCUCU	CGGCUCCAUC	UAGUACUACA	GCAACCCCG	CAGACAAGGA	GCACCGUCCU	180
AAAUCGUCGU	CCAGCAAUAA	UGCGGUCUCG	GUCAACGAAG	UCGAUGCGCU	UAUUGCGCAC	240
CUGCCAGAAG	ACGAGAGGCA	GGUCUUGAAG	ACGCAGCUGG	AGGAGAUCAA	AGUAAACAUC	300
UCCUUCUUCG	GUCUCUGGGC	GUAUGCAACA	AAGAUGGAUA	UACUUAUCAU	GGUAAUCAGU	360
ACAAUCUGUG	CCAUUGCUCG	CGCGUCGACU	UUCCAGAGGA	UAAUGUUUAU	UCAAUUCUG	420
UACGACGAGU	UCUAUGAUGA	AUUGACCAAG	AACGUACUGU	ACUUCGUUAU	CCUCGGUAUC	480
GGCGAGUUUG	UCACUGUCUA	UGUUAGUACU	GUUGGCUUCA	UCUAUACCGG	AGAACACGCC	540
ACGCAGAAGA	UCCGCGAGUA	UUACCUUGAG	UCUAUCCUGC	GCCAGAACAU	UGGCUAUUUU	600
GAUAAACUCG	GUGCCGGGGA	AGUGACCACC	CGUAUAACAG	CCGAUACAAA	CCUUAUCCAG	660
GAUGGCAUUU	CGGAGAAGGU	CGGUCUCACU	UUGACUGCCC	UGGCGACAUU	CGUGACAGCA	720
UUCAUUUUCG	CCUACGUCAA	AUACUGGAAG	UUGGCUCUAA	UUUGCAGCUC	AACAAUUGUG	780
GCCCUCGUUC	UCACCAUGGG	CGGUGGUUCU	CAGUUUAUCA	UCAAGUACAG	CAAAAAGUCG	840
CUUGACAGCU	ACGGUGCAGG	CGGCACUGUU	GCGGAAGAGG	UCAUCAGCUC	CAUCAGAAAU	900
GCCACAGCGU	UUGGCACCCA	AGACAAGCUU	GCGAAGCAGU	AUGAGGUCCA	CUUAGACGAA	960
GCUGAGAAAU	GGGGAACAAA	GAACCAGAUU	GUCAUGGGUU	UCAUGAUUGG	CGCCAUGUUU	1020
GGCCUUUUGU	ACUCGAACUA	CGGUCUUGGC	UUCUGGAUGG	GUUCUCGUUU	CCUGGUAGAU	1080
GGUGCAGUCG	AUGUGGGUGA	UAUUCUCACA	GUUCUCAUGG	CCAUCUUGAU	CGGAUCGUUC	1140
UCCUUGGGGA	ACGUUAGUCC	AAAUGCUCAA	GCAUUUACAA	ACGCUGUGGC	CGCGGCCGCA	1200
AAGAUUUUUG	GAACGAUCGA	UCGCCAGUCC	CCAUUAGAUC	CAUAUUCGAA	CGAAGGGAAG	1260
ACGCUCGACC	AUUUUGAGGG	CCACAUGAG	UUACGCAAUG	UCAAGCAUUA	UUACCCAUCU	1320
AGACCCGAGG	UCACCGUCAU	GGAGGAUGUU	UCUCUGUCAA	UGCCCCGUGG	AAAAACAACC	1380
GCUUUAGUCG	GCCCUCUGG	CUCUGGAAAA	AGUACGGUGG	UCGGCUUGGU	UGAGCGAUUC	1440
UACAUGCCUG	UUCGCGGUAC	GGUUUUGCUG	GAUGGCCAUG	ACAUCAAGGA	CCUCAUUCUC	1500
CGCUGGCUUC	GCCAACAGAU	CUCUUUGGUU	AGCCAGGAGC	CUGUUCUUUU	UGGCACGACG	1560
AUUUUAAGA	AUAUUAGGCA	CGGUCUCAUC	GGCACAAAGU	ACGAGAAUGA	AUCCGAGGAU	1620
AAGGUCCGGG	AACUCAUCGA	GAACGCGGCA	AAAUUGGCGA	AUGCUC AUGA	CUUUUUUACU	1680
GCCUUGCCUG	AAGGUUAUGA	GACCAAUGUU	GGGCAGCGUG	GCUUUCUCCU	UUCAGGUGGC	1740
CAGAAACAGC	GCAUUGCAAU	CGCCCUGGCC	GUUGUAGUG	ACCCAAAAAU	CCUGCUCCUG	1800
GAUGAAGCUA	CUUCGGCCUU	GGACACAAAA	UCCGAAGGCG	UGGUUCAAGC	AGCUUUGGAG	1860
AGGGCAGCUG	AAGGCCGAAC	UACUAUUGUG	AUCGCUCAUC	GCCUUUCCAC	GAUCAAAACG	1920
GCGCACAAACA	UUGUGGUUCU	GGUCA AUGGC	AAAAUUGCUG	AACAAGGAAC	UCACGAUGAA	1980

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UUGGUUGACC	GCGGAGGCGC	UUAUCGCAAA	CUUGUGGAGG	CUCAACGUAU	CAAUGAACAG	2040
AAGGAAGCUG	ACGCCUUGGA	GGACGCCGAC	GCUGAGGAUC	UCACGAAUGC	AGAUAUUGCC	2100
AAAAUCAAAA	CUGCUCUCAA	CGCAUCAUCC	GAUCUCGACG	GAAAACCCAC	AACCAUUGAC	2160
CGCACGGGCA	CCCACAAGUC	UGUUUCCAGC	GCGAUUCUUU	CUAAAAGACC	CCCCGAAACA	2220
ACUCCGAAAU	ACUCAUUUAG	GACGCUGCUC	AAAUUUGUUG	CUUCCUUCAA	CGCCCUGAA	2280
AUCCCGUACA	UGCUCUACGG	UCUUGUCUUC	UCAGUGUUAG	CUGGUGGUGG	CCAACCCACG	2340
CAAGCAGUGC	UAUAUGCUAA	AGCCAUCAGC	ACACUCUCGC	UCCAGAAUC	ACAAUAUAGC	2400
AAGCUUCGAC	AUGAUGCGGA	UUUCUGGUCA	UUGAUGUUCU	UCGUGGUUGG	UAUCAUUCAG	2460
UUUAUCACGC	AGUCAACCAA	UGGUGCUGCA	UUUGCCGUU	GCUCCGAGAG	ACUUAUUCGU	2520
CGCGGAGAA	GCACUGCCUU	UCGGACGAUA	CUCCGUCAAG	ACAUUGCUIU	CUUUGACAAG	2580
GAAAGAAUA	GCACCGGCGC	UCUGACCUCU	UUCCUGUCCA	CCGAGACGAA	GCAUCUCUCC	2640
GGUGUUAGCG	GUGUGACUCU	AGGCACGAUC	UUGAUGACCU	CCACGACCCU	AGGAGCGGCU	2700
AUCAUUUUG	CCCUGGCGAU	UGGGUGGAAA	UUGGCCUUG	UUUGUAUCUC	GGUUGUGCCG	2760
GUUCUCCUGG	CAUGCUGUUU	CUACCGAUUC	UAUAUGCUAG	CCCAGUUUCA	AUCACGCUCC	2820
AAGCUUGCUU	AUGAGGGAUC	UGCAAACUUU	GCUUGCGAGG	CUACAUCGUC	UAUCCGCACA	2880
GUUGCGUCAU	UAACCCGGGA	AAGGGAUGUC	UGGGAGAUUU	ACCAUGCCCA	GCUUGACGCA	2940
CAAGGCAGGA	CCAGUCUAAU	CUCUGUCUUG	AGGUCAUCCC	UGUUUAUUGC	GUCGUCGCG	3000
GCACUUGUUU	UCUUCUGCGU	UGCGCUCGGG	UUUUGGUACG	GAGGGACACU	UCUUGGUCAC	3060
CACGAGUAUG	ACAUUUUCCG	CUUCUUUGUU	UGUUUCUCCG	AGAUUCUCUU	UGGUGCUCAA	3120
UCCGCGGCA	CCGUCUUUUC	CUUUGCACCA	GACAUGGCA	AGGCGAAGAA	UGCGGCCGCC	3180
GAAUCCGAC	GACUGUUCGA	CCGAAAGCCA	CAAAUGAUA	ACUGGUCUGA	AGAGGGCGAG	3240
AAGCUCGAAA	CGGUGGAAGG	UGAAAUCGAA	UUUAGGAACG	UGCACUUCAG	AUACCCGACC	3300
CGCCAGAAAC	AGCCUGUCCU	GCGCGGCUUG	GACCUGACCG	UGAAGCCUGG	ACAAUAUGUU	3360
GCGCUUGUCG	GACCCAGCGG	UUGUGGCAAG	AGUACCACCA	UUGCAUUGCU	UGAGCGCUUU	3420
UACGAUGCGA	UUGCCGGGUC	CAUCCUUGUU	GAUGGGAAGG	ACAUAAAGUA	ACUAAAUAUC	3480
AACUCCUACC	GCAGCUUUUC	GUCACUGGUC	AGCCAGGAGC	CGACACUGUA	CCAGGGCACC	3540
AUCAAGGAAA	ACAUCUUACU	UGGUUUUGUC	GAAGAUGACG	UACCGGAAGA	AUUCUUGAAU	3600
AAGGCUUGCA	AGGACGCUAA	UAUCUACGAC	UUCAUCAUGU	CGUCCCGGA	GGGCUUUAU	3660
ACAGUUGUUG	GCAGCAAGGG	AGGCAUGUUG	UCUGGCGGCC	AAAAGCAACG	UGUGGCCAAU	3720
GCCCGAGCCC	UUCUUCGGGA	UCCCAAAUUC	CUUCUUCUCG	AUGAAGCGAC	GUCAGCCUC	3780
GACUCCGAGU	CAGAAAAGGU	CGUCCAGGCG	GCUUUGGAUG	CCGCUGCCCG	AGGCCGAACC	3840
ACAAUCGCCG	UUGCACACCG	ACUCAGCAGC	AUUCAAAAGG	CGGACGUUUA	CUAUGUUUUC	3900
GACCAAGGCA	AGAUCGUCGA	AAGCGGAACG	CACAGCGAAC	UGGUCCAGAA	AAAGGGCCGG	3960
UACUACGAGC	UGGUCAACUU	GCAGAGCUUG	GGCAAGGCC	AU		4002

I claim:

1. A method for determining the fungal multiple drug resistance (MDR) inhibition activity of a compound which comprises:

a) placing a culture of fungal cells, transformed with a vector which expresses a nucleic acid encoding an atrD protein consisting essentially of the amino acid sequence of SEQ ID NO:2, in the presence of:

(i) an antifungal agent to which said fungal cell is resistant, but to which said fungal cell is sensitive in its untransformed state;

(ii) a compound suspected of possessing *Aspergillus nidulans* MDR inhibition activity; and

b) determining the fungal MDR inhibition activity of said compound by measuring the ability of the antifungal agent to inhibit the growth of said fungal cell.

**29**

2. The method of claim 1 wherein the fungal cell is *Saccharomyces cerevisiae*.
3. The method of claim 1 wherein the culture of fungal cells is transformed with a vector which expresses a nucleic

**30**

acid encoding an atrD protein of the amino acid sequence of SEQ ID NO:2.

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