Supplementary Material

Structural and functional features of the intracellular amino-terminus of DEG/ENaC ion channels

Tavernarakis, Everett, Kyrpides, Driscoll

Materials and Methods

Sequences

GeneBank accession numbers for the DEG/ENaC protein sequences analyzed are: DEG-1: L34414, DEL-1: U76403, FLR-1: AB012617, MEC-4: U53669, MEC-10: P34886, UNC-8: U76402, UNC-105: Q09274, C18B2.6: U40413, C24G7.1: U88310, C24G7.2: U88310, C24G7.4: U88310, C27C12.5: Z69883, F23B2.3: Z82266, T28B8.5: Z81133, T28F2.7: AF000198, ZK770.1: U97404, FaNaCh: X92113, αrENaC: X70497, βrENaC: X77932, γrENaC: X77933, δENaC: 4506819, BNC1: U57352, BNaC2: U78180, βASIC: CAA07080, ACCN3: NM_004769, DmNaCh: AAD09149, PPK: AF043263 and RPK: AF043264. Accession numbers for other sequences used were: Procaricain: 2098464, Procathepsin L: 5822035, Procathepsin K: 6435592, Procathepsin B: 2982152, Aminopeptidase C (PEPC_STRTR): Q56115, Aminopeptidase G (PEPG_LACHE): P94870, Cathepsin C precursor (CATC_SCHMA): Q26563, Cysteine proteinase precursor (CYSP_THEAN): P25781, Prepro-cathepsin C (CATC_HUMAN): 1582221, Cathepsin K: 5542106, Cathepsin H: 4139678, Cathepsin L: 4503155 and Papain: 494472. The accession number for the eukaryotic thiol (cysteine) proteases histidine active site motif in the Prosite databese is PS00639. Prosite documentation on this motif can be accessed with the entry code PDOC00126. The amino acid sequence pattern for the motif is as follows: [LIVMGSTAN]-x-H-[GSACE]-[LIVM]-x-[LIVMAT](2)-G-x-[GSADNH]. The accession number for the Soybean trypsin inhibitor (Kunitz) protease inhibitors family signature in the Prosite database is PS00283. Prosite documentation on this motif can be accessed with the entry code

PDOC00255. The amino acid sequence pattern for the motif is as follows: [LIVM]-x-D-x-[EDNTY]-[DG]-[RKHDENQ]-x-[LIVM]-x(5)-Y-x-[LIVM].

Database Mining

The Block Maker algorithm [1, 2] was run on the Blocks Server web site: (http://blocks.fhcrc.org/). Blocks identified were subjected to Multiple EM for Motif Elicitation algorithms [3, 4], run on the MEME system, web based, server (http://www.sdsc.edu/MEME/meme/website/). BLAST searches [5] were performed with the National Center for Biotechnology Information web based servers (NCBI; http://www.ncbi.nlm.nih.gov/BLAST/). Prosite searches were performed with the Expert Protein Analysis System (ExPASy) proteomics web based server at the Swiss Institute of Bioinformatics (SIB; http://www.expasy.ch/tools/scnpsit1.html).

Alignments

Multiple sequence alignments were generated using the Baylor College of Medicine Search Launcher (http://dot.imgen.bcm.tmc.edu:9331/multi-align/multi-align.html) with the ClustalW algorithm [6] and displayed with SeqVu (The Garvan Institute of Medical Research, Sydney, Australia) and BoxShade 3.21 (http://www.ch.embnet.org/software/BOX_form.html). We assessed the statistical significance of the similarity between degenerin intracellular amino-termini and thiol protease active sites by generating blocks using the Block Maker algorithm [7, 8], from both groups of sequences and aligning them with ClustalW. The blocks aligned with a p-Value of 1.23e-34. Next, the quality of the alignment was calculated to a p-Value of

1.86e-05 using the FASTA package PRSS3 algorithm [7] to uniformly shuffle the sequences. We conclude that there is a significant level of sequence similarity between the intracellular amino-terminal region that is situated immediately before the first membrane spanning domain of DEG/ENaC proteins, and thiol-cysteine protease active sites. The same stringent criteria were applied to evaluate the similarity between the extreme amino terminus of MEC-4 and pro-domains of cathepsins. In this case the blocks generated aligned with a p-Value of 1.03e-27. The quality of the alignment was calculated to a p-Value 1.87e-18 after uniformly shuffling the sequences

3D Modeling

The PDB database (Brookhaven National Laboratory, http://www.rcsb.org/pdb/) of solved protein structures was scanned for sequences similar to MEC-4 intracellular N-terminus. The proposed model of the MEC-4 cytosolic amino terminus (residues 1-80) was based upon procaripain (25% identity, 62% similarity, over 80 aa; PDB ID: 1PCI). Sequence similarity was established via FASTA sequence comparison. (http://www.fasta.genome.ad.jp). The model was constructed with the aid of MSI's InsightIIã software suite. Alignment gaps (all ≤ 2 aa) were satisfied with the structural analog of procaripain, procathepsin L (PDB ID: 1CS8, RMS [1PCI{12-80}|1CS8{1-78}]: .483 Å). The model was refined via subjection to energy optimization with InsightII (5 Å hydration shell; Forcefields: cvff, amber) and energy minimization with ISI's Sculptä . The structure of the remaining 30 residues of the N-terminus (residues 81-111) was tentatively predicted via shared similarity with a Napthalene Dioxygenase and a Histone Acetyltransferase domain (30% identity, 66% similarity over 30 aa; PDB ID: 1NDO and

1CMO respectively). Secondary structure prediction was aided by the Jpred[2] server (http://jura.ebi.ac.uk:8888). Association of the 30-residue remainder (residues 81-111) with first 80 residues was accomplished via MSI's docking module. InsightIIã from MSI together with RasMol 2.7.1 (http://www.umass.edu/microbio/rasmol/ and http://www.bernstein-plus-sons.com/software/rasmol/) were used for visualization and presentation of protein 3D models.

Materials and Methods References

1. Henikoff S, Henikoff JG: **Automated assembly of protein blocks for database searching**. ***Nucleic Acids Res*** 1991, **19**:6565-6572.

2. Henikoff S, Henikoff JG, Alford WJ, Pietrokovski S: **Automated construction and graphical presentation of protein blocks from unaligned sequences**. ***Gene*** 1995, **163**:17-26.

3. Timothy LB, Elkan C: **Fitting a mixture model by expectation maximization to discover motifs in biopolymers**. In: ***Second International Conference on Intelligent Systems for Molecular Biology***; 1994; Menlo Park, California. 28-36.

4. Timothy LB, Gribskov M: **Combining evidence using p-values: application to sequence homology searches. *Bioinformatics*** 1998, **14**:48-54.

5. Altschul SF, Madden TL, Schaffer AA, Zhang J, Zhang Z, Miller W, Lipman DJ: **Gapped BLAST and PSI-BLAST: a new generation of protein database search programs**. ***Nucleic Acids Res*** 1997, **25**:3389-3402.

6. Thompson JD, Higgins DG, Gibson TJ: **CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice**. ***Nucleic Acids Res*** 1994, **22**:4673-4680.

7. Pearson WR: **Rapid and sensitive sequence comparison with FASTP and FASTA**. ***Methods Enzymol*** 1990, **183**:63-98.

Supplementary Figure Legends

Figure 3. A conserved motif, similar to thiol-protease histidine active sites is present in the intracellular domain of DEG/ENaC superfamily members.

Amino-acid alignment of five representative DEG/ENaC superfamily members from different species and five representative cysteine proteases, around the histidine active site. Listed are selected DEG/ENaC family members, representative thiol-proteases from 5 different organisms and the Prosite signature consensus for thiol proteases. Residue positions are noted on both sides of the alignments for each of the designated sequences. When sequence conservation is greater that 50% identical residues are highlighted in dark blue. Conservative substitutions are indicated in light blue shading.

Figure 4. Schematic representation of DEG/ENaC ion channel subunit structure and topology.

Colored boxes indicate defined channel modules. These include the two Membrane Spanning Domains (MSDs; dark-blue shading), and the three Cysteine-Rich Domains (CRDs; red shading; the first CRD is absent in mammalian channels and is depicted by light red shading). The small light-blue oval depicts the putative Extracellular Regulatory Domain (ERD) identified by García-Añoveros and co-workers in *C. elegans* degenerins [1]. The green box overlapping with CRDIII denotes the Neurotoxin-related domain (NTD) [2]. The conserved intracellular region with similarity to thiol-protease histidine active sites is shown in yellow. Shown in pink is the amino-terminal domain modeled based on protease Pro-domains. The brown dot near MSDII in (b) represents the amino-acid position (Alanine 713) affected in dominant, toxic mutants in degenerins.

Figure 4 References

1. Tavernarakis N, Driscoll M: ***Caenorhabditis elegans*** **degenerins and vertebrate ENaC ion channels contain an extracellular domain related to venom neurotoxins.** *J Neurogenet* 2000,**13**:257-264.

2. Garcia-Anoveros J, Ma C, Chalfie M: **Regulation of *Caenorhabditis elegans* degenerin proteins by a putative extracellular domain.** *Curr Biol* 1995, **5**:441-448.

Figure 5. The trans-suppressor mutation in the UNC-8 conserved intracellular, N-terminal region.

UNC-8 is expressed in motor neurons and command interneurons of the nematode nervous system and has been shown to mediate proprioception and regulation of locomotion of this simple organism [1]. Dominant, gain-of-function mutations in the *unc-8* gene cause transient swelling and dysfunction of the above neurons and render the canonical sinusoidal movement of the worm severely uncoordinated. Absence of the UNC-8 protein as witnessed in *unc-8* loss-of–function mutant strains results in a pronounced reduction of the amplitude and wavelength of the normal sinusoidal movement. Interestingly, the effects of a dominant mutation in the UNC-8 protein can be completely blocked by mutating the absolutely conserved, active-site, histidine residue to tyrosine within the thiol-potease motif, highlighting the functional importance of this motif. This suppression is observed both when the histidine substitution resides in cis, on the same protein molecule as the dominant mutations or in trans, on different co-expressed molecules as observed in heterozygote animals carrying a dominant allele on one chromosome and a histidine-substituted allele on the other. Such a pattern of genetic suppression suggests that UNC-8 proteins interact to form a dimeric or multimeric complex where more than one molecules associate to form a channel.

Figure 5 Reference

1. Tavernarakis N, Shreffler W, Wang S, Driscoll M: ***unc-8*, a DEG/ENaC family member, encodes a subunit of a candidate mechanically gated channel that modulates *C. elegans* locomotion**. *Neuron* 1997, **18**:107-119.

Supplementary Figures

Figure 3

Tavernarakis et al., Supplementary Material

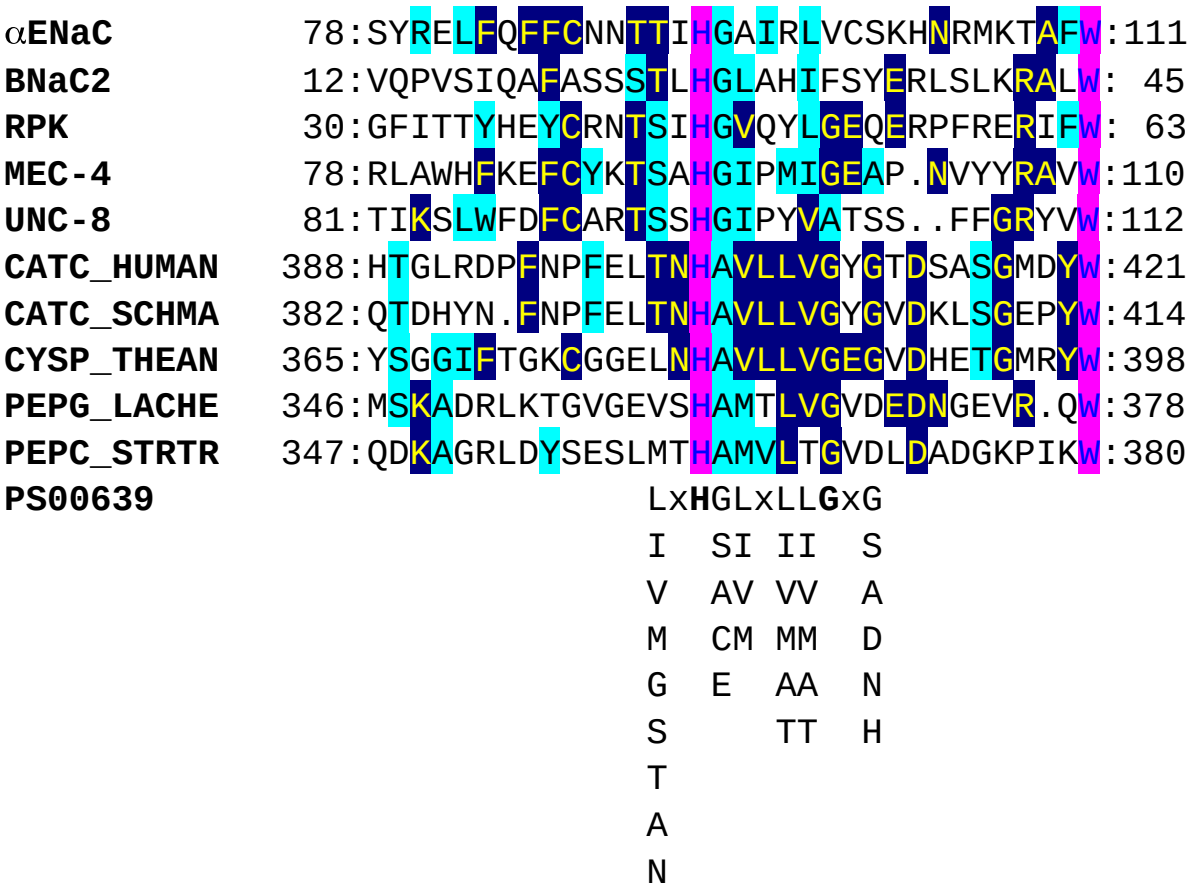

Figure 4
Tavernarakis et al., Supplementary Material

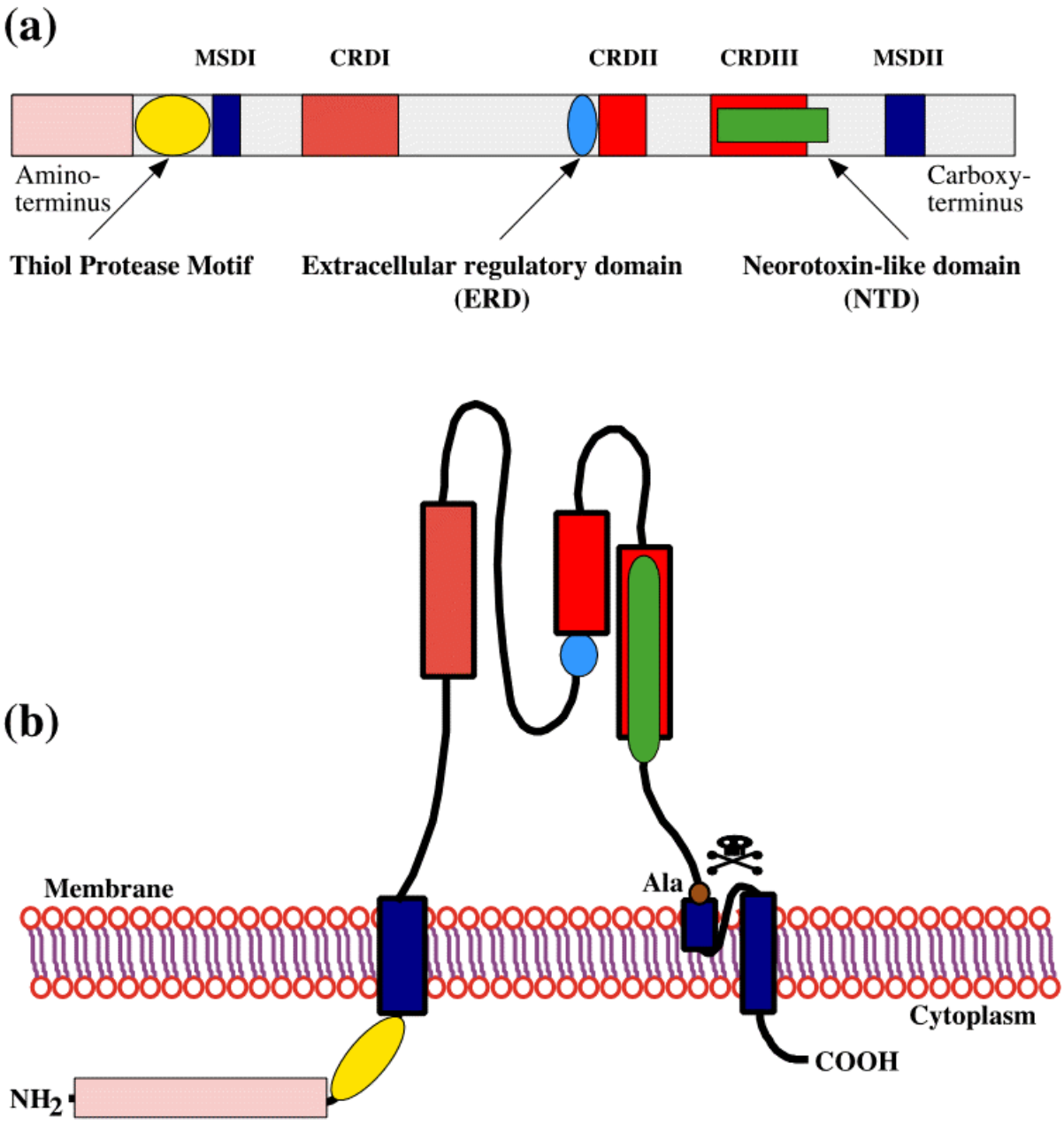

Figure 4
Tavernarakis et al., Supplementary Material

Figure 5

Tavernarakis et al., Supplementary Material

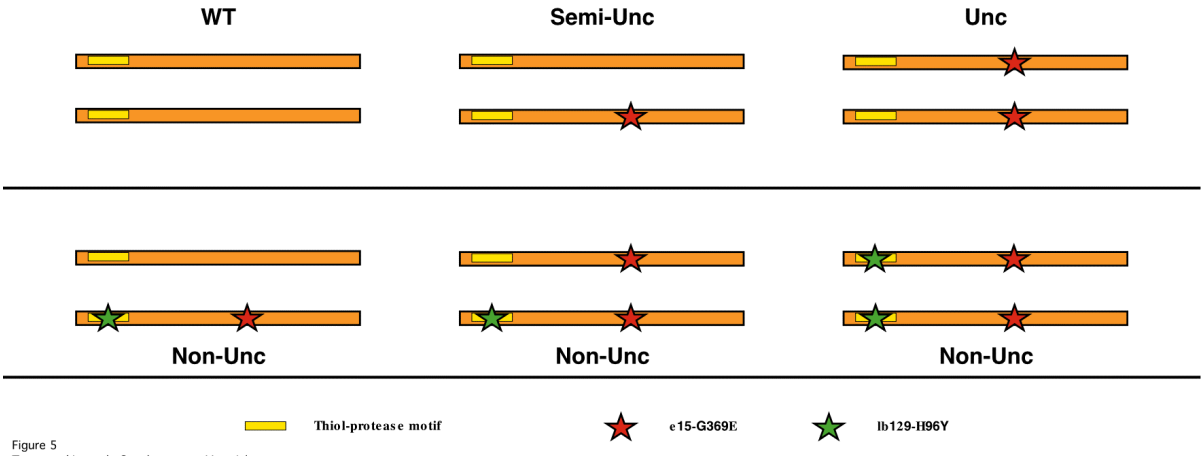

Figure 5
Tavernarakis et al., Supplementary Material

Model Coordinates (PDB Format)

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TITLE    2 DEGENERIN MEC-4
COMPND    MOL_ID: 1;
COMPND   2 MOLECULE: MEC4_N_TERMINUS;
KEYWDS    DEGENERIN, ENAC CHANNEL, TOUCH RECEPTOR
EXPDTA    THEORETICAL MODELLING
AUTHOR    J.K.EVERETT, N. TAVERNARAKIS
REMARK 220
REMARK 220 EXPERIMENTAL DETAILS
REMARK 220
REMARK 220 EXPERIMENT TYPE                : THEORETICAL MODELLING
REMARK 220
REMARK 220 REMARK {Method}:
REMARK 220         STRUCTURE GENERATED BY HOMOLOGY MODELING ONTO THE
REMARK 220         X-RAY CRYSTAL STRUCTURES OF 1PCI, 1CS8 AND
REMARK 220         1CJL. ENERGY MINIMIZATIONS RESTRAINED BY LOCKING
REMARK 220         THR 66. THIS MODEL REPRESENTS THE FIRST SUBDOMAIN
REMARK 220         (SUBDOMAIN I) OF THE MEC-4 AMINO TERMINUS. LOCKING
REMARK 220         THR 66 PREVENTS HELIX D FROM DRIFTING DURING
REMARK 220         ENERGY MINIMIZATIONS WHICH WOULD NOT BE INDICATIVE
REMARK 220         OF OUR PROPOSED MODEL. THE ABSENCE OF SUBDOMAIN II
REMARK 220         RESIDUES (67 - 112) NECESITATES THIS LOCK DOWN.
REMARK 220
REMARK 220 REMARK {Structural}:
REMARK 220         HELIX C POSSESSES A ~20 DEGREE BEND CENTERED AROUND
REMARK 220         PRO 27. HELIX C IS REPORTED AS A SINGLE HELIX RATHER
REMARK 220         THAN TWO. THE BEND IS MOST LIKELY REPRESENTIVE OF
REMARK 220         A BREAK THEN A BEND.
REMARK 220
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HELIX    2  B  PRO     16  MET     20  1                                   4
HELIX    3  C  SER     21  GLU     40  1                                   19
HELIX    4  D  GLU     57  ILE     65  1                                   8
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ATOM    161  CA  ASP    15      -7.941  35.872   9.000
ATOM    162  C   ASP    15      -7.841  34.520   8.179
ATOM    163  O   ASP    15      -8.653  34.321   7.271
ATOM    164  CB  ASP    15      -9.168  36.780   8.681
ATOM    165  CG  ASP    15      -9.375  37.223   7.234
ATOM    166  OD1 ASP    15      -9.824  36.484   6.371
ATOM    167  OD2 ASP    15      -9.024  38.525   7.020
ATOM    168  H   ASP    15      -6.128  36.758   8.074
ATOM    169  N   PRO    16      -6.910  33.542   8.437
ATOM    170  CA  PRO    16      -6.691  32.364   7.530
ATOM    171  C   PRO    16      -7.845  31.340   7.273
ATOM    172  O   PRO    16      -8.001  30.873   6.142
ATOM    173  CB  PRO    16      -5.406  31.732   8.096
ATOM    174  CG  PRO    16      -5.323  32.215   9.543
ATOM    175  CD  PRO    16      -5.924  33.617   9.533
ATOM    176  N   SER    17      -8.689  31.047   8.274
ATOM    177  CA  SER    17      -9.979  30.321   8.065
ATOM    178  C   SER    17     -10.975  30.920   6.996
ATOM    179  O   SER    17     -11.696  30.158   6.350
ATOM    180  CB  SER    17     -10.689  30.198   9.439
ATOM    181  OG  SER    17     -10.276  29.061  10.213
ATOM    182  H   SER    17      -8.419  31.478   9.162
ATOM    183  HG  SER    17     -10.864  29.003  10.985
ATOM    184  N   GLU    18     -11.038  32.254   6.825
ATOM    185  CA  GLU    18     -11.949  32.939   5.867
ATOM    186  C   GLU    18     -11.246  33.355   4.527
ATOM    187  O   GLU    18     -11.930  33.457   3.506
ATOM    188  CB  GLU    18     -12.637  34.076   6.675
ATOM    189  CG  GLU    18     -13.357  35.168   5.843
ATOM    190  CD  GLU    18     -12.472  36.318   5.381
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ATOM    191  OE1 GLU    18     -11.885  36.341   4.304
ATOM    192  OE2 GLU    18     -12.449  37.331   6.283
ATOM    193  H   GLU    18     -10.327  32.770   7.359
ATOM    194  N   TYR    19      -9.926  33.627   4.481
ATOM    195  CA  TYR    19      -9.258  34.155   3.245
ATOM    196  C   TYR    19      -8.309  33.214   2.419
ATOM    197  O   TYR    19      -8.205  33.393   1.202
ATOM    198  CB  TYR    19      -8.615  35.542   3.542
ATOM    199  CG  TYR    19      -7.334  35.697   4.401
ATOM    200  CD1 TYR    19      -7.024  36.979   4.862
ATOM    201  CD2 TYR    19      -6.474  34.641   4.728
ATOM    202  CE1 TYR    19      -5.883  37.202   5.625
ATOM    203  CE2 TYR    19      -5.319  34.868   5.472
ATOM    204  CZ  TYR    19      -5.019  36.150   5.912
ATOM    205  OH  TYR    19      -3.872  36.358   6.633
ATOM    206  H   TYR    19      -9.459  33.634   5.399
ATOM    207  HH  TYR    19      -3.134  35.886   6.215
ATOM    208  N   MET    20      -7.603  32.240   3.025
ATOM    209  CA  MET    20      -6.639  31.355   2.301
ATOM    210  C   MET    20      -7.321  30.502   1.173
ATOM    211  O   MET    20      -7.962  29.488   1.445
ATOM    212  CB  MET    20      -5.893  30.480   3.355
ATOM    213  CG  MET    20      -4.989  31.211   4.372
ATOM    214  SD  MET    20      -3.248  30.824   4.103
ATOM    215  CE  MET    20      -2.498  32.086   5.143
ATOM    216  H   MET    20      -7.799  32.147   4.027
ATOM    217  N   SER    21      -7.178  30.886  -0.109
ATOM    218  CA  SER    21      -7.900  30.206  -1.226
ATOM    219  C   SER    21      -7.118  29.016  -1.876
ATOM    220  O   SER    21      -7.393  27.862  -1.541
ATOM    221  CB  SER    21      -8.413  31.278  -2.209
ATOM    222  OG  SER    21      -8.965  30.655  -3.371
ATOM    223  H   SER    21      -6.800  31.838  -0.196
ATOM    224  HG  SER    21      -8.993  31.323  -4.090
ATOM    225  N   GLN    22      -6.109  29.256  -2.736
ATOM    226  CA  GLN    22      -5.111  28.200  -3.112
ATOM    227  C   GLN    22      -4.217  27.686  -1.922
ATOM    228  O   GLN    22      -4.067  26.477  -1.750
ATOM    229  CB  GLN    22      -4.266  28.710  -4.315
ATOM    230  CG  GLN    22      -3.569  27.621  -5.183
ATOM    231  CD  GLN    22      -2.802  26.494  -4.486
ATOM    232  OE1 GLN    22      -3.321  25.405  -4.266
ATOM    233  NE2 GLN    22      -1.569  26.711  -4.111
ATOM    234  H   GLN    22      -5.983  30.245  -2.975
ATOM    235 1HE2 GLN    22      -1.204  25.983  -3.490
ATOM    236 2HE2 GLN    22      -1.227  27.676  -4.202
ATOM    237  N   VAL    23      -3.664  28.586  -1.089
ATOM    238  CA  VAL    23      -2.844  28.220   0.116
ATOM    239  C   VAL    23      -3.509  27.178   1.102
ATOM    240  O   VAL    23      -2.918  26.123   1.333
ATOM    241  CB  VAL    23      -2.346  29.554   0.789
ATOM    242  CG1 VAL    23      -1.122  29.397   1.719
ATOM    243  CG2 VAL    23      -1.949  30.659  -0.223
ATOM    244  H   VAL    23      -3.824  29.557  -1.368
ATOM    245  N   TYR    24      -4.711  27.419   1.661
ATOM    246  CA  TYR    24      -5.591  26.332   2.193
ATOM    247  C   TYR    24      -5.916  25.154   1.194
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ATOM    248  O   TYR    24      -5.849  23.988   1.592
ATOM    249  CB  TYR    24      -6.871  26.995   2.789
ATOM    250  CG  TYR    24      -7.875  25.962   3.314
ATOM    251  CD1 TYR    24      -7.504  25.140   4.380
ATOM    252  CD2 TYR    24      -9.045  25.679   2.599
ATOM    253  CE1 TYR    24      -8.249  24.009   4.682
ATOM    254  CE2 TYR    24      -9.789  24.542   2.905
ATOM    255  CZ  TYR    24      -9.370  23.693   3.925
ATOM    256  OH  TYR    24      -9.951  22.472   4.093
ATOM    257  H   TYR    24      -5.088  28.356   1.477
ATOM    258  HH  TYR    24      -9.226  21.869   4.313
ATOM    259  N   GLY    25      -6.255  25.432  -0.079
ATOM    260  CA  GLY    25      -6.448  24.389  -1.133
ATOM    261  C   GLY    25      -5.413  23.246  -1.272
ATOM    262  O   GLY    25      -5.664  22.145  -0.771
ATOM    263  H   GLY    25      -6.298  26.439  -0.279
ATOM    264  N   ASP    26      -4.266  23.494  -1.928
ATOM    265  CA  ASP    26      -3.154  22.500  -2.000
ATOM    266  C   ASP    26      -3.024  21.447  -0.825
ATOM    267  O   ASP    26      -3.121  20.274  -1.173
ATOM    268  CB  ASP    26      -1.824  23.164  -2.449
ATOM    269  CG  ASP    26      -1.193  24.182  -1.514
ATOM    270  OD1 ASP    26      -1.727  25.230  -1.172
ATOM    271  OD2 ASP    26       0.017  23.768  -1.054
ATOM    272  H   ASP    26      -4.175  24.464  -2.266
ATOM    273  N   PRO    27      -2.841  21.709   0.509
ATOM    274  CA  PRO    27      -2.787  20.635   1.554
ATOM    275  C   PRO    27      -4.067  19.761   1.777
ATOM    276  O   PRO    27      -3.942  18.536   1.801
ATOM    277  CB  PRO    27      -2.354  21.416   2.808
ATOM    278  CG  PRO    27      -2.886  22.825   2.569
ATOM    279  CD  PRO    27      -2.676  23.055   1.077
ATOM    280  N   LEU    28      -5.276  20.336   1.917
ATOM    281  CA  LEU    28      -6.544  19.537   1.934
ATOM    282  C   LEU    28      -6.755  18.567   0.714
ATOM    283  O   LEU    28      -6.981  17.373   0.924
ATOM    284  CB  LEU    28      -7.734  20.501   2.192
ATOM    285  CG  LEU    28      -9.070  20.139   1.485
ATOM    286  CD1 LEU    28     -10.136  19.614   2.462
ATOM    287  CD2 LEU    28      -9.633  21.360   0.753
ATOM    288  H   LEU    28      -5.260  21.362   1.844
ATOM    289  N   ALA    29      -6.640  19.044  -0.539
ATOM    290  CA  ALA    29      -6.481  18.150  -1.716
ATOM    291  C   ALA    29      -5.312  17.106  -1.609
ATOM    292  O   ALA    29      -5.566  15.947  -1.284
ATOM    293  CB  ALA    29      -6.383  19.080  -2.940
ATOM    294  H   ALA    29      -6.346  20.028  -0.570
ATOM    295  N   TYR    30      -4.050  17.500  -1.842
ATOM    296  CA  TYR    30      -2.863  16.600  -1.798
ATOM    297  C   TYR    30      -2.710  15.731  -0.508
ATOM    298  O   TYR    30      -3.016  14.544  -0.563
ATOM    299  CB  TYR    30      -1.619  17.489  -2.103
ATOM    300  CG  TYR    30      -0.206  16.884  -1.984
ATOM    301  CD1 TYR    30       0.547  17.145  -0.834
ATOM    302  CD2 TYR    30       0.381  16.167  -3.033
ATOM    303  CE1 TYR    30       1.874  16.730  -0.752
ATOM    304  CE2 TYR    30       1.703  15.744  -2.945
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ATOM    305  CZ  TYR    30       2.454  16.047  -1.816
ATOM    306  OH  TYR    30       3.777  15.705  -1.761
ATOM    307  H   TYR    30      -3.952  18.502  -2.065
ATOM    308  HH  TYR    30       4.298  16.398  -2.221
ATOM    309  N   LEU    31      -2.261  16.286   0.628
ATOM    310  CA  LEU    31      -2.043  15.520   1.898
ATOM    311  C   LEU    31      -3.036  14.333   2.173
ATOM    312  O   LEU    31      -2.618  13.206   2.464
ATOM    313  CB  LEU    31      -2.050  16.546   3.068
ATOM    314  CG  LEU    31      -0.774  17.397   3.300
ATOM    315  CD1 LEU    31      -0.808  18.074   4.674
ATOM    316  CD2 LEU    31       0.493  16.541   3.205
ATOM    317  H   LEU    31      -2.182  17.310   0.596
ATOM    318  N   GLN    32      -4.350  14.582   2.036
ATOM    319  CA  GLN    32      -5.387  13.513   2.014
ATOM    320  C   GLN    32      -5.226  12.451   0.864
ATOM    321  O   GLN    32      -4.749  11.346   1.135
ATOM    322  CB  GLN    32      -6.792  14.186   1.985
ATOM    323  CG  GLN    32      -7.246  15.040   3.212
ATOM    324  CD  GLN    32      -8.363  16.088   3.097
ATOM    325  OE1 GLN    32      -8.217  17.216   3.557
ATOM    326  NE2 GLN    32      -9.513  15.804   2.544
ATOM    327  H   GLN    32      -4.538  15.528   1.685
ATOM    328 1HE2 GLN    32     -10.192  16.569   2.564
ATOM    329 2HE2 GLN    32      -9.647  14.855   2.187
ATOM    330  N   GLU    33      -5.606  12.751  -0.394
ATOM    331  CA  GLU    33      -5.476  11.800  -1.537
ATOM    332  C   GLU    33      -4.017  11.374  -1.926
ATOM    333  O   GLU    33      -3.882  10.468  -2.743
ATOM    334  CB  GLU    33      -6.304  12.356  -2.730
ATOM    335  CG  GLU    33      -6.706  11.344  -3.835
ATOM    336  CD  GLU    33      -7.031   9.927  -3.362
ATOM    337  OE1 GLU    33      -8.013   9.645  -2.682
ATOM    338  OE2 GLU    33      -6.113   9.019  -3.788
ATOM    339  H   GLU    33      -6.048  13.675  -0.506
ATOM    340  N   THR    34      -2.928  11.960  -1.388
ATOM    341  CA  THR    34      -1.536  11.409  -1.564
ATOM    342  C   THR    34      -1.252  10.037  -0.855
ATOM    343  O   THR    34      -0.681   9.129  -1.463
ATOM    344  CB  THR    34      -0.455  12.500  -1.277
ATOM    345  OG1 THR    34       0.698  12.246  -2.069
ATOM    346  CG2 THR    34       0.062  12.641   0.167
ATOM    347  H   THR    34      -3.145  12.626  -0.626
ATOM    348  HG1 THR    34       0.940  11.316  -1.939
ATOM    349  N   THR    35      -1.725   9.870   0.392
ATOM    350  CA  THR    35      -1.789   8.547   1.088
ATOM    351  C   THR    35      -2.792   7.515   0.451
ATOM    352  O   THR    35      -2.390   6.390   0.144
ATOM    353  CB  THR    35      -2.066   8.790   2.607
ATOM    354  OG1 THR    35      -1.489  10.012   3.057
ATOM    355  CG2 THR    35      -1.480   7.714   3.532
ATOM    356  H   THR    35      -2.151  10.717   0.784
ATOM    357  HG1 THR    35      -2.215  10.607   3.297
ATOM    358  N   LYS    36      -4.067   7.884   0.220
ATOM    359  CA  LYS    36      -5.022   7.062  -0.584
ATOM    360  C   LYS    36      -4.590   6.707  -2.049
ATOM    361  O   LYS    36      -4.848   5.587  -2.485
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ATOM    362  CB  LYS    36      -6.422   7.722  -0.492
ATOM    363  CG  LYS    36      -7.643   6.829  -0.829
ATOM    364  CD  LYS    36      -7.660   5.399  -0.244
ATOM    365  CE  LYS    36      -8.016   5.306   1.250
ATOM    366  NZ  LYS    36      -7.070   4.391   1.907
ATOM    367  H   LYS    36      -4.288   8.841   0.519
ATOM    368 1HZ  LYS    36      -6.138   4.829   1.990
ATOM    369 2HZ  LYS    36      -7.346   4.170   2.878
ATOM    370  N   PHE    37      -3.877   7.587  -2.772
ATOM    371  CA  PHE    37      -3.138   7.230  -4.024
ATOM    372  C   PHE    37      -2.163   6.006  -3.898
ATOM    373  O   PHE    37      -2.347   5.017  -4.603
ATOM    374  CB  PHE    37      -2.412   8.509  -4.548
ATOM    375  CG  PHE    37      -3.216   9.451  -5.461
ATOM    376  CD1 PHE    37      -4.254   8.944  -6.249
ATOM    377  CD2 PHE    37      -2.889  10.804  -5.562
ATOM    378  CE1 PHE    37      -4.950   9.774  -7.122
ATOM    379  CE2 PHE    37      -3.582  11.635  -6.436
ATOM    380  CZ  PHE    37      -4.614  11.120  -7.214
ATOM    381  H   PHE    37      -3.794   8.517  -2.338
ATOM    382  N   VAL    38      -1.163   6.030  -2.996
ATOM    383  CA  VAL    38      -0.324   4.819  -2.679
ATOM    384  C   VAL    38      -1.165   3.527  -2.333
ATOM    385  O   VAL    38      -0.798   2.431  -2.754
ATOM    386  CB  VAL    38       0.755   5.138  -1.586
ATOM    387  CG1 VAL    38       2.010   4.240  -1.702
ATOM    388  CG2 VAL    38       1.292   6.588  -1.594
ATOM    389  H   VAL    38      -1.112   6.895  -2.445
ATOM    390  N   THR    39      -2.305   3.657  -1.628
ATOM    391  CA  THR    39      -3.290   2.540  -1.428
ATOM    392  C   THR    39      -3.911   1.939  -2.746
ATOM    393  O   THR    39      -3.813   0.733  -2.975
ATOM    394  CB  THR    39      -4.396   2.999  -0.421
ATOM    395  OG1 THR    39      -3.862   3.712   0.693
ATOM    396  CG2 THR    39      -5.195   1.849   0.198
ATOM    397  H   THR    39      -2.562   4.642  -1.495
ATOM    398  HG1 THR    39      -4.362   4.543   0.763
ATOM    399  N   GLU    40      -4.485   2.772  -3.628
ATOM    400  CA  GLU    40      -4.900   2.381  -5.012
ATOM    401  C   GLU    40      -3.755   2.217  -6.094
ATOM    402  O   GLU    40      -4.059   2.108  -7.284
ATOM    403  CB  GLU    40      -5.939   3.453  -5.473
ATOM    404  CG  GLU    40      -6.796   4.120  -4.361
ATOM    405  CD  GLU    40      -6.910   5.640  -4.466
ATOM    406  OE1 GLU    40      -6.076   6.360  -5.008
ATOM    407  OE2 GLU    40      -8.033   6.113  -3.863
ATOM    408  H   GLU    40      -4.544   3.754  -3.318
ATOM    409  N   ARG    41      -2.461   2.195  -5.717
ATOM    410  CA  ARG    41      -1.291   2.245  -6.642
ATOM    411  C   ARG    41      -1.274   3.478  -7.622
ATOM    412  O   ARG    41      -1.795   3.427  -8.743
ATOM    413  CB  ARG    41      -1.016   0.854  -7.284
ATOM    414  CG  ARG    41       0.325   0.803  -8.053
ATOM    415  CD  ARG    41       0.703  -0.583  -8.585
ATOM    416  NE  ARG    41       2.069  -0.463  -9.165
ATOM    417  CZ  ARG    41       2.438  -0.842 -10.381
ATOM    418  NH1 ARG    41       1.675  -1.482 -11.209
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ATOM    419  NH2 ARG    41       3.635  -0.564 -10.757
ATOM    420  H   ARG    41      -2.340   2.262  -4.698
ATOM    421 1HH1 ARG    41       0.749  -1.711 -10.840
ATOM    422 2HH1 ARG    41       2.069  -1.701 -12.130
ATOM    423 1HH2 ARG    41       4.189  -0.011 -10.096
ATOM    424 2HH2 ARG    41       3.876  -0.803 -11.720
ATOM    425  N   GLU    42      -0.651   4.584  -7.187
ATOM    426  CA  GLU    42      -0.574   5.860  -7.968
ATOM    427  C   GLU    42       0.689   6.709  -7.572
ATOM    428  O   GLU    42       1.440   7.146  -8.449
ATOM    429  CB  GLU    42      -1.892   6.683  -7.849
ATOM    430  CG  GLU    42      -3.134   6.167  -8.617
ATOM    431  CD  GLU    42      -4.090   5.341  -7.766
ATOM    432  OE1 GLU    42      -4.124   5.380  -6.538
ATOM    433  OE2 GLU    42      -4.888   4.541  -8.520
ATOM    434  H   GLU    42      -0.579   4.579  -6.162
ATOM    435  N   TYR    43       0.942   6.955  -6.273
ATOM    436  CA  TYR    43       2.061   7.824  -5.794
ATOM    437  C   TYR    43       3.139   7.103  -4.910
ATOM    438  O   TYR    43       2.874   6.137  -4.188
ATOM    439  CB  TYR    43       1.387   9.011  -5.026
ATOM    440  CG  TYR    43       0.848  10.235  -5.790
ATOM    441  CD1 TYR    43       0.610  10.270  -7.171
ATOM    442  CD2 TYR    43       0.652  11.400  -5.038
ATOM    443  CE1 TYR    43       0.172  11.443  -7.779
ATOM    444  CE2 TYR    43       0.213  12.571  -5.648
ATOM    445  CZ  TYR    43      -0.027  12.587  -7.017
ATOM    446  OH  TYR    43      -0.423  13.738  -7.628
ATOM    447  H   TYR    43       0.303   6.476  -5.631
ATOM    448  HH  TYR    43      -1.399  13.765  -7.643
ATOM    449  N   TYR    44       4.361   7.656  -4.916
ATOM    450  CA  TYR    44       5.368   7.453  -3.831
ATOM    451  C   TYR    44       4.898   7.844  -2.375
ATOM    452  O   TYR    44       4.868   6.985  -1.488
ATOM    453  CB  TYR    44       6.708   8.123  -4.272
ATOM    454  CG  TYR    44       6.760   9.665  -4.365
ATOM    455  CD1 TYR    44       5.999  10.345  -5.322
ATOM    456  CD2 TYR    44       7.517  10.400  -3.446
ATOM    457  CE1 TYR    44       5.950  11.737  -5.324
ATOM    458  CE2 TYR    44       7.466  11.793  -3.449
ATOM    459  CZ  TYR    44       6.663  12.457  -4.370
ATOM    460  OH  TYR    44       6.568  13.824  -4.324
ATOM    461  H   TYR    44       4.499   8.373  -5.637
ATOM    462  HH  TYR    44       6.215  14.077  -3.451
ATOM    463  N   GLU    45       4.559   9.124  -2.112
ATOM    464  CA  GLU    45       4.417   9.683  -0.741
ATOM    465  C   GLU    45       3.054   9.366  -0.025
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ATOM    467  CB  GLU    45       4.812  11.193  -0.776
ATOM    468  CG  GLU    45       3.918  12.268  -1.470
ATOM    469  CD  GLU    45       3.515  12.127  -2.945
ATOM    470  OE1 GLU    45       3.156  11.089  -3.488
ATOM    471  OE2 GLU    45       3.579  13.324  -3.592
ATOM    472  H   GLU    45       4.682   9.750  -2.920
ATOM    473  N   ASP    46       3.091   8.495   1.003
ATOM    474  CA  ASP    46       1.915   8.189   1.871
ATOM    475  C   ASP    46       2.000   8.967   3.227
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ATOM    476  O   ASP    46       2.456   8.437   4.246
ATOM    477  CB  ASP    46       1.740   6.655   2.032
ATOM    478  CG  ASP    46       2.983   5.777   1.940
ATOM    479  OD1 ASP    46       3.562   5.514   0.892
ATOM    480  OD2 ASP    46       3.385   5.351   3.167
ATOM    481  H   ASP    46       4.019   8.083   1.195
ATOM    482  N   PHE    47       1.586  10.238   3.236
ATOM    483  CA  PHE    47       1.630  11.109   4.444
ATOM    484  C   PHE    47       0.379  12.049   4.430
ATOM    485  O   PHE    47       0.018  12.628   3.398
ATOM    486  CB  PHE    47       3.005  11.819   4.632
ATOM    487  CG  PHE    47       3.596  12.656   3.484
ATOM    488  CD1 PHE    47       2.767  13.520   2.765
ATOM    489  CD2 PHE    47       4.967  12.625   3.196
ATOM    490  CE1 PHE    47       3.291  14.329   1.762
ATOM    491  CE2 PHE    47       5.489  13.432   2.189
ATOM    492  CZ  PHE    47       4.650  14.285   1.481
ATOM    493  H   PHE    47       1.140  10.556   2.368
ATOM    494  N   GLY    48      -0.349  12.108   5.554
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ATOM    496  C   GLY    48      -1.950  14.118   5.805
ATOM    497  O   GLY    48      -1.056  14.955   5.658
ATOM    498  H   GLY    48       0.188  11.928   6.418
ATOM    499  N   TYR    49      -3.185  14.468   6.188
ATOM    500  CA  TYR    49      -3.578  15.883   6.428
ATOM    501  C   TYR    49      -3.454  16.282   7.944
ATOM    502  O   TYR    49      -4.348  16.889   8.540
ATOM    503  CB  TYR    49      -4.985  16.056   5.784
ATOM    504  CG  TYR    49      -5.459  17.511   5.680
ATOM    505  CD1 TYR    49      -4.569  18.508   5.266
ATOM    506  CD2 TYR    49      -6.761  17.864   6.044
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ATOM    537  C   PHE    53      -3.824  24.274   5.870
ATOM    538  O   PHE    53      -4.613  24.106   4.940
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ATOM    541  CD1 PHE    53      -3.894  22.054  10.363
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ATOM    544  CE2 PHE    53      -5.456  19.851   9.695
ATOM    545  CZ  PHE    53      -4.929  19.968  10.977
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ATOM    551  CB  ASN    54      -4.211  27.844   5.875
ATOM    552  CG  ASN    54      -3.588  28.498   7.119
ATOM    553  OD1 ASN    54      -2.875  29.495   7.054
ATOM    554  ND2 ASN    54      -3.844  27.964   8.283
ATOM    555  H   ASN    54      -2.627  25.488   6.880
ATOM    556 1HD2 ASN    54      -3.361  28.380   9.090
ATOM    557 2HD2 ASN    54      -4.418  27.119   8.269
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ATOM    563  OG  SER    55       0.995  26.017   5.483
ATOM    564  H   SER    55      -2.010  25.323   3.505
ATOM    565  HG  SER    55       0.310  25.497   5.941
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ATOM    567  CA  THR    56       1.741  26.309  -0.126
ATOM    568  C   THR    56       3.143  25.795   0.395
ATOM    569  O   THR    56       3.448  25.868   1.590
ATOM    570  CB  THR    56       1.880  27.426  -1.217
ATOM    571  OG1 THR    56       2.564  28.570  -0.714
ATOM    572  CG2 THR    56       0.579  27.919  -1.869
ATOM    573  H   THR    56       1.017  27.719   1.407
ATOM    574  HG1 THR    56       1.996  28.958  -0.021
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ATOM    582  OE1 GLU    57       6.902  24.549  -4.777
ATOM    583  OE2 GLU    57       8.586  25.002  -3.302
ATOM    584  H   GLU    57       3.662  25.208  -1.457
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ATOM    586  CA  SER    58       6.698  28.363   1.178
ATOM    587  C   SER    58       6.281  28.314   2.690
ATOM    588  O   SER    58       7.137  28.423   3.571
ATOM    589  CB  SER    58       6.169  29.632   0.455
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ATOM    591  H   SER    58       5.665  27.392  -0.519
ATOM    592  HG  SER    58       7.208  31.110   1.257
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ATOM    594  CA  GLU    59       4.436  28.101   4.355
ATOM    595  C   GLU    59       4.559  26.723   5.110
ATOM    596  O   GLU    59       4.735  26.742   6.331
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ATOM    615  CB  GLN    61       9.707  25.094   3.839
ATOM    616  CG  GLN    61       9.727  23.819   2.940
ATOM    617  CD  GLN    61      10.551  23.929   1.658
ATOM    618  OE1 GLN    61      10.174  24.571   0.682
ATOM    619  NE2 GLN    61      11.668  23.258   1.574
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ATOM    621 1HE2 GLN    61      12.169  23.351   0.689
ATOM    622 2HE2 GLN    61      11.852  22.586   2.332
ATOM    623  N   CYS    62       8.305  27.229   6.151
ATOM    624  CA  CYS    62       8.419  28.344   7.133
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ATOM    626  O   CYS    62       8.272  28.606   9.530
ATOM    627  CB  CYS    62       7.952  29.613   6.391
ATOM    628  SG  CYS    62       8.183  31.094   7.429
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ATOM    636  CD  GLU    63       3.116  30.677   8.797
ATOM    637  OE1 GLU    63       2.050  30.835   9.378
ATOM    638  OE2 GLU    63       3.769  31.647   8.101
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ATOM    651  C   ILE    65       6.154  20.868  10.257
ATOM    652  O   ILE    65       5.808  20.003   9.445
ATOM    653  CB  ILE    65       7.783  23.014  10.293
ATOM    654  CG1 ILE    65       8.119  24.334   9.532
ATOM    655  CG2 ILE    65       9.033  22.093  10.219
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ATOM    664  CG2 THR    66       6.896  16.745  12.220
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