# **Supporting Information**

# Structure-Based Virtual Screening and Biological Evaluation of *Mycobacterium tuberculosis* APS Reductase Inhibitors

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## Contents of Supporting Information:

**Supplementary Figure 1.** Structure based sequence alignment of 17 APS reductases from prokaryotes. The ClustalW Multiple Sequence Alignment program was used. Strictly conserved residues are outlined in red, red letters indicate conserved residues and conserved regions are boxed in blue. Alignment pictures were rendered with the server ESPript 2.2 (http://espript.ibcp.fr)

**Supplementary Figure 2.** Structure based sequence alignment of *Pseudomonas Aeruginosa* and *Micobacterium tuberculosis* APS reductases. The ClustalW Multiple Sequence Alignment program was used. Strictly conserved residues are outlined in red, red letters indicate conserved residues and conserved regions are boxed in blue. Residues flanking the active site are outlined in green.

### **Experimental Section.**

#### Supplementary Figure 1.

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Corynebacterium\_glut

Corynebacterium\_effi

Bacillus\_subtilis Pseudomonas\_aerugino Azotobacter\_vineland Pseudomonas\_syringae Pseudomonas\_putida Methylococcus\_capsul Pyrobaculum aerophil Desulfitobacterium\_h Clostridium\_thermoce Rhizobium meliloti Bordetella parapertu Ralstonia\_eutropha Dechloromonas aronat Wolinella\_succinogen consensus>50 Mycobacterium\_tuberc 62 Corynebacterium\_glut 71 Corynebacterium effi 71 Bacillus\_subtilis 39 Pseudomonas\_aerugino Azotobacter\_vineland 57 34 Pseudomonas\_syringae 34 Pseudomonas\_putida Methylococcus capsul 34 32 Pyrobaculum\_aerophil Desulfitobacterium h 38 39 Clostridium\_thermoce 35 Rhizobium\_meliloti 51 Bordetella\_parapertu Ralstonia\_eutropha 39 59 Dechloromonas\_aromat 38 Wolinella succinogen 20 consensus>50 Mycobacterium\_tuberc 125 Corynebacterium\_glut 134 Corynebacterium\_effi 134 Bacillus subtilis 105 Pseudomonas\_aerugino 123 Azotobacter vineland 100 Pseudomonas syringae 100 100 Pseudomonas\_putida Methylococcus\_capsul 98 Pyrobaculum\_aerophil Desulfitobacterium\_h 105 105 Clostridium thermoce 101 Rhizobium meliloti 117 Bordetella\_parapertu 105 Ralstonia\_eutropha 129 Dechloromonas\_aromat 104 Wolinella\_succinogen 87 consensus>50 Mycobacterium\_tuberc 186 Corynebacterium\_glut 195 Corynebacterium\_effi 195 Bacillus\_subtilis 166 Pseudomonas\_aerugino Azotobacter\_vineland 191 168 Pseudomonas\_syringae 168 Pseudomonas putida 168 Methylococcus\_capsul 165 Pyrobaculum\_aerophil 170 Desulfitobacterium\_h 169 Clostridium\_thermoce 165 Rhizobium\_meliloti Bordetella\_parapertu 181 169 Ralstonia\_eutropha 193 Dechloromonas\_aronat 168 Wolinella\_succinogen 151 consensus>50 Mycobacterium\_tuberc 248 Corynebacterium\_glut 256 Corynebacterium\_effi Bacillus\_subtilis 256 228 Pseudomonas\_aerugino 255 Azotobacter\_vineland Pseudomonas\_syringae 232 232 Pseudomonas\_putida 232 Methylococcus\_capsul 229 Pyrobaculum\_aerophil 240 Desulfitobacterium h 233 229 Clostridium thermoce Rhizobium\_meliloti 245 Bordetella\_parapertu 233 Ralstonia\_eutropha Dechloromonas\_aromat 257 232 Wolinella\_succinogen 215 consensus>50

	SGHRGWTTCNY
MSFQLVNALKNTGSVKDPEISPEGPRTTTPLSPEVAKHNEKLVEKHAAALYDASAQEILI	ENTAEHAPGAI
MSFVTVNALKNAGPTODPEVSPEGPRTTAPLPEEVAHRNRELVDKHADELYHADAATIL	EWAAEHVPGRV
	AAFE. HEGDE
	AFD HEGDD
MSQPFDVAELATTYATKSAQDILK	LAFEHFGDD
MSOFFDVAALAATTANKSPODILKI	LAFEHFGDD
MEREVTOLEVEELSLEFENSTALELLS	ALNEFYP.NI
MNRSELDLELDEINQAFAGEDFRKLLA	<b>YVVEKIGPARI</b>
MVQLDLEKLNKEYSDKSPEDIVRI	VVENIGIEKV
MTTQSLKAEAVALEADVMALDAEAKALNDKLESLDLAGRI	LALIAGLEGRA
MEANFLAR	LAIIARQYPDA
MTPSLINITELNISVAV KTEVIAL	ADIATNWSSA
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VVASN. MADANLVDLAAKVRPGVFVIFIDAGYRFVETIGTRDAIESVT.DVRVL	NVTPEHTVAEQ
AVTIS MENTULAR LABELL CADFLELD OF STREET LEVARS VDERV. SOLLY	TALPILTBAEO
VYACSFGIEGIVLIDLIYEVEEDAEIVFLDTCLHFEETYETIEEVEERYPGLNII	LKKPDLTLEEQ
LWISFSGAEDVVLVDMAWKLNRNVKVFSLDTCRLHPETYRFIDQVREHYGIAIDVI	LSPDPRLLEPL
LWISFSGAEDVULLDMAMKLNKNVKVFSLDTGRLHPETYRFIEQVREHYGLAIEV	LSPDARLLEPL
LWISTSGAEDVWLVDMAWKLNKNVKVFSIDAFRLHAGTTRFIEDVREHTKIELEIN	VSPDHSKLEPF CORAKLEPF
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ALAFSGOAEDVYVLDIMHKVAPDKIRVFMLDTCRLPEEIYELVDKVREHYGVEIEIY	YYPDTKEIEEF
ALASSLEISDOVITOMLIKVDARARIFFIDTGRNFOOTYDLMEETMCRYKFHYEV	YAPENSELEPF
ALASSLSIEDQVLTDILLXINPKVRVFFLDTGRHFQQTYDLMEETMHRYGFHYEV	YAPESKELEQA
VFTTSLGIEDOVITAAIGSNRLDIEVATLKTGRLFNETVALIDQTEETYDILIKN	YPERADIDAY
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DSLYZKNLYRSN PTACCBMREVEPLAASSSPYAGNITCLERSDGP.TRACAPALSL	ATGRL
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VKRYZINPFYRDVELRHLZCKINZVNPZLRAZSCLDAZITZLERDOFF.TUATTRKIQI	HD HYGT
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LAETOPNAFYDKVELROKCCELRIVNDIORVU SAVDGWICGIDREOST. TDOEIGLLEW VSKTOPNFFYESVELRKKOCEIRIVNDIKRVU STVDAWICGIDREOSI. TDOEIWIFFW VAOTSWNGFYESVELRKACCEIRIVNDIKRVU STVDAWICGIDREOSI. TDOELWIFFW VDAHOMHAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELDFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELSFEED VRMSTINAFYESVELRKACCEIRIVEDIRRAJAGRGAWITGOREOAV. TDAELSFEED VRMSTINAFYESVELRKECGIRIVEDIRRAJGGENTIGOREOAV. TDAELSFEED V. G. GIN. TY. d CC. IRKVEPL. F. L. G. AWITGIRRAGST. TDAELSSVET V. G. GIN. TY. d CC. IRKVEPL. F. L. G. AWITGIRRAGST. TDAELSSVET V. G. GIN. TY. d CC. IRKVEPL. F. L. G. AWITGIRRAGST. TEACH VSVMTLAAWTDODVELTAEDRVINDEVENDEVECTPSIGCAFCTAEF. AEGADDES SISPIITWSLEETNEFIADNNLIDHPITHOGTPSIGCAFCTAEV. AEGODFOR VSVCLIHWTWKDIWRYTSINELDYNSLEDGTPSIGCAFCTAFA. FTAEDIS YEFNPLSMTSEEVWGYIRMLELDYNSLERGFISIGCEFCTRFV. LPNOHED YSFNPLAONSSEIWGYIRMLEIPYNSLERGFISIGCEFCTRFV. LPNOHED YSFNPLAQWISSEIWGYIRMLELPYNSLERGFISIGCEFCTRFV. LPNOHED YSFNPLAQWISSEIWGYIRMLELPYNSLERGFISIGCEFCTRFV. LPNOHED YSFNPLAAWISSOVUDYITACEIFFNALHKGVSIGCEFCTRFV. LPNOHED YSFNPLAAWISSOVUDYITACEIFFNALHKGVSIGCEFCTRFV. LPNOHED	BH         H         AI           GL         H         AI           GL         H         SI           GL         H         GL           GL         AGNAKT           GL         M           GL <t< td=""></t<>
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LAETOPNET YD XVELROR.CELRIVNDIORYU SAVDGWICGLOREOST. TDOEIGLLEM VS KYOPNET YESVELREKCCEIRIVNDIORYU SAVDGWICGLOREOST. TDOEIGLLEM VAOYOMNGT YESVELREKCCEIRIVNDIORU SAVDAWICGLOREOST. TDOELNIFEW VAOYOMNGT YESVELREKCCEIRIVEDIORAA DGASYWITGLOREOSA. TDOELNIFEW VAOYOMNGT YESVELREKCCEIRIVEDIORAA DGASYWITGLOREOSA. TDOELNIFEW LKKECLNAF YDSVELREKCCEIRIVEDIORAA SHADAWLTGORREOSA. TDOELNIFEW UNNESINAF YESVELREKCCEIRIVEDIORAA SHADAWLTGORREOSA. TDOELNIFEY ERELCEWGMRESLENRHRCCRVRSIEDIXEA AGRGAWITGCAREOSI. TDAELFFEO VRWEISLENRHRCCRVRSIEDIXEA AGRSAMVTGLOREOSI. TDAELFSVEF V.e.GIN.FY.GCC.IRKVEDI.F.L.G. AWITGRAEGSI. TDAELKSVEF V.e.GIN.FY.GCC.IRKVEDI.F.L.G. AWITGRAEGSI. TDAELKSVEF V.E.GIN.FY.GCC.IRKVEDI.F.L.G. AWITGRAEGSI. TDAELKSVEF V.SVMDLAAWTDODVQEYTADNDVLVNDIVREGYPSIGCATCTLFV. AEGODFOS KISPIITWSLEETNEFIADNNLIDHPITHOGYPSIGCATCTLFV. AEGODFOS VSVCDLIHWTWSLEETNEFIADNNLIDHPITHOGYPSIGCATCTLFV. AEGODFOS VSVCDLIHWTWSDIWRYTSRNELDYNPIHOGYPSIGCATCTLFV. LFNOHE VSFNDLSSMTSEEVWGYIRMLELPYNSLHERGTISIGCEFCTRFV. LFNOHE VSFNDLAQWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHE VSFNDLAQWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHE VSFNDLAQWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHE SISPICOWTWDEVWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHE SISPICAWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHES SISPICAWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHES SISPICAWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. LFNOHES SISPICAWSSEIWGYIRMLELPYNSLHERGFISIGCEFCTRFV. AFGOD	DSH. H.AT GL. H.ST UE. H.ST UE. GLAST DVE. GLAST DEA. B.GT DEA. B.GT DEG. N.GL ETF. DL D RW AGNAST GNN AGNAST GNN AGNAST GNN AGNAST GNN MEEATHS GNN WEEATHS GNN WEEATH
LAETOPNAFYDKVELROKCCELRIVNDIORV SAVDGWICGIDREOST.TDOEIGLLEW VSKTOPNAFYTESVELRKKCCEIRIVNDIORV STVDAWICGIDREOST.TDOEIGLEN VAOTOMNGFYESVELRKACCEIRIVNDIORV STVDAWICGIDREOSY.TDOEIGLEN EKKEDINAFYESVELRKACCEIRIVEDIORAA SGRGAWITGORROAV.TDAELPFED URWESINAFYESVELRKACCEIRIVEDIORAA SHADANLTGORROAV.TDAELPFED URWESINAFYESVELRKACCEIRIVEDIORAA SHADANLTGORROAV.TDAELPFED URWESINAFYESVELRKACCYARIVEDIORAA SKANTGORAEQAN.TDGALAIREY ERELSEWGMRESLENRHRCGRVDSIEDIXEA AGRKANITGORAEQAN.TDGALAIREY V.G.GIN.FY.GCC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.GCC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.GCC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.GCC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.G.A.CC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.G.A.CC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.G.A.CC.IRKVEDI.F.L.G.AWITGARAEQAI.TDGALAIREY V.G.GIN.FY.C.AEGODIA VIVADLAAWTDODVQEYIADNDVLVNDIVRECYPSIGCAFCTAKF.AEGODIA VIVADLAAWTDODVQEYIADNULDHPUTHOCYPSIGCAFCTAFV.AEGODIA VIVADLAAWTDOVGVIRKYTSRNELDYNDINGETIGGEPTTRPV.LEV.AEGODIA VIVADLAGUSEEIWGYIRMLELYNSINERGYISIGCAPTAFV.LPV.AEGODIA VIVADLAQWSEEIWGYIRMLELYNSINERGYISIGCEPTTRPV.LPNQHED VEFNDLAQWSEEIWGYIRMLELYNSINERGYISIGCEPTTRPV.LPNQHED VEFNDLAQWSEEIWGYIRMLELYNSINERGFISIGCEPTRPV.LPNQHED VEFNDLAQWSEEIWGYIRMLELYNSINERGFISIGCEPTRPV.LPNQHED VEFNDLAQWSEEVWGYIRMLELYNSINERGFISIGCEPTRPV.AFFOQHED VEFNDLAQWSEEVWGYIRMLELYNSINERGFISIGCEPTRPV.AFFOQHED VEFNDLAQWSEEVWGYIRMLELYNSINERGFISIGCEPTRPV.AFFOQHED VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VYFNLAAWSEEOVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VYFNLAAWSEOVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPV.AFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRPYCAAFFOGDIA VEFNDLAQWSEEVWGYIRKYNFYCRUPYCKUTSIGCEPTRAVV.AFFOGDIA	BH         H         AI           GL         H         AI           GL         H         SI           GVE         R         GL           DV         R         GL           DV         R         GL           DE         R         GL           DE         F         GL           DE         F         OL           GR         GRAKT         GRAKT           RN         ME <eathk< td="">         SAK           RN         ME<eathk< td="">         SAK           RN         &lt;</eathk<></eathk<></eathk<></eathk<></eathk<></eathk<>
LAETOPNAFYDKVELROKCCELROVNDIORV SAVDGWICGIDREOST.TDOEIGLLEW VSKTOPNAFYTESVELRKKOCEIROVNDIKRV STVDAWICGIDREOST.TDOEIGLHIFW VAQTOMNGYTESVELRKACCEIROVNDIKRV STVDAWICGIDREOST.TDOELWIFFW VAQTOMNGYTESVELRKACCEIROVEPIRRAAGGRGAWITGOREOAV.TDAELPFEC URMSINAYTESVELRKACCEIROVEPIRRAAGGRGAWITGOREOAV.TDAELPFEC VRWSINAYTESVELRKACCEIROVEPIRRAAGGRGAWITGOREOAV.TDAELPFEC VRWSINAYTESVELRKACCEIROVEPIRRAAGGRGAWITGOREOAV.TDAELPFEC VRWSINAYTESVELRKACCEIROVEPIRRAAGGRGAWITGOREOAV.TDAELPFEC VRWSINAYTESVELRKACCYARVEPIRRAAGGRGAWTGOREOAV.TDAELPFEC VRWSINAYTESVELRKACCYARVEPIRRAAGGRGAWTGOREOAV.TDAELPFEC VRWSINAYTESVELRKACCYARVEPIRRAAGGRGAWTGOREOAV.TDAELPFEC VRWSINAESLENRHRCORVDSIEDIKEAKGRSAWYGIDAEOSI.TDAELKSVEF V.e.GID.FY.dCC.IRKVEPI.F.L.G.AWITGORAEOSI.TDAELKSVEF V.E.GID.FY.dCC.IRKVEPI.F.L.G.AWITGORAEOSI.TDAELKSVEF V.E.GID.FY.d.AKGGOROFINIGORFIGCAPITAKF.AEGODFG SISTIITWSLEETNEFIADNKLIDHPITHOCTPSIGCAFITLPV.AEGODFG VEVOELIHWTWKDIWRYTSRNELDYNDINGEVFSIGCAFITSPA.FTAEDI.S YNFNPLSSMTSEEVWGYIRMLEIPYNSIBERGYISIGCEFTRPV.LPNQHED YNFNPLAGNSSEIWGYIRMLEIPYNSIBERGYISIGCEFTRPV.LPNQHED YNFNPLAGNSSEIWGYIRMLELPYNSIBERGFISIGCEFTRPV.LPNQHED YNFNPLAQWSSEIWGYIRMLELPYNSIBERGFISIGCEFTRPV.RPQCHED SISTICDWTWDEVWGYIRKYFYFYRIFYRSIGCEFTRPV.RPQCHED SISTICDWTWDEVWGYIRKYFYFYRIFYRSIGCEFTRPV.APGCHED YNFNPLAQWSSEIWGYIRMLELPYNSIBERGFISIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRMLELPYNSIBERGFISIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRMLELPYNSIBERGFISIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRMLELPYNSIBERGFISIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRKFYFYRFYRIFYRGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRKFYNFYRSIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRKFYNFYRSIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRKYNFYRSIGCEFTRPV.RPGCHED YNFNPLAQWSSEIWGYIRKFYNFYNSIYNGFRSIGCOFTRPV.RPGCHEL YNFNPLAQWSSEORWEYIKKYNFYNSIYNGFRSIGCOFTRPV.RPGCHELX YNNLAAWSEORWEYIKKYNFYNFYRSIYNGFRSIGCEFTRAV.RPGCHELX YNNLAAWSEORWEYIKKYNFYNFYNSIYNGFRSIGCEFTRAV.RPGCHELX YNNLAAWSEORVWEYIKYNFYNSIYNGFRSIGCEFTRAV.RPGCHELX YNNLAAWSEORVWEYIKKYNFYNSIYNGFRSIGCEFTRAV.RPGCHELX	BH         H         AI           GL         H         AI           GL         H         SI           GL         H         SI           GL         H         SI           GL         H         SI           DV         F         GL           DEA         H         SI           DEG         N         GI           DETF         DL         I           DETF         N         AGNAKT           BN         AGNAKT         IN           BN         MWEEATHK         IN           BN         WEEATQK         IN           BN         WEDFALK         IN <td< td=""></td<>
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LAETOPNAFYDRWELRORCCELRIVNDIORW SAVDGWICGLEREOST.TDOEIGLLEW VSKYOPNEFYESVELREKCCELRIVNDICRUSSVDAWICGLEREOSI.TDOELWIFFW VAQTOWNGFYESVELREKCCEIRIVEDICRAADGASYWITGLEREOSI.TDOELWIFFW VAQTOWNGFYESVELREKCCEIRIVEDICRAADGASYWITGLEREOSI.TDOELWIFFW LKKECLNAFYDSVELREKCCEIRIVEDICRAADGASYWITGLEREOSI.TDOELWIFFW LKKECLNAFYDSVELREKCCEIRIVEDICRAADGASWITGCEREOAV.TDAELPFEEQ VRWESINAFYESVELREKCCEIRIVEDICRAADGASWITGCEREOAV.TDAELPFEEQ VRWESINAFYESVELREKCCEIRIVEDICRAADGASHDITGCEREOAV.TDAELPFEEQ VRWESINAFYESVELREKCCEIRIVEDICRAADGASHDITGCEREOAV.TDAELPFEEQ VRWESINAFYESVELREKCCEIRIVEDICRAADGASHDITGCEREOAV.TDAELPFEEQ VRWESINAFYESVELREKCCERVESIEFIXEAAGKSANVTGLEAEOSI.TEALKSVEF V.e.GIN.FY.dCC.IRKVEPL.F.L.G.AWITGCAAEOSI.TEALKSVEF V.e.GIN.FY.dCC.IRKVEPL.F.L.G.AWITGLEAEOSI.TEALKSVEF V.e.GIN.FY.d.XECTORINGIEFIXEAAGKSANVTGLEAEOSI.TEALKSVEF V.E.GIN.FY.A.ECONDUCINDIVERECTPSIGCATCILFV.AEGODFAS SISTIITWSLEETNEFIADNNLIDHPITHOETPSIGCATCILFV.AEGODFAS VSVDLAAWTSDEVWGYIRMLELPYNSIBERGTISIGCEFCIRFV.LPNOHEDS YSFNLAGWSSEEIWGYIRMLELPYNSIBERGTISIGCEFCIRFV.LPNOHEDS YSFNLAGWSSEEIWGYIRMLELPYNSIBERGFISIGCEFCIRFV.LPNOHEDS YSFNLAGWSSEEIWGYIRMLELPYNSIBERGFISIGCEFCIRFV.LPNOHEDS YSFNLAAWTSAOVWGYIRKYNLPYCKLYDRGTISIGCEFCIRFV.AFGADVES YSFNLAAWSEEDVWYIRXENFYSSIGCEFCIRFV.AFGADVES YSFNLAAWSEEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRFV.AV.AFGADVES YSFNLAAWSEEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRFV.RFGADVES YSFNLAAWSEEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRFV.RFGADVES YSFNLAAWSEEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRFV.RFGADVES YSFNLAAWSEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRFV.RFGADVES YSFNLAAWSEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRAV.RFGEDVES LSISDICDWTWDEVWGYIKKYNLPYCKLYDRGTISIGCEFCIRAV.RFGEDVES YSFNLAAWSEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRAV.RFGEDVES YSFNLAAWSEDVWGYIKKYNLPYCKLYDRGTISIGCEFCIRAV.RFGEDVES KSFNLAAWSEDVWGYIKKYNLPYCKLYDRAFGISIGCEFCIRAV.RFGEDVES KSFNLAAWSEDVWGYIKKYNLPYNDIASKGFRSIGCOPCIRAV.RFGEDVES KSFNLAAWSEDVWGYIKKYNLPYNDIASKGFRSIGCOPCIRAV.RFGEDVES KSFNLAAWSEDVWGYIKKYNLPYNDIASKGFRSIGCEFCIRAV.RFGEDVES KSFNLAAWSEDVWGYIKKYNLPYNDIASKGFRSIGCEFCIRAV.RFGEDVES KSFNLAAWSEDVWGYIKKYNLPYNDIASKGFRSIGCEFCIRAV.RFGEDVES	SH. H.AT GL. H.AT GL. H.ST VE. R.GL VE. R.GL VE. R.GL DV. F.GL EA. R.GT DEG. N.GL GETF. DL OL CETF. DL OL CETF. DL OL CETF. ST RW AGNAXT SRW AGNAXT SRW AGNAXT SRW AEATHK SRW WEEATHK SRW WEATHK SRW WEEATHK SRW WEATHK
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LAETOPNAFYDKVELROKCOELGIVNDIORVU SAVDGWICGIDREOSI.TDOEIGLLEM VSKTOPNEFYESVELRKKOCEIGNVNDIKRVU STVDAWICGIDREOSI.TDOELWIFFW VAOTOMNGFYESVELRKACCEIGNVNDIKRVUSTVDAWICGIDREOSI.TDOELWIFFW VAOTOMNGFYESVELRKACCEIGNVEFIRRAAGGRGAWITGORROAS.TDGELPDEER LKKHELNAFYDSVELRKECCGIRVUEFIRRAAGGRGAWITGORROAV.TDAELPFEC LKKHELNAFYDSVELRKECCGIRVUEFIRRAAGGRGAWITGORROAV.TDAELPFEC LKKHELNAFYDSVELRKECCGIRVUEFIRRAAGGRGAWITGORROAV.TDAELPFEC LKKHELNAFYDSVELRKECCGIRVUEFIRRAAGGRGAWITGORROAV.TDAELPFEC LKKHELNAFYDSVELRKECCGIRVUEFIRRAAGGRGAWITGORROAV.TDAELAF LKHELSWERTGOLAR.COVANUEFIRRAAGGRGAWITGORROAV.TDAELAF ERELSEWGNRESLENRHROCRVDSIEDIKEAFGGRGATTTONGEAQAT.TDGALAIREY ERELSEWGNRESLENRHROCRVDSIEDIKEAFGGRSAVTGIDAEOSI.TDAELKSVEF v.e.GIn.fy.dCC.IRKVEFL.F.L.g.aWITGIRAEGSI.TDAELKSVEF v.e.GIN.fy.dCC.IRKVEFL.F.L.g.aWITGIRAEGSI.TDAELKSVEF v.e.GIN.fy.dCC.IRKVEFL.F.L.g.aWITGIRAEGSI.TDAELKSVEF v.e.GIN.fy.dCC.IRKVEFL.F.L.g.aWITGIRAEGSI.TDAELKSVEF v.e.GIN.fy.dCC.IRKVEFL.F.L.g.aWITGIRAEGSI.TDAELKSVEF v.e.GIN.fy.dCC.IRKVEFL.F.L.G.AWITGIRAEGFISIGCATCILFV.AEGODFA SISPIITWSLEETNEFIADNNLIDHPITHOGYPSIGCATCILFV.AEGODFA VEVOFLIAWTSLEETNEFIADNNLIDHPITHOGYPSIGCATCILFV.AEGODFA VEVOFLIAWSLEETNEFIADNNLIDHPITHOGYPSIGCATCILFV.LPNCHEDS YSFNLAQMSSEVWGYIRMLELPYNSIHERGYISIGCEFCTRFV.LPNCHEDS YSFNLAQWSSEVWGYIRMLELPYNSIHERGFISIGCEFCTRFV.LPNCHEDS YSFNLAQWSSEVWGYIRMLELPYNSIHERGFISIGCEFCTRFV.LPNCHEDS YSFNLAQWSSEVWGYIRMLELPYNSIHERGFISIGCEFCTRFV.APGGHEDS YSFNLAAWTSAOVWDYITACEIFFNALKGTVSIGCEFCTRFV.RPGGHEDS YSFNLAAWSAOVWDYITACEIFFNALKGTVSIGCEFCTRFV.RPGGHEDS YSFNLAAWSEORVWYIKKYNFYNDYSSYKGFRSIGCOPCTRAV.RPGGUVGSUS YSINFIVFWSEDRVWYIKKYNFYNDYSSYKGFRSIGCOPCTRAV.RPGGUVGA YSFNLAAWSEORVWYIKKYNFYNDYNSYSKGFRSIGCOPCTRAV.RPGGUVGA YSFNLAAWSEDRVWYIKALGIPYNDHDRAKGYPSIGCEFCTRAV.RPGGUVGA SFNPLAAWSEDRVWYIKALGIPYNDHDRAKGFPSIGCEFCTRAV.RPGGUVGA SFNPLAAWSEDRVWYIKARHVPYNDHAKGFPSIGCEFCTRAV.RPGGUVGA SFNPLAAWSEDRVWYIKARHVPYNDHAKGFPSIGCEFCTRAV.RPGGUVGA SFNPLAAWSETEVFYIKKANAPYNDHAKGFPSIGCEFCTRAV.RPGGUVGA SFNPLAAWSETEVFYIKKANAPYNDHAKGFPSIGCEFCTRAV.RPGGUVGA SFNPLAAWSETEVFYIKKANAFYNDYNALHOKFYPSIGCAFCTR	BH         H         AI           GL         H         AI           GL         H         SI           GVE         H         GI           DFV         F         GL           DETF         OL         I           SETF         OL         I           CH         AGNAKT           RW         AGNAKT           RW         AGNAKT           RW         ME           RW         ME           RW         WE           RW         ME
LAETOPNET YDEVELROECCELROVNDIORV SAVDGWICCLEREOST. TDOEIGLLEM VSKYOPNET YESVELREKCCELROVNDIKRV STVDAWICCLEREOSI. TDOEIGLENIFW VAQTOWNGTYESVELREKCCEIROVEDIKRALSTVDAWICCLEREOSI. TDOELNIFW VAQTOWNGTYESVELREACCEIROVEDIKRALAGRGAWITCCEREOSA. TDOELNIFW LKKECLNAFYDSVELREACCEIROVEDIKRALAGRGAWITCCEREOSA. TDOELDER LKKECLNAFYDSVELRECCGIROVEDIKRALAGRGAWITCCEREOSA. TDOELDIKIN ERELCEWGMRESLENRHRCCRVRNIEDIKRALAGRGAWITCCEREOSI. TDAELFFEO VRWEINAFYESVTLREACCYARVEDIKRALAGRSAMVTGLEAEOSI. TDAELFSVEF V.e.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.e.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.e.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.E.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.E.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.E.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.E.GIN.FY.GCC.IRKVEDIT.L.G. AWITGIRIGAEOSI. TDAELKSVEF V.E.GIN.FY.C. AEGODFA VINTLAAWTDODVQEYIADDVLVNDIVREGTPSIGCATCILFV. AEGODFA VSVDILAAWTSLETNEFIADNNLIDHPITHQGTPSIGCATCILFV. AEGODFA VSVCILIHWTWKDIWRYTSRNELDYNDIHOTGSVEGATCILFV. LPNOHES YSFNDLAQMSSEIWGYIRMLELPYNSIHERGTISIGCEFCTRFV. LPNOHES YSFNDLAQMSSEIWGYIRMLELPYNSIHERGFISIGCEFCTRFV. LPNOHES YSFNDLAQMSSEIWGYIRMLELPYNSIHERGFISIGCEFCTRFV. LPNOHES YSFNDLAQWSSEIWGYIRMLELPYNSIHERGFISIGCEFCTRFV. LPNOHES YSFNDLAQWSSEIWGYIRMLELPYNSIHERGFISIGCEFCTRFV. APGADVS YSFNDLAAWTSAOVWGYIRKYNLYNSIHERGFISIGCEFCTRFV. APGADVS YSFNDLAAWSAOVWGYIRKYNLYNSIYSGFSIGCOFCTRAV. APGADVS YSINFIAAWSAOVWGYIRKYNLYNSIYSGFSIGCOFCTRAV. APGADVS YSINFIAAWSEDVWGYIRKYNLYNSIYSGFSIGCEFCTRAV. RPGEDVS YSINFIAAWSEDVWGYIRKSYNLPYSSIYNEGFSIGCEFCTRAV. RPGEDVS YSINFIAAWSEDVWGYIRKSYNLPYSNSIYSIGCEFCTRAV. RPGEDVS YSINFIAAWSEDVWGYIRKSYNLPYSNSIYSIGCEFCTRAV. RPGEDVS YSINFIAAWSEDVWGVIRALGIPYNPIHSRGFSIGCEFCTRAV. RPGEDVS YSINFIAAWSEDVWGVIRALGIPYNPIHSRGFSIGCEFCTRAV. RPGEDVS YSINFIAAWSEDVWGVIRALGIPYNPIHSRGFSIGCEFCTRAV. RPGEDVS SSINFICHAAWSEDVWGVIRALGIPYNDHAAKGTPSIGCEFCTRAV. RPGEDVA YSFNLAAWSEDVWGVIRALGIPYNDHAAKGTPSIGCEFCTRAV. RAGENVA SSINFICHAAWSEDVWYNDLAAKGYSIGCEFCTRAV. RAGENVA YSFNLAAWSEDVWG	SH. H.AT GL. H.AT GL. H.ST VE. B.GL VE. B.GL VE. B.GL DFV. F.GL DEA. B.GT DEG. N.GL SETF. DL D. GLAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. SGAKT SHW. SHARK SHW. SEATHK SHW. SHW. SHW. SHW. SHW. SHW. SHW. SHW.
LAETOPNAFYDKVELROKCOELROVNDIORVO SAVDGWICGLOREOST.TDOEIGLLEW VSKTOPNEFYESVELRKKCOEIROVNDIERVISTVDAWICGLOREOST.TDOEIWIFW VAQTOWNGFYESVELRKACCEIROVEDIERALAGGRAWITGCOREOST.TDOELWIFW VAQTOWNGFYESVELRKACCEIROVEDIERALAGGRAWITGCOREOST.TDOELWIFW LKKEDLNAFYDSVELRKACCEIROVEDIERALAGGRAWITGCOREOST.TDOELWIFW LKKEDLNAFYDSVELRKACCEIROVEDIERALAGGRAWITGCOREOST.TDOELWIEN ERELCEWGMRESLENRHRCCRVRSIEDIERALAGRSAMVTGLOAEOSI.TDOELAIRET ERELCEWGMRESLENRHRCCRVRSIEDIERALAGRSAMVTGLOAEOSI.TDAELSVEF V.e.GIN.FY.GCC.IRKVEDIERALAGRSAMVTGLOAEOSI.TDAELSVEF V.e.GIN.FY.GCC.IRKVEDIERALAGRSAMVTGLOAEOSI.TDAELSVEF V.e.GIN.FY.GCC.IRKVEDIERALAGRSAMVTGLOAEOSI.TDAELSVEF V.E.GIN.FY.GCC.IRKVEDIERALAGRSAMVTGLOAEOSI.TDAELSVEF V.E.GIN.FY.GCC.IRKVEDIERALAGRSAMVTGLOAEOSI.TDAELSVEF V.E.GIN.FY.GCC.IRKVEDIERALAGRSAMVTGLOAEOSI.TDAEVSI. KISDIITWSLEETNEFIADNNLIDHPITHOCTPSIGCATCTLFV.AEGODIA VIVEDLAAWTDODVQEYTADNDVLVNPIVREGTPSIGCATCTLFV.AEGODIA VIVEDLAAWTSEEVWGYIRMLELYNSLERGTISIGCEFCTRFV.LPNCHE VSFNLASMTSEEVWGYIRMLELYNSLERGTISIGCEFCTRFV.LPNCHE VSFNLAQWSSEEIWGYIRMLELPYNSLERGTISIGCEFCTRFV.LPNCHE VSFNLAQWSSEEIWGYIRMLELPYNSLERGFISIGCEFCTRFV.LPNCHE VSFNLAAWTSAOVWGYIRMLELPYNSLERGFISIGCEFCTRFV.LPNCHE VSFNLAAWTSAOVWGYIRMLELPYNSLERGFISIGCEFCTRFV.LPNCHE VSFNLAAWSEEVWGYIRMLELPYNSLERGFISIGCEFCTRFV.RFGADVES VSFNLAAWSEEVWGYIRMLELPYNSLERGFISIGCEFCTRFV.RFGADVES VSFNLAAWSEEVWGYIRMLELPYNSLERGFISIGCEFCTRFV.RFGADVES VSFNLAAWSEEVWGYIRKYNLPYCKLYDRGTTSIGCEFCTRFV.RFGADVES VSFNLAAWSEEVWYIRKYNLPYCKLYDRGTSIGCEFCTRFV.RFGADVES VSFNLAAWSEDVWYIRKYNLPYCKLYDRGTSIGCEFCTRFV.RFGADVES VSFNLAAWSEDVWYIRKYNLPYNSLYSGFPEIGCEFCTRFV.RFGADVES VSFNLAAWSEDVWYIRKYNLPYCKLYDRGTSIGCEFCTRFV.RFGADVES VSFNLAAWSEDVWYIRKYNLPYCKLYDRGTSIGCEFCTRFV.RFGADVES VSFNLAAWSEDVWYIRKYNLPYCKLYDREGTSIGCEFCTRFV.RFGADVES SIINPLAAWSEDVWYIRKYNLPYNDLASGFPEIGCEFCTRFV.RFGADVES SIINPLAAWSEDVWYIRKYNLPYNDLASGFPEIGCEFCTRFV.RFGADVES SIINPLAAWSEDVWYIRKYNNYNDUSKEGTSIGCEFCTRFV.RFGADVES SIGCEFTRF.AS.CCCCCCFFC.SCCCFFCRF.NK.RFSIGCEFCTRFV.RFGADVES SIGCEFTRF.SDEFTRFV.RFGANFFFCFCFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF	SH. H.AI GL. H.AI GL. H.SI VE. R.GL VE. R.GL DV. F.GL EA. R.GI DETF. DL DETF. DL D. AGNAXI SHW. AGNAXI SHW. AGNAXI SHW. AGNAXI SHW. AGNAXI SHW. AGNAXI SHW. SGAXI SHW. SEATHX SHW. SHW. SHW. SHW. SHW. SHW. SHW. SHW.
LAET OP NAFY YD KVELROK CELROVNDI ORVO SAVDGWICGLOREOST. TDOEIGLLEW VS KY OP NFFYESVELRKKCCEIROVNDI KRVI STVDAWICGLOREOST. TDOEIGLFDER VAQTSWNGFYESVELRKACCEIROVEDIKAALSGRGAWITGORAOSA. TDOELPIFEM VAQTSWNGFYESVELRKACCEIROVEDIKAALSGRGAWITGORAOSA. TDOELPIFEM VADHSWNAFYESVELRKACCEIROVEDIKAALSGRGAWITGORAOSA. TDOELPIFEM VRWELNAFYESVELRKACCYAROVEDIKAALSGRAWITGORAOSA. TDOELAIREY ERELSEWGRRESLENRHRCCGINVEDIKAALSGRAWITGORAOSA. TDOELAIREY VRWELNAFYESVELRKACCYAROVEDIKAALSGRSAWITGIAAEOSA. TDOELAIREY VRWELAAWTDOEVQEYIADNDVLVNDEVKECYPSIGCAFCARF. AEGADFS V. e. GIN. fy. d CC. IRVOEL F. L. g. aWITGIRADSP. TR. q e I VVVVDLAAWTDOEVQEYIADNDVLVNDEVKECYPSIGCAFCARF. AEGADFS NISDIITWSLEETNEFIADNNLIDHPITHOGYPSIGCAFCAFF. AEGADFS SKISDIITWSLEETNEFIADNNLIDHPITHOGYPSIGCAFCAFFV. AEGADFS SKISDIITWSLEETNEFIADNNLIDHPITHOGYPSIGCAFCAFFV. AEGADFS VVVCLIHWTWKDIWRYTSRNELDYNDEURGFISIGCEFCAFFV. LEPNHES YSFNDLSSMTSEEVWGYIRMLEIPYNSLERGYISIGCEFCAFFV. LEPNHES YSFNDLSSMTSEEVWGYIRMLEIPYNSLERGYISIGCEFCAFFV. LEPNHES YSFNDLAQWISSEEIWGYIRMLEIPYNSLERGFISIGCEFCAFFV. LEPNHES YSFNDLAQWISSEEIWGYIRMLEIPYNSLERGFISIGCEFCARFV. LEPNHES YSFNDLAQWISSEEIWGYIRMLEIPYNSLERGFISIGCEFCARFV. LEPNHES YSFNDLAQWISSEEIWGYIRMLEIPYNSLERGFISIGCEFCARFV. LEPNHES YSFNDLAQWISSEEIWGYIRMLEIPYNSLERGFISIGCEFCARFV. LEPNHES YSFNDLAAWTSAOVWDYITRCEIFFNALHLKGTVSIGCEFCARFV. REGORDS YSINDIVFWSEDRWEYIRKENIPYSSLYNKGFRSIGCOFCARAV. REGORDS YSINDIVFWSEDRWEYIRKENIPYSSLYNKGFRSIGCOFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYSSLYNKGFRSIGCOFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYSSLYNKGFRSIGCOFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYSSLYNKGFRSIGCOFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYNDLAKKTYSIGCEFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYSSLYNKGFRSIGCOFCARAV. REGENDS YSINDIVFWSEDRWEYIRALSINIPYNSLYNKGFRSIGCOFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYNDLASKGFSIGCEFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYNDLASKGFSIGCEFCARAV. REGENDS YSINDIVFWSEDRWEYIRKENIPYNSLYNKGFRSIGCEFCARAV. REGENDS YSINDIVFWSEDRWEYYIRKENIPYNSLYNKGFRSIGCEFCARAV. REGENDS YSINDIVFWSEDRWEYYIRKENIPYNSLYNEFSGIGSFSIGCEFCARAV. REGENDS YSINDIVFWSEDRWE	BH       H       AI         GL       H       AI         GL       H       SI         GU       H       GI         GU       H       GI         DV       F       GL         DE       F       GI         SR       AGNAKT         SR       M
LAETGPNAFTDKVELRGSGELNKVRDIGKVRDIGKVDGIGGIGNEGSI.TNGELGLEW VSKTGPNEGTESVELRKKGELNKVRDIGKVDJSTVDAGIGGIGNEGSI.TNGELPDER LKENGLNAGTDSVALRKAGEGINSVEDIRNALSHADALTGGURAGSA.TNGELPDER LKENGLNAFTDSVELRKEGEGINSVEDIRNALSHADALTGGURAGSA.TNGELPDER LKENGINAFTDSVELRKAGEGINSVEDIRNALSHADALTGGURAGSA.TNGELPDER VRNHZINAFTDSVELRKEGEGINSVEDIRNALSHADALTGGURAGSA.TNGELPDER VRNHZINAFTDSVELRKEGEGINSVEDIRNALSHADALTGGURAGSA.TNGELARLFT ERELZWGNREGLENHRHEGRVENIEPSKAASAGNATTGNALGAA.TNGELARLFT VRNDLAAMTDODVGETIADNDVLVNPUXREGTBIGGATGTLPV.AEGOPTA V.e.GIN.TY.dCC.IRKVEPL.T.L.G.AWITGIRTGFP.T.AEGADF SISPIITWSLEETNEFIDNNLIDHPITNGGTPBIGGATGTLPV.AEGOPTA VVVDPLAAMTDODVGETIADNNLUNPUXREGTBIGGATGTLPV.AEGOPTA VVVDPLAAMTDODVGETIADNNLUDHPITNGGTPBIGGATGTLPV.AEGOPTA VVVDPLAAMTDOLVGETIADNNLUDHPITNGGTPBIGGATGTLPV.AEGOPTA VSVDPLAAMTDOLVGETIADNNLUDHPITNGGTPBIGGATGTLPV.AEGOPTA VSVDPLAAMTSSETUNGTIRNLELYNSIHERGTIBIGGEPGTRFV.LPV.AEGOPTA VSVDPLAQMSSETUNGTIRNLELYNSIHERGTIBIGGEPGTRFV.LPV.AEGOPTA VSVDPLAQMSSETUNGTIRNLELYNSIHERGTIBIGGEPGTRFV.LPNQHES VSFNDLAQMSSETUNGTIRNLELYNSIHERGTIBIGGEPGTRFV.LPNQHES VSFNDLAQMSSETUNGTIRNLELYNSIHERGTIBIGGEPGTRFV.LPNQHES VSFNDLAAMTSAQVNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNGHES VSFNDLAAMSSQUNDTITACEIPFNALHLKGTVSIGGEPGTRFV.LPNQHES VSFNDLAAMSSGUNATIKKYNIPYNSLYSKGFRSIGGOPGTRFV.LPNQHES VSFNDLAAMSSGUNATIKKYNIPYNSLYSKGFRSIGGOPGTRFV.LPNGHES VSFNDLAAMSSTUVYTIKALAANSKGUNATIKSHNVPVNDLAKGTSSIGGEPGTRFTV.LPNGHESTAN VSFNDLAAMSSTUVYTIKALAANLSKTTSLAGTISSGESPUNAL SCGLHAGNLISKA CGLHAGNLISKA CGLHAGNLISKA	SH. H.AI GL. H.AI GL. A. H. SI GL. B. GL OVE. B. GL DV. S. GL DV. S. GL DE G. S. GL DE TF. DL DE TF. DL DE TF. DL DE TF. DL DE TF. SC RW. A GNAKT SRW. A GNAKT SRW. A GNAKT SRW. A GNAKT SRW. SGAKT SRW. SGAKT SRW. SCALK SRW. SCA
LAETGPNAFTDENVELROS CELENVRDIORVE SAVDGIC CIDREOS . TROEIGLEN VSKYGPNEFTYESVELRKACCE INSVIDIENUS STVDAICGIDREOSI. TROEIDEN VAQTOMNGTYESVELRKACCE INSVIDIENUS STVDAICGIDREOSI. TROEIDEN VAQTOMNGTYESVELRKACCE INSVIDIENUS STVDAICGIDREOSI. TROEIDEN UKASCHAFTDEVELRKACCE INSVIDIENAA GARGANITTE IDROES A. TROEIDE VENEDINAFYESVELRKACCE INSVIDIENAA GARGANITTE IDROES A. TROEIDE VRHECINAFYESVELRKACCE INSVIDIENAA GARGANITTE IDAELSE A. TROEIDE VRHECINAFYESVELRKACCE INSVIDIENCE INTERVENT KISPIITTWSLEETNEFIADNNLIDHPITYKESVE IGAA GARGANITTE IDAELSE VRIVELEETNEFIADNNLIDHPITYGETP SIGGAT GILPV. AEGODE A. KISPIITWSLEETNEFIADNNLIDHPITYGETP SIGGAT GILPV. AEGODE A. KISPIITWSLEETNEFIADNNLIDHPITYNEGTE SIGGAP GISPA. FFAEDIAS YRFNDLAGMSSEETWGYIRMLE LPYNSIHERGTISIGGEP GISPV. LPNQHE YRFNDLAGMSSEETWGYIRMLE LPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAQMSSEETWGYIRMLE LPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAQMSSEETWGYIRMLE LPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAAMISE VWGYIRMLE LPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHE SYVNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHE YSFNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHES YSFNDLAAMISE VWGYIRMLELPYNSIHERGFISIGGEP GISPV. LPNQHES YSFNDLAAMISE VWGYIRKYNNING YN SIGGEP GISPV. A. PGCHAGNESE VWGYIRKEN YN YNN YN SHARGYNSIGGEP GISPV. A. PGCHAGNESE VWGYIRKEN YN YNN YNN SHARGYNSIGGEP GISPV. A. PGCHAGNISTING YN YN SHARGYNSIG GISPERAN YN SPACANIS SECUNGYN YN AR SON YN YN AR SON YN SAN AN AN ACON YN A SACON YN AR SON YN YN A SAC	BH       H       AI         GL       H       AI         GL       H       SI         GL       H       SI         GL       H       SI         GV       F       GL         DEA       R.GI         DEGA       R.GI         DETF       OL         CANNART       AGNART         RW       AGNART         RW       AGNART         RW       AGNART         RW       MEEATHK         RW       WEEATHK         RW       WEDPSKK         RW       WEDPSKK         RW       MEDPSKK         RW       SDSK
LARTO PARTYDRVELAQKGGELDEVND DRVD SEVDGN ICGLOREQCE. TRQEIGLLEM VSKTO PHFFYESVELRKKCGELDEVND DKNV SEVDGN ICGLOREQCE. TRQEINIFEN VAQTONNGFYESVELRKACGELDEVND DKNV SEVDGN ICGLOREQCE. TRGELPIEN UNADOMNAFYESVELRKACGELDEVND DKNV SEVDGN DKNV SEQUACEA. TRGELPDER LKKHCKARTYDSVELRKACGELDEVNED DKNA ACKRAW ITGORACEA. TRGELPDER V. NHEGINAFYESVELRKACGELDEVNED TREACHERS SANVTELDARCEI. THALKSVER V. NHEGINAFYESVELRKACGENEN V. NHEGINAFYESVELRKACGENEN V. NHEGINAFYESVELENDEVEN DKNA ACKRAW ITGORACEA. TRGELPDER KINSTITWSLEETNERIADNICHPTHYCHTELGTEGETTLEV. AEGODPA KINSTITWSLEETNERIADNICHPTHYGGTESIGCAFCTLEV. AEGODPA KINSTITWSLEETNERIEDNNLIDHPTHQGTESIGCAFCTLEV. AEGODPA VVVCLIMWWKDIWRYTSRHELDYNSIBERGTISIGCAFCTREV. LFNQHEES YSFROLAQMSSEIWGYIRMLELPYNSIBERGTISIGCEFCTREV. LFNQHEES YSFROLAQMSSEIWGYIRMLELPYNSIBERGTISIGCEFCTREV. LFNQHEES YNFROLAQMSSEIWGYIRMLELPYNSIBERGTISIGCEFCTREV. LFNQHEES YNFROLAQMSSEIWGYIRMLELPYNSIBERGTISIGCEFCTREV. LFNQHEES YNFROLAQMSSEIWGYIRMLELPYNSIBERGTISIGCEFCTREV. LFNQHEES YNFROLAAWSEOVWAYIRKENIFYSSIFNEGTSIGCEFCTREV. LFNQHEES YNFROLAAWSEOVWAYIRKENIFYSSIFNEGTSIGCEFCTREV. LFNQHEES YNFROLAAWSEOVWAYIRKENIFYSSIFNEGTSIGCEFCTREV. LFNQHEES YNFROLAAWSEOVWAYIRKENIFYSSIFNEGTSIGCEFCTREV. LFNQHEES YNFROLAAWSEOVWAYIRKENIFYSSICHNEGTSIGCEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWYSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWSVIRAEGTFYNDIGGEFCTREV. RFGEDVIS KINSTUFWSEDAWSFERWENTYNSV	BH       H       AI         GL       H       AI         GL       H       SI         GL       H       SI         GL       H       SI         GL       F       GL         DFV       F       GL         DEA       R.GI         DETF       OL         DETF       OL         CRW       AGNAKT         DRW       WEEATHK         DRW       WEATHK         DRW </td
LAETC PARTYDRVELRORC CHIRVNED ORVE SAVDGWICG LOREOSF. TROEIGLLEM VSKTC PHEFYESVELRKEC CHIRVNED LKNUSTVDAMICG LOREOSF. TROEIGLEN FFW VAOY MHGYYESVELRKACCKIINVED LKNUSTVDAMICG LOREOSG. NAATTPFALA VDAME MHAFYESVELRKACCKIINVED LKNUSTVDAMICG LOREOSG. NAATTPFALA VDAME MHAFYESVELRKACCKIINVED LKNUSHAAAGKANAMITGMAAEGAA. TROELPPEER LKKMS LKAFYDSVELRKACCKINIVED LKNUSAAAGKANAMITGMAAEGAA. TROELAINEY ERELZEWGMRESLENRHRCCHNIVED LKNUSAAGKANAMITGMAAEGAA. TROELAINEY V. G. GI. ÉY. G CC. IKKVEPL T. L. G AWITGHAAEGAA. TROELAINEY ERELZEWGMRESLENRHRCCHNIVITIED KEARKGKSAVITELAEGT. THAELKSVEP V. G. GI. ÉY. G CC. IKKVEPL T. L. G AWITGHAAEGAA. TROELKSVEP KISTITWSLEETNEFIADNULTUND VRECTPISCATCLEV. AEGODPA KISTITWSLEETNEFIADNULTUND VRECTPISCATCLEV. AEGODPA KISTITWSLEETNEFIADNULTUND VRECTPISCATCLEV. AEGODPA KISTITWSLEETNEFIADNULTUND VRECTPISCATCLEV. AEGODPA KISTITWSLEETNEFIADNULTUND VRECTPISCATCLEV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSSEIWGYIRMLELPYNSIHERGTISIGCEPTREV. LPNGHER YKFNCLAGMSEEVWGYIKKYNLPYCKIYDRSTFISGCOPTRAV. AFGADVIS YKINCLAAWSEEVWGYIKKYNLPYCKIYDRSTFISGCOPTRAV. RPGCHER YKNCLAAWSEEVWGYIKKYNLPYCKIYDRSTFISGCOPTRAV. RPGCHER YKNCLAAWSEEVWGYIKKYNLPYCKIYDRSTFISGCOPTRAV. RPGCHER YKFNCLAAMSEEVWYIKKYNLPYCKIYDRSTFISGCOPTRAV. RPGCHER YKFNCLAAWSEEVWYIKKYNLPYCKIYDRSTFISGCOPTRAV. RPGCHER YKFNCLAAWSEEVWYIN KYNNIYNSIYSSER SCOLE SCOLEACHISKA	SH. H.AI GL. H.AI GL. A. H.SI VE. B. GL PV. F.GL EA. B.GI DEG. N.GL SETF. DL C. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. AGNAKT SHW. SHAKT SHW. SHW. SHAKT SHW. SHW. SHAKT SHW. SHW. SHAKT SHW. SHW. SHAKT SHW. SHW. SHW. SHW. SHW. SHW. SHW. SHW.
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### **Supplementary Figure 2.**



**Virtual Screening Calculations.** The AutoDock 4.0 (AD4)<sup>1,2</sup> software package, as implemented through the graphical user interface called AutoDockTools (ADT),<sup>3</sup> was used to dock small molecules to APS reductase. The enzyme file was prepared using published coordinates (PDB 2GOY).<sup>4</sup> The terminal residues were modified to charged quaternary amine and carboxylate forms. The [4Fe-4S] cluster was retained with the protein structure. Charges of this group were manually assigned. In our case, the cluster is believed to have two ferric (+3) and two ferrous (+2) irons.<sup>5</sup> Since the eight sulfur atoms (four belonging to the cluster and four belonging to the four cysteines) have a net charge of -1, the total net charge of the system should be of -2. Noodleman and co-workers calculated the ESP charges for models of the cluster in this oxidation state.<sup>6</sup> These charges were added to APS reductase iron-sulfur cluster atoms and to the four sulfur of the coordinating cysteines (Table 1).

**Table 1.** Calculated Charges for  $[Fe_4S_4(SCH_3)_4]^{2-}$ 

Atom	ESP Charges
Fe <sub>ox</sub>	+0.642 (_2)
$\mathrm{Fe}_{\mathrm{red}}$	+0.635 (_2)
S* <sub>ox</sub>	-0.584 (_2)
$S*_{red}$	-0.580 (_2)
Sox	-0.574 (_2)
$\mathbf{S}_{\mathrm{red}}$	-0.571 (_2)

All other atom values were generated automatically by ADT. The docking area was assigned visually around the enzyme active site. A grid of 80 Å x 80 Å x 80 Å with 0.375 Å spacing was calculated around the docking area for 13 ligand atom types using AutoGrid4. These atom types were sufficient to describe all atoms in the NCI database. For VS, compound structures of the NCI Diversity Set and the ones derived ZINC from the similarity search were prepared using the database server (http://zinc.docking.org/upload.shtml)<sup>7</sup> to take into account the different protomeric and tautomeric states of each compound. All the ligands were then converted in the AutoDock format file (.pdbqt). For each ligand, 100 separate docking calculations were performed. Each docking calculation consisted of 10 million

energy evaluations using the Lamarckian genetic algorithm local search (GALS) method. The GALS method evaluates a population of possible docking solutions and propagates the most successful individuals from each generation into the subsequent generation of possible solutions. A low-frequency local search according to the method of Solis and Wets is applied to docking trials to ensure that the final solution represents a local minimum. All dockings described in this paper were performed with a population size of 150, and 300 rounds of Solis and Wets local search were applied with a probability of 0.06. A mutation rate of 0.02 and a crossover rate of 0.8 were used to generate new docking trials for subsequent generations, and the best individual from each generation was propagated to the next generation. The docking results from each of the eight calculations were clustered on the basis of root-meansquare deviation (rmsd) between the Cartesian coordinates of the atoms and were ranked on the basis of free energy of binding. The top-ranked compounds were visually inspected for good chemical geometry. Pictures of the modelled ligand/enzyme complexes were rendered with PMV.<sup>3</sup>

**Preparation of NCI Compounds.** Compounds determined by AD4 to have low binding energies to APS reductase were requested in groups of 40 and received from the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute (http://dtp.nci.nih.gov/branches/dscb/repo\_request.html). Chemical compounds were dissolved in DMSO to 10 mM final concentration and stored at room temperature.

Enzyme purification. Purification of APS reductase was carried out as previously described.<sup>4</sup>

**APS Reductase Activity Assay.** APS reductase activity was assayed using a modification of an assay for monitoring  ${}^{35}SO_4{}^2$  release from ATP-sulfurylase as follows.<sup>5</sup> Reactions were performed in a final volume of 100 µL. At various time points, a 10 µL aliquot was removed from the reaction and added to 0.5 mL of a 2% (w/v) charcoal solution containing 20 mM Na<sub>2</sub>SO<sub>3</sub>. The suspension was vortexed, clarified by centrifugation and a 400 µL aliquot of the supernatant solution, containing the radiolabeled sulfite product, was counted in 10 mL of scintillation fluid. <sup>35</sup>S-labeled APS was synthesized and purified as previously described<sup>8</sup> with the inclusion of an additional anion exchange purification step (5 ml Fast Flow Q column (GE Healthcare) eluting with a linear gradient of ammonium bicarbonate, pH 8.0, from 0.005 to 0.7 M.

**General Kinetic Methods.** Unless otherwise specified, the reaction buffer was 100 mM Bis-Tris pH 7.5, 5 mM DTT, and the temperature was 30 °C. The auxillary protein reductant, thioredoxin was added at

10  $\mu$ M. With the exception of slow reactions, the enzymatic reactions were monitored to completion ( $\geq 3$  half lives) and rate constants were obtained by nonlinear least-squares fit to a single exponential (Kaleidagraph). To ensure single-turnover reactions, the concentration of APS reductase was kept in excess of the concentration of labeled APS (~1 nM). Two or three concentrations of APS reductase were chosen that were at least 10-fold below the  $K_{\rm M}$  value. Under these conditions, the observed rate constant was linearly dependent on enzyme concentration. Thus, reactions were first order in APS and APS reductase in all cases. Under subsaturing conditions, with [APS]  $\ll K_{\rm M}$ , the Michaelis-Menton equation (eq 1) simplifies to equation 2.<sup>9</sup> The reaction progress curve was plotted as a function of time and the fractional extent of reaction, and fit by a single-exponential function (eq 3) to yield  $k_{\rm obs}$ , which is the product of enzyme concentration and the apparent second-order rate constant (eq 4). Kinetic data were measured in at least two independent experiments and the standard error was typically less than 15%.

$$V_{\rm obs} = [E][S]k_{\rm cat}/(K_{\rm m} + [S])$$
 (1)

$$V_{\rm obs} = (k_{\rm cat}/K_{\rm m})[{\rm E}][{\rm S}]$$
<sup>(2)</sup>

fraction product = 
$$1 - e^{-kobst}$$
 (3)

$$k_{\rm obs} = (k_{\rm cat}/K_{\rm m})[{\rm E}]$$
(4)

**Inhibitor Screening.** For initial screening, compounds were tested in kinetic assays at 100  $\mu$ M final concentration. Compounds that inhibited more than 50% at this concentration were analyzed further as described below.

Analog Dissociation Constants. The standard assays and conditions described above were used to monitor the  $K_{cat}/K_{M}$  for reduction of APS in the presence and absence of inhibitor. Values of  $K_{i}$  were determined from the dependence of the observed rate constant  $(k_{obs})$  on inhibitor concentration. With subsaturing APS, the inhibition constant is equal to the dissociation constant  $(K_{i} = K_{d})$ . Except in cases where solubility was a limiting factor, a range of inhibitor concentrations was employed from at least 5-fold below to 10-fold above the inhibition constant. Nonlinear least-squares fits of the equation for competitive inhibition (eq 5) gave excellent fits in all cases, and the standard error was typically less than 15%.

$$(k_{\rm cat}/K_{\rm M})^{\rm obs} = (k_{\rm cat}/K_{\rm M})/(1 + [\rm I]/K_{\rm i})$$
 (5)

Catalytic inactivation of APS reductase by 2-nitro-9,10-phenanthrenedione. APS reductase (9  $\mu$ M) was incubated with compound 23180 (0.9  $\mu$ M) or DMSO and enzyme activity was measured at 1, 15 and 30 min. No statistical difference was observed in the activity of the enzyme in these experiments indicating that compound 23180 did not catalytically inactivate APS reductase.

**Thiol Quantitation.** Labeling of APS reductase by the thiol-reactive probe NBDCl was carried out using a modification of a following the published procedure.<sup>10</sup> Briefly, APS reductase (10  $\mu$ M) was incubated, at room temperature, in a final volume of 1 mL of buffer containing 50 mM BisTris (pH=7.5), 1 mM EDTA, and 1 mM DTT with (a) DMSO or (b) 10  $\mu$ M compound 23180. NBDCl (50  $\mu$ M) was added to each of the resulting solutions and incubated for 30 minutes at room temperature. Excess NBDCL was removed from the labeled APS reductase by ultracentrifugation prior to the UV-vis scan. No loss in APS reductase thiol labeling was observed in the presence of inhibitor.

**Promiscuous Inhibition.** At the suggestion of one reviewer, we tested members of each structural class of inhibitor for promiscuous inhibition. Assays were carried out as described above in the presence of 0.01% Triton, and showed no significant difference in Kd with the assay without detergent. We also performed a gel shift assay of trypsin activity acting on APS reductase in the presence of inhibitors. By this gel assay, none of the inhibitors at concentrations of 50 uM changed the proteolysis pattern of trypsin and qualitatively indicates that the compounds are not inhibiting trypsin.

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