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(54) Titre : COMPOSITIONS ET PROCEDES POUR LA PRODUCTION DE COMPOSES
(54) Title: COMPOSITIONS AND METHODS FOR THE PRODUCTION OF COMPOUNDS

(57) **Abrégé/Abstract:**

The present disclosure provides proteins, nucleic acids, vectors, and host molecules useful for the production of compounds of interest, and methods for their use.

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COMPOSITIONS AND METHODS FOR THE PRODUCTION OF COMPOUNDS

Abstract of the Invention

The present disclosure provides proteins, nucleic acids, vectors, and host molecules useful for
5 the production of compounds of interest, and methods for their use.

COMPOSITIONS AND METHODS FOR THE PRODUCTION OF COMPOUNDS

Background

Polyketide natural products are produced biosynthetically by polyketide synthases (PKSs), e.g., type I polyketide synthases, in conjunction with other tailoring enzymes. Polyketide synthases (PKSs) are a family of large, multi-domain proteins whose catalytic functions are organized into modules to produce polyketides. The basic functional unit of polyketide synthase clusters is the module, which encodes a 2-carbon extender unit, e.g., derived from malonyl-CoA. The modules generally present in a polyketide synthase include i) a loading module; ii) extending modules; and iii) releasing modules. Within the module, the minimal domain architecture required for polyketide chain extension and elongation includes the ketosynthase (KS), acyl-transferase (AT) and the ACP (acyl-carrier protein) domains, and the specific chemistry of each module is encoded by the AT domain and by the presence of the β -ketone processing domains: ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) domains. Polyketide synthase biosynthesis proceeds by two key mechanisms: polyketide chain elongation with a polyketide synthase extending module and translocation of the polyketide intermediate between modules. Productive chain elongation depends on the concerted function of the numerous catalytic domains both within and between modules.

Combinatorial biosynthesis is a general strategy that has been employed to engineer polyketide synthase (PKS) gene clusters to produce novel drug candidates (Weissman and Leadlay, Nature Reviews Microbiology, 2005). To date, these strategies have relied on engineering PKS domain deletions and/or domain swaps within a module or by swapping an entire module from another cluster to produce a chimeric cluster. The problem with this approach is that protein engineering of the polyketide megasynthases via wholesale domain and/or module replacement, insertion, or deletion can perturb the “assembly line” architecture of the PKS, thus drastically reducing the amount of polyketide synthesized.

Summary of the Invention

The present disclosure provides compositions and methods for use in combinatorial biosynthesis of polyketides without a significant loss of compound production by module swapping between polyketide synthase genes. Bioinformatics approaches may be used to predict module interface compatibility and therefore, the likelihood that a heterologous module may be swapped into a PKS gene. The resulting compatibility information may be used to engineer a polyketide synthase with an increased likelihood of functioning in assembly-line polyketide biosynthesis.

Accordingly, in one aspect, the disclosure provides an engineered polyketide synthase that includes one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the engineered polyketide synthase is capable of producing a polyketide when expressed under conditions suitable to allow expression of a compound by the engineered polyketide synthase and wherein the one or more heterologous modules do not substantially inhibit polyketide translocation during polyketide biosynthesis.

In another aspect, the disclosure provides an engineered polyketide synthase including one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the engineered polyketide synthase is capable of producing a polyketide when expressed under conditions

suitable to allow expression of a compound by the engineered polyketide synthase and wherein the one or more heterologous modules include linking sequences which are compatible to the linking sequences of the modules adjacent thereto.

5 In another aspect, the disclosure provides an engineered polyketide synthase including one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the engineered polyketide synthase is capable of producing a polyketide when expressed under conditions suitable to allow expression of a compound by the engineered polyketide synthase and wherein the polyketide expression level of the engineered polyketide synthase is at least 1% (e.g., at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 110%, at least 120%, at least 130%, at least 140%, at least 150%) of the polyketide expression level of the reference polyketide synthase.

15 In some embodiments, the polyketide expression level of the engineered polyketide synthase is at least 1-10% (e.g. at least 1-10%, at least 11-20%, at least 21-30%, at least 31-40%, at least 41-50%, at least 51-60%, at least 61-70%, at least 71-80%, at least 81-90%, at least 91-100%, at least 101-110%, at least 111-120%, at least 121-130%, at least 131-140%, at least 141-150%). In some embodiments, the engineered polyketide synthase includes one or more heterologous modules with native linking sequences.

20 In some embodiments, the engineered polyketide synthase may include one, two, three, or more heterologous modules. In some embodiments in which the engineered polyketide synthase contains multiple heterologous modules, the heterologous modules may be adjacent in the engineered polyketide synthase. In some embodiments in which the polyketide synthase contains multiple heterologous modules, any of the modules may be separated by one or more native modules in the engineered polyketide synthase.

25 In some embodiments of any of the above described aspects, at least one of the one or more heterologous modules is an elongation module which modifies a β -carbonyl unit in the variable region of the polyketide.

In some embodiments of any of the above described aspects, at least one of the one or more heterologous modules includes a portion having at least 90% identity to any one of SEQ ID NO: 1-165.

30 In some embodiments of any of the above described aspects, at least one of the one or more heterologous modules includes a portion having the sequence of any one of SEQ ID NO: 1-165.

SEQ ID NO: 1

35 QPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPVDRGWDVDGLYDPDPDVP GKSYTVEGGFLDAVTGFDAPFF
GISPREALAMDPQQLVLEASWEAFERAGIEPGSVRGSDTG VFMGAFFPGGYGTGADLGGFGMTGGAASVLSGRVSYF
FGLEGPAMTVDTVCSSSLVALHQAGYALRHGECSLALVGGVTVMSTPQT FVEFSRQRGLAADGRCKAFSDDADGTGW
SEGVGVLLVERLSDAQARGHNILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTGADV DVVEAHGTGTT
LGDPIEAQAVIATYGQDRDQPVLLGSLKSNLGH TQAAAGVSGVIKMVMALQNGVVPRTLHVEEPSRHVDW TAGAVEL
VTENQPWPELGRARRAAVSSFGLSGTNAHVILESAPDQPPAPSTDSPVSAVTAGVVPLPISAKTLPALADLEDR LRT
40 YLTTTPD TDLPAVASTLATRSLFEHRAVLLGEDTVTGTAIPDPRVVFVFPQGQWQWQGMGSALLTSSTVFAERMAE
CAAALSEFVDWDL LTVLDDPSVVDRVDVVQPACWAVMISLA AVWQAAGIHPDIVLGHSQGEIAAACLAGAISLPDAA

RIVAQRSQLIAHQGLGHGAMASISLPADDIPTTDQVWIAAHNGTSTVIAGDPQAVEAVLATCETRGARVRKINVDYAS
HTPHVEQIRTELLEDITTTGIEAHTPAVPWLSTTDNTWIDQPLDPTYWYRNLREPVRFGPAIDLLQTQDNNLFIEISAS
PVLLQTMDNAATVATLRRDEDTTTHRLLTAFAEAHVHGATINWPTVLDTTTTTPVDLPTYPFQRQRYWATSNGHPADLT
PEALLKVVRDSAAMVLGHASADTVPTATAFQELGLDSLTAVELRNSLTAKATGLRLPATMAFDYPTPDALAARL

5

SEQ ID NO: 2

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDAITDFPTDRGWDTDTLFDPDPDTPGKTYTVHGGFLDDVAGFDAPFF
GISPREAVAMDPQQRLVLESSWEAFERAGIQPDSIRGSDTGVFMGAYPDGYGIGADLAGFGVTAGAGSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQAAAYALRQGECSLALVGGVTVMPSRPTFIEFSRQRGLAADGRSKAFADAADGTGF
10 SEGVGVLVERLSDAQAKGHNILALVRSSAVNQDGASNGLTAPNGPSQQRVIQSALAGAGLTSADVVDVVEAHGTGTT
LGDPIEAQAVLATYGGQDRDRPVLLGSLKSNLGHTQAAAGVSGVIKVMALQHNTVPATLHVDAPSRHVDWTAGAVRL
ATENQWPETNRPRRAGVSSFGVSGTNAHVILEQAPAASPVEPVDTTDVVPLVVSARSSGSLSDQADRLAALVGSP
DAPALTSLADALLTRRTVFSQRAVVVAGSHEQAAAGLRALAAGDSHPALVTGAAGPARVVLVFPGQGSQWAGMGAE
LDASPVFAARIAECAEALRPWVDWSLDEVLRGDASADVLGRVDVVQPASFVVMVGLAAVWESAGVRPDAVLGHSQGE
15 IAAAYVAGALSLTDAKIVAVRSRLIAARLGRGGMASVALAPEEAAKLGRTELAAVNSPASVVIAGDAEALDETLAM
LEGEGRVRRVAVDYASHTPHVEELEQSMAEALADVRSRQPRVRFLSTVTGDWVTEAGALDGGYWYRNLRQPVRFGP
AVASLAEAGYTVFVEASAHPLVQPVAEETLDRDPAVVTGTLRRQDGGPLRLLTSMAELFVGGVPVNWPVLLPAGAVR
GWVDLPTYAFDHQRYWLENRELTPALLKLVCGRAAAVLGHVDADAVPVAAAFRDLGVDSLTAVELRNSLAKATGLR
LPATLVFDYPTPTVLAGRL

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SEQ ID NO: 3

EPLAIVGMACRLPGGVLSPEDLWRLVESGGDAISGFVDRGWDVENLFDPDPAAGRTYAVRGGFLDGAAGFDASFF
GISPREAQAMDPQQRLVLEVSWEAFERAGIEPGSVRGSDTGVFMGAYPGGYGMGTDLGGFGMTSVAVSVLAGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMPTPQTFVEFSRQRGLAADGRCKAFADAADGTGF
25 SEGVGVLVERLSDAQARGHNILAVVRGSAVNQDGASNGLTAPNGPSQQRVIQSALAGAGLTSADVVDVVEAHGTGTT
LGDPIEAQAVIATYGGQDRDQPVLLGSLKSNLGHTQAAAGVSGVIKVMALQNGVVPRTLHIDEPSRHIDWTAGAVEL
VTENQSWPETGRDRRAAVSSFGISGTNAHVILESAPAQPVPVDPVSDVTAGVVPLPISARTVPALADLEDRLRAY
LTTTPETDLPAVASTLAMTRSVFEHRAVLLGEETVTGIAVSDPRVVFVFSGQGSQRVGMGEELAAAFPLFARLHRQV
WDLLEDVPDLEVDDTGYVQPALFALQVALFGLLESWGVPRQAVLGHSVGEVAAGYVAGVWSLEDACTLV SARARLMQA
30 LPAGGAMVAVPVSEEQARAVLVDGVEIAAVNGPASVVLSGDESAVLRVAEGLGRWTRLSASHAFHSVRMEPMLLEEFR
QVASELTYREPRIVMAAGEQVTTPEYWVRQVRDTPVRFQDQVAAFQDAVFLEIGPDRTLSRLIDGIAMLDGDDEVRAA
VAALAVMHVQGVGVDPAILGTTTGRVLDLPTYAFQHERYWMVIQELSPEALLKIVRDSAAMVLGHANADTVPTATA
FQELGLDSLTAVELRNSLTAKATGLRLPATMAFDYPTPAALAGRL

35

SEQ ID NO: 4

EPLAIVGMACRLPGGVSTPEDLWRLVESGTDAITDFPTDRGWDTDLFDPDPTPGKTYTVHGGFLDDVAGFDASFF
GISPREALAMDSQQRLVLEASWEAFERAGIEPGSVRGSDTGVFMGAYPDGYGIGVDLGGFGATAGAGSVLSGRLSYF
FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVIANPQIFVEFSRQRGLAADGRCKAFADNADGTGF
SEGVGVLLVERLSDAQARGHNILALVRSSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTGAEVVDVVEAHGTGTT
40 LGDPIEAQAVLATYGGQDRDQPVLLGSLKSNLGHTQAAAGVSGVIKVMALRHDTVPATLHIDEPSRHIDWTAGAVEL
VTENQWPVLDPRRAAVSAFGVSGTNAHVILESAPDQPPASATDTPAPAVTAGVVPLPISAKTVPALADLEDRLRA
YLTTTPETDLPAVASTLATRSLFEHRAVLLGEDTVTGTTIPDPRIVFVFPGQGWQWQGMGSALLTSSTVFAERMAE

PATENT
50869-016WO2

CAAALSEFVDWDLTLVLDDPSIVDRVDVVQPACWAVMISLAAVWQAAGIHPDIVLGHSQGEIAAACLAGAISLPDAA
RIVAQRSQLIAHQLGHGAMASISLPADDIPTTDKVVIAAHNGTSTVIAGDPQAVEAILATCETR GARVRKINVDYAS
HTPHVEQIRTELDDITTGIEAHTPTVPWLSTTDNTWIDQPLDPTYWYRNLREPVRFGPAIDLLQTQDNNLFIEISAS
PVLLQTMDNATTVATLRRDEDTTQRLLTAF AEAHVHGATINWPTVLNTTTTTPVDLPTYPFQRQRYWATSNDRLNGRT
5 SVEQHRIMVELVLAHATSVLGHESPD A IAPDRAFKDLGMDSLTAIELRNHLVAETGVRLPATTAFDHPTADDLAKRL

SEQ ID NO: 5

EPIAIVSMSCRAPGGVDSPESLWRLVESGTD AITDFPGDRGWDVAGLYSPDPTGYKTYCVQGGFLDAAADFDAFFG
ISPREALGMDPQQRLLLETSWEAIERARIDPRSLPGRNVGVYVGGA AQGYGVGAIDQQRDNVITGSSISLLSGRLSY
10 ALGLEPGVTVDTACSSSLVALHLACQALRQRECSMALVSGVSVIPTPDVFVEFSRQRGLAADGRCKSF SASADGTI
WAEGVGVLVLERLSEATRLGHRVLAVVRGSAVNSDGASNGLTAPNGVSQQRVIRQALTGAGLTAADVDVVEAHGTGT
KLGDP IEAEAILATY GQDRSTPVCLGSLKSNIGHAMAASGVLAVIKMVEAMRHGLIPRTLHVEEPSPHVDWASGDVA
LLTENQWPDDAKLRRAGVSSFGLSGTNAHVVLEQYRAPAAPDITTEHQPLAWTLSARDPKALREQAGRLHAALTE
SPRWRPLDIGYSLATTRSNFAHRAVAVGSDRELLRALS KLADGSAWPALVTATAKDRRVAYLFDGQGSQRPDMSGSL
15 YERFP AFARAWDRISA EFGKHL D HSLTDVYLGRGDAATADLVDDTLYAQAGLFTMEIALFELLA EWGVRPDFVSGHS
IGETAAAYAAGVLSLEDVTKLIVARGRALRQVPPGAMVALRAGEDEAREFLGRTGAALDLAAVNSPTSVVVS GASEA
VAGFRARWTESGREARTLNVRHAFHSRHVEAVLGEFREVLES LTFRTPALPVVSTVTGR LIEPTELSTSEYWL RQVR
QTVRFHDAVRELSGQGVGT FVEIGPSGALASAGLECLGDEASFHAVQRPGSPGDVCLMTAVAE LHAGGTTVDWATVL
AGGRATDLPVYPFQHGSYWLAPARPSAPEEPRTMLELVRLEAAIALSITDPGLIADDSSFLDLGFDSISALRLSNRL
20 AAVTG L D L P P S L L F D H P T P A E L A A R L D

SEQ ID NO: 6

EPLAIVGMACRLPGGVSSPDDLWRLVASGTD A ISEFPADRGWDVDNLYDPDPDAPGKTYTVLGGFLDGVAGFDASFF
GISPREALAMDPQQRLMLEVSWEAFEHAGIPPRSVRGSDTGVMGAFPSGYNAGLEEFGMTGDAVS VLSGRVSYFFG
25 LEGPAITVDTACSSSLVALHQASSALRQGECSLALVGGVTVLATPQTFVEFSRQRGLALDGRSKAFADAADGAGWAE
GVGVLVVERLS DARA KGHQI WGVIRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLAPHEVDVVEAHGTCTMLG
DPIEAQAVIATY GQDREQPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHDTV PATLHVDAPSRHVDWTAGAVELVT
ENRPWPETGRVRRAGVSSFGISGTNAHVILESAPEQPASPPEAVAPVVASDRVPLVISAKTPAALAEMENRLRAYLA
AAPGADPRAVASTLATARSVFEHRAVLLGENTITGTVAGADPRVVFVFPQGQWQQLGMGRALRESSPVFAARMAECA
30 AALSEFVDWDLFTMLDDPAVIDRIDVLQ PACWAVMMSLA AVWQAAGVRPDAVIGHSQGEIAAACVAGALSRLDAARI
VALRSQLLAREMGHGVM A AVALPADDIPLVDGVWIGARNGPSSTVISGTPEAVEVVVAACEERGARVRRITAAVASH
SPLGEKIRTELLGISASIPSRTPVVPWLSTADGIWIEAPLDPAYWWRNLREPVGFGPAVDLLQARGENVFLEMSASP
VLLPAMNDAVTVATLRRDDDT PDRMLTALAEAHAGVIVDWPRVFGSTTRVLDLPTYAFEHQRYWAVNGRP ADLTPE
ALLKLVCGRAAAVLGHVDADAVPVAVAFRDLGVDSL TAVELRNSLAKATGLRLPATLVFDYPTPTVLAGRL
35

SEQ ID NO: 7

EPLAIVGMACRLPGGVLSPEDLWRLVESGGDAISGFVDRGWDVENLFDPD PDAAGRTYAVRGGFLDGAAGFDASFF
GISPREAQAMDPQQRLVLEVSWEAXERAGIEPGSVRGSDTGVMGAYPGGXGXGTDLGGFGMTSVAVSVLAGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMPTPQTFVEFSRQRGLAADGRCKAFADAADGTGF
40 SEGVGVLVVERLSDAQARGHNILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLAGAEVDVVEAHGTGTT
LGDP IEAQAVIATY GQDRDQP VLLGSLKSNLGH TQAAAGVSGVIKMVMALRHDTV PATLHIDEPSRHIDWTAGAVEL
VTENQSWPETGRDRRAAVSSFGISGTNAHVILESAQAQPVPPMDTPVSAVTAGVVPLPISARTVPALADLEDRLRAY

LTATPETDLP(AVASTLAVTRSVFEHRAVLLGEETVTGIAVSDPRVVFVFSGQGSQRVGMGEELAAAFPLFARLHRQV
WDL(DVPDLEVDDTGYVQPALFALQVALFGLLESWGVRPQAVIGHSVGEVAAGYVAGVWSLED(CTLVSARARLMQA
LPAGGAMVAVPVSEERARAVLVDGVEIAAVNGPASVVL(SGDESAVLRVAEGLGRWTRLSASHAFHSVRMEP(MLEEFR
QVASELTYREPRIVMAAGEQVTTPEYWVRQVRD(TVRF'GDQVAAF'GDAVFLEIGPDRTLSRLIDGIPTLHGDDEQH(AV
5 VAALAELHVQGVPIDWSSILGVNPARVDLPTYAFQH(ERYWMVIQELSPEALLKIVRDSAAMMLGHPNTDAIAATTAF
RDLGVDSLIAVELRNSLAKATGLRLPATLVF'DYPTPTVLAGRL

SEQ ID NO: 8

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD(AITDFPTDRGWD(TDDLFD(PDPDTPGKTYTVHGGFLDDVAGFDASFF
10 GISPREAQAMDPQQRLVLEAAWEAFERAGIEPGSVRGSDTG(VFMGAYPGGYGIGVDLGGFGATAGAGSVLSGRLSYF
FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVT(VIANPQIFVEFSRQRGLAADGRCKAFADSADGTGW
SEGVGVLLVERLSDAQARGHNILAVVRGS(AVNQDGASNGLTAPNGPSQQRVIRQALANAGLAGAEVDVVEAHGTGTT
LGDPIEAQAVIATY(GQDRDQPVLLGSLKSNLGH(TQAAAGVSGVIKMMALQNGVVPRTLHADQPSRHIDWTAGAVEL
VTENQ(PWPELGRPRRAAVSAFGVSGTNAHVILESA(PAQPVPPVDTPVSAVTAGVVPLPISARTVPALADLEDRLRAY
15 LTATPETDLP(AVASTLATTRSVFEHRAVLLGEDTVTGTAIPDPRIVFVFSGQGSQRVGMGEELAAAFPLFARLHRQV
WDL(DVPDLDVDDTGYVQPALFALQVALFGLLESWGVRPQAVIGHSVGEVAAGYVAGVWSLED(CTLVSARARLMQA
LPAGGAMVAVPVSEEQARAVLVDGVEIAAVNGPASVVL(SGDEAAVLRVAEGLGRWTRLSASHAFHSVRMEP(MLEEFR
QVVSRLTYREPRIVMAAGEQVTTPEYWVRQVRET(VRFGDQVAAF'GDAVFLEIGPDRTLSRLIDGIAMLDGDDEVRAA
VAALAVMHVQGVGVDPAILGTTTGRVLDLPTYAFQH(ERYWMANNGRPADLTPEALLKVVRDSAAMVLGHANADTVP
20 AATAFQELGLDSLIAVELRNSLAKATGLRLPATMVFDYPTPAALAGRL

SEQ ID NO: 9

EPLAIVGMACRLPGGVSSPEDLWRLVESGFDAITGFPTDRGWD(VDNLYD(PDPDAPGKSTTLHGGFLDDVAGFDASFF
GISPREAVAMDPQQRLAMEVSWEAFERAGIEPGSVRGSDTG(VFMGAYPGGYGIGAE(LGGFMLTGRAGSVLAGRVSYF
25 FGLEGPAMTVDTACSSSLVALHQAAAYALRQGECSLALVGGVT(VMPTPVMFVEFSQQQNLADDGRCKAFADSADGTGW
SEGVGVLLVERLSDAQARGHNILAVVRGS(AVNQDGASNGLTAPNGPSQQRVIRSALTSAGLTTADV(VVEAHGTGTT
LGDPIEAQAVLATY(GQDRDQPVLLGSLKSNLGH(TQAAAGVSGVIKMMALQNGVVPRTLHV(EEPSRHHVDWTAGAVEL
VTENQ(SWPETGRARRAAVSSFCFSGTNAHVILESA(PAQPVPPMDTPAPT(VTTGVVPLPISAKSLPALADLEDQLRAY
LTATPETDLP(AVASTLAMTRSVFEHRAVLLGEETVTGTAIPDPRIVFVFSGQGSQRVGMGEELAAAFPLFARLHRQV
30 WDL(DVPDLDVDDTGYVQPALFALQVALFGLLESWGVRPQAVIGHSVGEVAAGYVAGVWSLED(CTLVSARARLMQA
LPAGGAMVAVPVSEEQARAALVDGVEIAAVNGPASVVL(SGDEAAVLRVAEGLGRWTRLSASHAFHSVRMEP(MLEEF
QVASELTYQEPRIVMAAGEQVTTPEYWVRQVRD(TVRF'GDQVAAF'GDAVFLEIGPDRTLSRLIDGIAMLDGDDEVRAA
VAALAELHVQGVPIDWPAILGTTTGRVLDLPTYAFQH(QRYWAASTWLAGLAPEERE(GALMKVV(RDTAAVVLGHADAG
TIPVTAAFKDLGLDSLTAVELRNSLAKSTGLRLPATMVFDYPTPASLAARLD

35

SEQ ID NO: 10

EPLAIVGMACRLPGGVESPEDLWRLVESGTD(AISGFPADRGWADLSLRGGFLGDAAHFDAAFFGISPREALAMDPQQ
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SSSLVALHQAGHALRQGECSLALVGGVT(VMPTPDIFVEFSRQGGLASDGRCKAFADAADGTSWSEGAGVLVVERLS(D
40 AERRGHTVLALVRGS(AVNQDGASNGLTAPNGPSQQRVIQ(AALANAGLTPHEVDVVEAHGTGTRLGDPIEAQAVIATY
GRDREHPLLLGSLKSNVGHTQAASGVSGLIKMMALRRGTVPRTLHVDEPSRHHVDWTAGAVQLAIENQ(PWPETGRPR
RAAVSSFGVSGTNAHVILEGVPEEPADSEEPAGLTPLLI(SAKTPAALAEFEDRLRARLTTEPNLS(AVASTLV(RTRSL

FDHRAVLLDGETVSGMAEPDPRVVFVFSGQGSQRAGMGDDLAAAFPVFAKIRQQVWDLLDIPDLPVDETGHQAQPALE
ALQVALFGLLDSWGVRPDALVGHSIGELAAGYVAGIWSLEDACALVSARARLMETLPPGGVMVAVPVSEEQARAVLT
DGVEIAAVNGPASVVLSGEETAVLQAAAAALGGRSKRLATSHAFHSARMEPMLDEFRAVAEQITYGSPRIPMAVGDGP
DYWVRQVRDITVRFGEQVAAHGDGAI FVELGPDGSLARLVDGIAVLDREDEPRAALTALARLHVGRGVKVDWP
5 LDLPTYPFQRQRYWAETPTARRAPTDLTLVRDITATVVGYPDNTAVTPTTAFTDLGIDSLTAIELRNNMATTGTLR
LPATLVFDYPTPATLAARLD

SEQ ID NO: 11

EPLAIIGMACRLPGGVTTPEDLWQLVETGTDAISGFPTDRGWDVESLYDPDPDAAGKSYCVEGGFLDAVADFDASFF
10 GISPREALAMDPQQRILETSWEAFERAGIDPADARGSDTGVMGAFETSGYGADLEGFGGTAGALSVLSGRVSYFFG
LEGPAATVDTACSSSLVALHQAGYSLRHGECSLALVGGVTVMATPRTFVEFSRQRGLASDGRCKAFGDTADGTGWSE
GVGVLLVERLSDAERNHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALDNAGLAPQDQDVVEAHGTGTTLG
DPIEAQAVIATYQONREQPLLLGSLKSNVGHTQAAAGVSGVIKMIMALRHGVVPRTLHVDEPSRHVDWTAGAVHLVR
ENQPWPDVDRPRRAGVSSFGVSGTNAHIIIESPPSQPAPEPAPALSPLVISAKTPQALAAYEDRLRTYLTAASTDA
15 RALAVTRSLFEHRAVLLGEDTVTGTALTEPRVVFVFPQGQWQWLGMGAALMESVVF AERMAECAAAELSEFVDWNLI
VLNDPAVIDQVDVVQPACWAVMVSLAAVWQAAGVRPDAVIGHSQGEIAAACVAGAI SLRDAARIVALRSRLISERLG
KGAMASITLPADQITLAEGAWIAAYNGPTSTVVAGTPQAIEQMHGERVRRIAVDYASHTPHVEQIRAEELDLTTDVS
SQTPTLPWYSTVDGTWIDSPLDGDYWRNLRQPVGFHFAVQTLQALGETVFVEVSASPVLLPAMDDAVTIATLRRDE
GTLTRMHTALAEAHVLGVTIDWPTVLGVTTRHVDLPTYAFQRQRYWVAELASLGPAERERARLKLVSDDTAAGILGHA
20 DSGTVPVTAAFRELGVDSLTAVELRNGLAKATGLRLPATMVFDYPTPQALADRL

SEQ ID NO: 12

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDIAIDFPADRGWDVESLYDPDPDAAGKSYCVRGGFLAAAAEFDAEFF
GISPREALAMDPQQRVLVLETSWEAFERAGIEPGSVRGSDTGVMGAFAGGYGAAVEGFGATAGATSVLSGRVSYFFG
25 LQGPATVDTACSSSLVALHQAGYSLRQGECSMALVGGVTVMATPQSFVEFSRQRGLAPDGRCKAFADTADGTGWSE
GVGVLLVERLSDAERNHRVLAVVRSSAVNQDGASNGLSAPNGPAQQRVIRQALANAGLAAADVDVVEAHGTGTTLG
DPIEAQAVLATYQDRERPLLLGSLKSNVGHTQAAAGVSGVIKMVMALRHGVVPRTLHVDEPSRHVDWTAGAVHLVT
ENQPWPDITDRPRRAGVSSFGVSGTNAHVIIIEGSPTSSPVAEPSGDVLPVLSAKTPQALTAYEDRLRAFLAAAPVTD
TRAVASTLAVTRSLFEHRAVLVGDNTVTGTALAEPRVVFVFPQGQWQWLGMGAALMESVVF AERMAECAAAALGEFVD
30 WDLLAVLDDSAVVDRVDVVQPACWAVMVSLAAVWQDAGVRPDAVIGHSQGEIAAACVAGAI SLRDAARIVALRSRLI
SERLGKGAMASITLPADQITLAEGAWIAAYNGPASTVVAGTPDAIEQMCGDRVRRIAVDYASHTPHVEQIRAEELDL
TAEVGSRTPTVPWYSTVDGTWIDSPLDGEYWRNLRQPVGFHFAVQTLQALGETVFVEVSASPVLLPAMDDAVTVAT
LRRDEGTLTRMHTALAEASHVLGVSIDWPHVLGDTGERMLDLPTYAFERHRYWSTARRNPSIAPDDLTVVRDSAAVV
LGYADGGAVPVTGAFKDLGIDSLTAVELRNGLAKATGLRLPATVAFDYPTPQALAARL
35

SEQ ID NO: 13

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDIAITGFPADRGWAEYSFQGGFLDDAADFDAAFFGISPREALAMDPQQ
RLVLETAWEAERAGIEPGSLRGSDTGVMGAYPGGYGIGADRAGFGATAGAGSVLSGRVSYFFGLEGPATVDTAC
SSSLVALHQAGHALRLGECSLALVGGVTVMATPDTFVEFSRQGGLAADGRSKAFADSADGAGFAEGAGVLLVERLS
40 AQRHGHQVLALVRGSAVNQDGASNGLTAPNGPSQQRVIQAALDNAGLTAAEVDVVEAHGTGTTLGDP
GQGRGEPLLLGSIKSNVGHTQAAAGVSGVIKVVMALRHGVVPRTLHVDEPSRHVDWTAGAVRLATENQSWPETGRPR
RAGVSSFGISGTNAHVILEGVPEEPAGHEEPAGLTPLLI SAKTPAALAEFEDRLRAYLTTEPSLP
PAVASTLARTRSL

FDHRAVVLDGDVVRGVAEPDRRVVFVFSGQGSQRAGMGDDLAAAFPVFAKIRQQVWDQLDIPDLPVDQGTGYAQPALF
ALQVALFGLLDSWGVRPDALVGHSIGELAAGYVAGIWSLEDACALVSARARLMQALPPGGVMVAVPVSEQQARGALT
DGVEIAAVNGPASVVLSGDEAAVLRAAAALGGRSKRLATSHAFHSARMEPMLDEFMVAERLSYGSPRISMAVGDGP
DYWVRQVREAVRFGEQVAAHDGAVFVELGPDGSLARLIDGIAMLDRDDEPRAALTALARLHVQGVKVDWPIGAGRRV
5 DLPTYPFQRQRYWIDRPTARRAPTDLLTLVRDTAATVLGYPDSSAVPATTAFKDLGVDSLTAIELRNGMATTTGLRL
PATLVFDYPTPAALAARL

SEQ ID NO: 14

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDALSGFPTDRGWAHESFQGGFLDGAGDFDAPFFGISPREARVMDPQQ
10 RLVLEASWEAFERAGIEPGTVRGSDTGVMGAYSGGYAAGADLAGFAATAGAGSVLSGRVSYFFGLEGPAVTVDTAC
SSSLVALHQAGHALRQGECSLALVGGVTVMATPDLFVEFARQQGLAADGRCKAFADNADGTGWSEGVGVLLVERLSD
AERNGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAAALDNAGLTPADIDVVEAHGTGTTLGDPIDIAQAVIATY
GQTREQPLLLGSLKSNVGHTQAAAGVSGVIKMMALRHGVVPRTLHVDEPSRHVDWTAGAVQLAVENQWPWNTGRPR
RAGVSAFGVSGTNAHVIIIEGSPTPSPVAEPSGDVPLVISAKTPQALTAYEDRLRTYLNATPEIDTRAVASTLAVTR
15 SLFEHRAVLLCDNTVSGTALTEPRVVFVFPQGQWQWLGMGAAALMESVVFMAERMAECAALSEFVDWNLITVLNDPAV
VDQVDVVQPACWAVMVSLAAVWQDAGVRPAAVIGHSQGEIAAACVAGAI SLRDAARIVALRSRLIGERLGRGAMASV
ALPADEIALVDEVWVAAYNGPASTVIAGAPDAIEQMLGDRVRRIAVDYASHTPQVEQIRAEELDLTAEVSSQAPTVP
WYSTVDGTWIDGPLDSYWYRNLRQPVGFHPAVEALGGLGETVFVEVSASPVLLPAMDDAVTVATLRRDEGTLTRMH
TALAEAHVLGVTIDWPAVVGDTGERMLDLPTYAFQHHRYWTTATARLEGRTGAEKHRLLLDIVLANAATVLGHDTAD
20 TIASDKPFKDLGIDSLTAVELRNSLARATELRLPATTAFDYPTPEALATRL

SEQ ID NO: 15

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDALITGFPADRGWPDDSRQGGFLDDAADFDAAFFGISPREALAMDPQQ
RLVLEAAWEAFERAGIEPGSLRGSDTGVMGAYPGGYGIGADQAGFGTTAGAGSVLSGRVSYLFGLEGPAVTVDTAC
25 SSSLVALHQAGHALRLGEC SLALVGGVTVMGTPDIFAEFSRQGGGLASDGRCKPFADAADGTGWAEGVGVLLVERLSD
AERHGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQSALIQAGLAPHEVDVVEAHGTGTTLGDPIDIAQAVIAAY
GQDRAQPLLLGSIKSNVGHTQAAAGVSGVIKMMALRHGVVPRTLHVDEPSRHVDWSAGAVRLATESQPWPD TGHPR
RAGVSSFGISGTNAHVILEGVPEEPADTGEPSGLVPLLLSAKTPAALTHLEDRLRAYLTTEPNLPVAVASTLAQTRSL
FDHRAVLLDGDVVRGVAEPDRRVVFVFSGQGSQRAGMGDDLAAAFPVFAKIRQQVWDLLDIPDLPVDETGHAQPALF
30 ALQVALFGLLDSWGVRPDALVGHSIGELAAGYVAGIWSLEDACALVSARARLMQALPPGGVMVAVSVSEEQARAVLT
DGVEIAAVNGPASVVLSGEETAVLQAAAAALGGRSKRLATSHAFHSARMEPMLDEFMVAERLSYGSPQIPMAVGDGP
DYWVRQVRETVRFGEQVAAHGGIFVELGPDGSLARLVDGIAVLDRDDEPRAALTALARLHVQGVKVDWPIAAGRRV
LDLPTYPFQHQRYSWATRPAARRAPTDLLTLVRDTAATVLGYPDSSAVPATTAFKDLGVDSLTAVELRNNLATSTGLR
LPATLVFDYPTPATLAARLD
35

SEQ ID NO: 16

EPLAIVGMACRLPGGVSTPEDLWQLVESGTDALISGF PADRGWDDYPYQGGFLT TAADFDAFFGISPREALAMDPQQ
RLILEASWEAFERAGINPADARGSDTGVMGAFSAGYGDDRDDSPATAGAVSVLSGRVSYFFGLEGPAMTVDTACSS
SLVALHQAGYSLRHGEC SMALVGGVTVMATPRTFVEFARQGGLAEDGRCKAFADTADGTGWAEGVGVLLVERLSDAE
40 RNGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAAALDNAGLAPQDQDVVEAHGTGTTLGDPIDIAQAVIATYQG
NRQQPLLLGSIKSNVGHTQAAAGVSGIIKMIMALRHGVVPRTLHVDEPSRHVDWTAGAVRLVTENQWPWDADRPRRA
GVSSFGISGTNAHIILEGVPEEPAQPDESPELTPLVISAKTAPALTQFEARLRSYLTTEPALS AVASTLAQTRSLFD

HRAVLLGGDTITGVAEPSRVVVFVFSGQGSQRAGMGDELAAAFPVFAKIRQQVWDLLDIPDLPVDETGHQAQPALFAL
QVALFGLLDSWGVRPDALIGHSIGELAAGYVSGIWSLEDACALVSARARLMQASPPGGAMVAVPVSEQQARAVLTDG
VELAAVNGPSSVVLSGDETAVLQAAAAALGGRSKRLATSHAFHSARMEPMLDEFRAVAEQLSYRSPQIPMAVG DGPEY
WVRQVRD TVRF'GEQVA AHDGAI F'VELGPDGSLVRLIDGIPMLDRDDEPRAALTALARLHVRGVNVAWPIAADRRELD
5 LPTYPFQ RERYWSTASLSALAPAEREQALRKVVS DSSAMVLCYAE GRAVAPTAAFKDLGVDSL TAVELRNSLT KATG
LRLPATIVF'DYPTPGALAVRL

SEQ ID NO: 17

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISRFPADRGWDVDGLYDPDPDAPGKSY SVEGGFLDAVADF DAAFF
10 GISPREALAMDPQQRLILEASWEAFERAGIEPGSLRGSDTG VFMGAYSSGYGIGADIPGLGV TAGAVSVVSGRVSYF
FGLEGPAVTVD TACSSSLVALHQAGHALRRRECSLALVGGVTVMATPFGFVEFSRQRGLASDGRCKAFADTADGT SW
SEGAGVLVVERLSDAERHGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAALANAGLTPHEVDVVEAHGTGTR
LGDPIEAQAVIATY GQARGEPLLLGSIKSNVGHTQAAAGVSGVIKMMALRHGVVPRTLHVDEPTRHVDWTTGAVRL
ATENQWPETERPRRAGVSSFGVSGTNAHI ILEGVAAEPAQPGESPELTPLLLSAKTPAALTHLEDRLRAYLTTEPN
15 LPAVASTLAQTRSLFDHRAVLLGGETVTGVAEPDPRVVFVFSGQGSQRAGMGDDLAAAFPAFAKIRQQVWDQLDIPN
LPVDETGHQAQPALFALQVALFGLLDSWGVRPDALVGHSIGELAAGYVAGIWSLEDACALVSARARLMQALPPGGVMV
AVSVSEEQARAVLTDGVEIAAVNGPASVVLSGEETAVLQAAAAALGGRSKRLATSHAFHSARMEPMLDEFRAVAEQLS
YGSPRIPMAVG DGPDYWVRQVRD TVRFGEQVA AHDGAI F'VELGPDGSLARLIDGIAVLDRDDEPRAALTALARLHVR
GVKVDWPIAAGRRELDLPTYPFQHORYWIDSRPTARRAPTDLTLVRD TTATVLGYPDNTAVTPTTAFTDLGIDSLT
20 AIELRNNMATT TGLRLPATLVFDYPTPATLAARLD

SEQ ID NO: 18

EPLAIIGMACRLPGGVTTPEDLWQLVETGTD AISALPTDRGWADHPYQGGFLTTAADFDAAFFGISPREALAMDPQQ
RLILETSWEAFERAGINPADAHGSDTG VFMGAYSSGYGIGADLAGFGATAGATSVLSGRVSYFFGLEGPAITVD TAC
25 SSSLVALHQAGHALRHGEC SLALVGGVTVMATPDIFVEFARQRGLAADGRCKAFADTADGTGWAEGVGVL LVERLS
AERNGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALDNAGLTPADIDVVEAHGTGTTLGDP IEAQALIATY
GQNREQPLLLGSLKSNIGHTQAAAGVSGVIKMMALQHGVVPRTLHV DDKPSRHVDWTAGAVRLLTESQPWPD TDRPR
RAGVSSFGVSGTNAHV IIEGSPTPSPVADPSGDVLP LVISAKTPAALAAAYEDRLR TYLNATPEIDTRAVASTLAVTR
SLFEHRAVLLGEDTVSGTALTEPRVVFVFPQGQWQWLGMGAALMESVVF AERMTECATALSEFVDWN LITVLNDPAV
30 IDQVDVVQPACWAVMVSLAAVWQAAGVRPDAVIGH SQGEIAAACVAGAI SLRDAARIVALRSRLISERLGKGAMASI
TLPADQITLAEGAWIAAYNGPTSTV VAGTPQAIEQM HGERVRRIAVDYASHTPHVEQIRAE LLDLT TDVSSQTPTLP
WYSTVDGTWIDSPLDGDYWYRNLRQPVGFHPAVQTLQALGETVFVEVSASPVLLPAMDDAVTIATLRRDEGTLTRMH
TALAEAHVLGV TIDWPHVLGDTGERMLDLPTYAF'QH HRYWTTAARLTGRTTAAQHRLMLDFVLGNVA AVLGHGSAGD
VAPDKPFKELGMDSLTSVELRNSLAKATGQRLPATIVFDHPTADALATYL
35

SEQ ID NO: 19

EPIAIVSMACRVPGGVTSPEGLWRLVESGTD AISSEFPGDRGWDVANLYSPDPDAPGKSYSLQGGFLDGAAAFDASFF
GISPREALGMDPQQRL LLET SWEAVERARIDPKSLRGRDVGVYVGGA AQGYGLGAAEAQRDNLITGGSISLLSGRLS
YALGLEGPGLTVDTACSSSLVALHLAAQALRQGECSLALVSGVSVMP TPDVFVEFSRQRGLAADGRCKSF AAAADGT
40 SWSEG VGVL LLERLS DARRLGHEILAVVRGTAVNSDGASNGLTAPNGASQQRVIRQALASAGLGPADVDAVEAHGTG
TKLGDPIEA EAILATY GKDRPTPVWLGSLKSNIGHTMAASGV LGVIK MVESMRHGVLPRTLHVDEPSPHVDWAAGDV
ALLTSNQWPAGRKPRRAGVSSF'GLSGTNAHV VLEQYRMPAAPVTTKEAGPLPWVLSAQTP EALRERAGQLATALAG

PATENT
50869-016WO2

DPAWHPLDVGYSLAATRSTFAHRAVVVGDDREFVRTLGKCLADGAGWPGLTTGVAKSRRIAIFMFDGQGTQRLAMGQGL
YARFPAFTRTWDTVSAEFAKHLDHTLTDVYLGGGGTAAAELVDDPLYAQAGIFAVEVALVELLAEWGVRPDVVTGHS
IGEAAAAYTAGMFSLADVITALITARGAALRSAPPGAMLALRAGEPEVRDFLDRTGAALDVAAVNGPAAVVVSGAPDA
VAGFASAWTASGRECRQLKVRRAFHSRHVEGVLGDFRTVLKSLTFRTPALPIVSTVTGRLIDPAEMGTPEYWLSQVR
5 QPVRFQDAVGELAGQGVSAFLEVGPSGTLASAGMECLDASFHALLRPRPAEDIGVLTALAELYAGGTAVDWATVLAG
GRPVDLPVYPFQHQSYWLSAPDEPRTVLEMVHLEVASILGITDPDAVQDDSSFLELGE'DSLSGVRLRNRLTQV'TGL
TLPATLLFDHDTPSALATELD

SEQ ID NO: 20

10 EPLAVVGMACRLPGGITSPEELWELVEDGGDAVGDFPTDRGWDVAALHAAAESATSRAGALMGAADFDAFFGISPR
EATALDPQQRILLEIAWEAIERAGIKADVLRGTDGTGVFVGGFYGYGAGADLGGFGAYSTQPAVLAGRLSYFFGLEG
PAVTVDTACSSSLVALHQAGQALRAGECSLALVGGVTVMAS PQSFVEFSRQGGVAPDGRCKAFADAADGTGFAEGAG
VLVVERLSDAERNGHTVLAVVRGSAVNQDGASNGISAPNGPAQQRVIRQALGSAGLAPADVDVVEAHGTGTVLGDP I
EAQAVLATYQGQREVPLLLGSLKSNIGHAQAAAGVAGVIKMMAMRRGVVPRTLHVDEPSSHVDWTTGAVELLTEAR
15 PWPESDRPRRAGVSAFGVSGTNAHVILEEVAESSVRSGGSSGLVPLPVSARTESSLAVQVERLGAYVRSGADLSAVA
DGLVRERVVFGHRAVLLGESTVAGVAEGELRTVVFVPGQGSQWVGMGRELMGASEVFAARMRECAAALEPHTGWDLL
DVLGEAVVADRVEVLQPASWAVAVSLAALWQAHGGTPDAVIGHSQGEIAAASVAGALSLEDAARIVALRSQTIAARL
GRGAMASIAIPSAEVEVMEGVWVAARNGPSSTVIAGDPAAVEQVLARYEAEGVRVRRIAVDYASHTPHVEAIQDELA
EVLEGVTAQVPTIPWWSTVDSWVTEPVDDDYWYRNLRQPVAMDTAIGELDGS LFI ECSAHPVLLPALDQERTVASL
20 RTDDGGWERFLTALAEAWTQGADVDWTILVEPAPHRLDLPTYPFDHKRYWLLERLGAMTGADRDAALLTLVRDCAA
VLGHVDAAGVPADA AFKDLGVDSL TAVELRNRLAAATGVRLPATLAFDHPTPRAIASRLD

SEQ ID NO: 21

EPLAIVGMACRLPGGVASPGDLWQMLDSGGDAVTGFPVDRGWDPSGLTGGPDADRGGFLSDAADFDAAFFGISPREA
25 LAMDPQQRILLETWEAFENAGIVPGTLRGSDTGVFMGAFSYGYGVGADLGGFGSIGVQPSVLTGRISYFYGLQGPA
FTVDTACSSSLVALHQAGHALRHGEC SLALVGGVTVMANPDG FVEFEQQGGLSPDGRCRAFADAANGTGWAEGAGVL
VVERLSDAERNGHTVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLGAADVDVVEAHGTGTVLGDP IEA
QAVLATYQGQREVPLLLGSLKSNIGHAQAAAGVAGVIKMMAMRRCVVPRTLHVDEPSSHVDWTAGAVEVVTEARPW
PESGRVPRAGVSSFGVSGTNAHVVLEGAPEPSSGAEASSGGGLVPLPVSARTESSLAVQVERLGAYVRGGADLGAVA
30 DGLVRGRAVFDRAVLLGESTVAGVAVEGARTVVFVPGQGSQWVGMGRELMGVSEVFAARMRECAAALEPYTGWDVL
DVLGEAVVADRVEVLQPASWAVAVSLAALWQAHGVVPDAVVGHSQGEIAAACVAGALSLEDAARVVALRSQTIAARL
GHGAMASIALPASAVEVMEGVWIAARNGP ESTVVAGDPAAVERVLARYEAAGVRVRRIAVDYASHTPHVEAIQDELA
DVLGGITSSAPDISWWSTVDSGWVTEAVGDDYWYRNLRQPVAMDTAVSEL DGS LFI ECSAHPVLLPALDQERTVASL
RTDDGGWDRFLTALAQAWTQGADVDWTTLIEPAQHRLDLPTYPFDHKRYWLQ PAGARNEVARHTDLLTLVRQKAAAL
35 LGHAGPEDVPEDAAFRQLGVDSL IAVQLRNGLNEATGLRLSATLVFDYPTPRALAGRI

SEQ ID NO: 22

EPVAIVGMACRLPGGVTSPEDLWRLVASGTDAITEFPADRGWDVDALFDPDPDAVGRSTTRHGGFLTEATGFDAAFF
GISPNEALAMDPQQRVLVLETWEAFEHAGIVPDTLRESDTGVFMGAF'HQGYGAGRD LGGLGVTATQTSVLSGRLSYF
40 YGLQGPVAVTVDTACSSSLVALHQAAQALRSGECSLALAGGVTVMATPGSFVEFSRQRGLSPDGRCKAFADSADGTGF
AEGVGVLVVERLSDAERNGHTVLAVVRGSAVNQDGASNGLSAPNGVAQQRVIRQALANAGLN GTD VDAVEAHGTGTV
LGDP IEAQAVLATYGQEREVPLLLGSVKSNVGHTQAAAGVAGVIKMMAMRRGVVPRTLHVDESSSHVDWSAGAVEV

VTEARPWPESGGARRAGVSSFCVSGTNAHVILEGVAESSVRSCGSSAGLVPLPVSARTESSLALQVERLGEYVRGGA
DLGAVADGLVRGRAVFGRRAVLLGESTVAGVAVEGARTVVFVPGQGSQWVGMGRELMGVSEVFAARMRECAAALEPH
TGWDVLDVLGEAVVADRVEVLQPASWAVAVSLAALWQAHGVVPDAVVGHSQGEIAAACVAGALSLEDAARVVALRSQ
TIAARLGHGAMASIALPASAVEVMEGVWIAARNGPESTVVAGDPAAVERVLARYEAAGVRVRRIAVDYASHTPHVEA
5 IQDELADV LGGITSSAPSV PWWSTVD SGWVTEPV DDDYWYRNLRQPVAMDTATGELDGS LFI ECSAHPVLLPALDQE
RTVASLRTDDGGWERFLTALAEAWTQGADVDWTTLIEPAQHRVDLPTYPFDHKRYWLQPARRTVVRTIGEDSGRDLLAV
VCGATAAVLGHADASEIGPATAFKDLGIDSLSGIRLRNSLAETTGVRLSATAVFDHPTPDALAARL

SEQ ID NO: 23

10 EPLAIVAMACRMPGGVDT PEDLWRLVESGGDAITEFPTDRGWDLAALYDPDPDAIGKVSVRHGGFLAGAADFD AEFF
GISPREALAMPQQRLILEVSWEAFERAGILPASVRGSDAGVFMGAFTQGYGAGVDLGGFGATGTPTS VLSGRLSYY
FGLEGPSVTVD TACSSSLVALHQAARSLRSGECSLALVGGVTVMATTTG FVEFSRQRGLAPDGRAKAFADTADGTSF
AEGAGVLIVERLS DATRLGHPVLAVVRGSAVNSDGASNGLSAPNGPAQRRVIERALDDAGLVPGDIDAVEAHGTGTR
LGDPIEAQALEAAYGLDRVHPLLIGSLKSNLGH TQAAAGVAGVIKMVLAMRHGVL PRTLHVDEPSRHVDWGGGVRL L
15 RRNEPWPVTGRVRRAGVSSFGISGANAHVVIEAGPPAAPATLPATEPVPEGV VWPVSARTPDGVRDVAGRLVALTAP
AAAIGHSLATTRTAMRHRAVVPARDAEAFARGE EEPGVVRGTADVTDARAVFVFPGQGSQWDGMGAELLATEPV FAR
RLGECAEALAPYTGWDL LDVIAARRPGAPALDRVDV VQPVSFAMMVALAELWRSRGVAPAAVVGHSQGEVAAACVAGV
LTLDDAAKVVALRSRLVATELGHGGMVSVPPADFDAAAWAGRLEVA AVNGPASIVVAGAADAVEELLAATPHARRIA
VDYASHTAHVETIRDALLDALADLTPGAPEVPFFSTVDEAWLDRPADAA YWYDNVRRPVRFGAATARLAE LGYRVFV
20 EASPHPVLT TALADTLAGHPNTAVTGTLRRGDGGARRFTSSLAELWVRGVPVSWPSGESRRVPLPTYPFRRDRYWID
AEAAPTAARDMLELVRTS AALVLGHRDAHAIEPTRA FKEVGFD SLTGVELRNRLADATGLTLPATLVFDHPTAQALA
AHL D

SEQ ID NO: 24

25 EPLAIVGMACRLPGGVASPEDLWRLLESGGDGITTFPGDRGWDVEALYDPDPEHPGTSTVRHGGFLSGAGDFDAGFF
GISPREAVAMPQQRVVMETSWEALEYAGIDPHTLRGSDTG VFMGCYFYGYCSGADRGGFGATSTQTSVLSGRLSYF
YGLEGPAVTVD TACSSSLVALHQAGQSLRTGEC SLALVGGVTVMASPSGFVDFSQQRGLAPDGRCKAF AEAAADGTGF
AEGSGVLVVERLS DAERHCHRVLAVVRGSAVNQDGASNGLSAPNGPSQERVIRQALANAGLQPSDVDAVEAHGTGTR
LGDPIEATALLATY GQDRATPLLLGSLKSNIGHTQAAAGVAGI IKMVLAMHHD TLPSTLHVDT PSSHVDWTACTVEL
30 LTDARPWPETS RPHRAAVSSFCVSGTNAHVILESHPRPT PAPDTGSSTHPVPLLISARTPRAL SEHTTRVSAFLDAG
GGDERAVASALLTRTAFTHRAALIGTDLITGTAVPDRRLV WLFSGQGSQRPGMGDELAAAYDV FARTRRDVLDALQV
PAGLDIHDTGYAQPAVFALQVALSAQLDAWCVRPDALVGHS IGELAAAYVAGVWSLDDACALVSARARLMQALPPGG
AMAAVIASERDALPLLREGVEIAAVNGPASIVLSGDEDAVLDVAARLGRFTRLRTSHAFHSARMEPMLDEF RDVAQR
LTYHEPKLPMAAGADCATPEYWVRQVRDTVRFGEQVAAYDGAALLEIGPDRNLARLVDGIPVLHGDD EARSAMTALA
35 RLHTGGVAVDWPEVIGAAPTHLNLPTYPFERTRYWLGSRDRIAGLTAADAEKAALAVVRECAAAVLGHEGPARIEAT
ATFKELGVDSLTA VRLRNAFTEATGVRLPATAVFD FPTPQAVAAKL

SEQ ID NO: 25

EPLAIVGMACRLPGGVASPEDLWRLLESGGDGITAFPADRGWDVEALYDPDPEHPGTSTVRHGGF'LSGAGDFDAGFF'
40 GISPREAIAMPQQRVVLETSWEALEQAGIVPGTLRGSDTG VFMGAFSDGYGLGTDLGGFGATGTQTSVLSGRLSYF
YGLEGPAVTVD TACSSSLVALHQAGQSLRTGEC SLALVGGVTVMASPGGFVEFSQQRGLAPDGRCKAF AEAAADGTAF
AEGSGVLVVERLS DAERRGHRI LAVVRGSAVNQDGASNGLSAPNGPSQERVIRQALANAGLRPSDVDAVEAHGTGTR

LGDPIEATALLATYGQDRATPLLLGSLKSNIGHTQAAAGVAGI IKMVLAMRHGSLPRTLYVDTPSSHVDWTAGGVEL
LTDARPWPAATTGPRRAAVSSFGVSGTNAHVILEAHAAPEPPALDSPVVEPSASLFATELTPLPVSARTSEAVDGQVQ
RLREHLATHPGDDPRAVAAALLATRTDFPHRAVLLGDGVVTGTALTAPRTVFVFPGQGSQWLGMGRKLMAESPVFAA
RMRQCADALAEHTGRDLIAMLDDPAVKSRVDVVPVCWAVMVSLAAVWEAAGVRPDAVIGHSQGEIAAACVAGAI SL
5 EDGARLVALRSALLVELAGRGAMGSIAFAAADVEAAAARIDGVWVAGRNGTATTIVSGRPDAVETLIADYETRGVWV
TRLVVDCPTHTPFVDPLYDELQRIVAATTSTRAPEIPWFSTADERWIDAPLDDEYWF'RNMRNPVGF'AAAVAAAREPGD
TVFIEVSAHPVLLPAINGTTVGTLRGGGADRLLDSLAKAHTVGVAVDWAHDAATGTADLPTYAFHHERYWIEPAE
RLPDLSRKEQEQVLLDVVRDTAATLLGHADARAVTATAAFKDLGVDSL TALGLRDR LAEALGIPLPATLVFDHPAAG
TL SRHL

10

SEQ ID NO: 26

EPLAIVGMACRLPGGVASPDLLWRLLESGGDGIGAFPGDRGWETGADGRGGFLSGAAGFDAAFFGVSPREALAMDPQ
QRVVLETSWEALEHAGIDPHTLNNGSDTG VFLGAFFQGYGIGADFDGYGTTSIHTSVLSGRLSYFYGLEGPAVTVDTA
CSSLVALHQAGQSLRTGEC SLALVGGVTVMASPA GFAD FSEQGGLAPDGRCKAF AEAAADGTAFSEGS GVLVVERLS
15 DAERHGHRI LAVVRGSAVNQDGASNGLSAPNGPSQERVIRQALANAGLQPSDVDAVEAHGTGTRLGDPIEATALLAT
YGQHRTTPLLLGSLKSNIGHTQAAAGVAGI IKMVLAMHHD TL PPTLHV DTPSSHVDWTTGGVELLTDARPWPTTTGP
RRAGISSFGVSGTNAHVILESP TPVPSPGAEPGARPVLPISARTPEALDEHTIRIRAFLDDNPGADHVAVAQTLAR
RTPFEHRAVLLGDTLITADPNAGSGPVVFVYSGQSTLHPHTGRQLAATYPVFADAWGEVLGHLDADQGPATHF AHQI
ALTALLRSWGIAPHAVIGHSLGEISAACAAGVLSLGDASALLAARSRLMDELPAGGAMVTVLTSEENALRALRPGVE
20 IAAVNGPHSVVLSGDEGPVLAVAQQ LGIHHRLPTRHAGHSARMDPLVAPLLEAASGLTYHQPRIAIPGDPTTAAYWA
RQVRDQVRFQAHAE RYPGATFLEIGPNQDLSPVVDGIPTQTGTPDEVQALHTALARLHTRGGVVDWPTVLGGDRAPV
ALPTYPFQHKDYWL RATELAVLPDDERADALLAFVRNSTATVLGHLGAEDIPATATFKELGIDSLTAVQLRNALTTA
TGVRLNATAVFD FPTPRALAARL

25

SEQ ID NO: 27

EPLAIVGMACRLPGGVASPEGLWRLVASGTDAITEFPADRGWDVDALYDPDPAIGKTFVRHGGFLDGATGFDAGFFC
ISPREALAMDPQQRVLLET SWEAFESAGITPDSARGSDTG VFIGAFSYGYGTGADTNGFGATGSQTSVLSGRLSYFY
GLEGPSVTVD TACSSLVALHQAGQSLRSGECSLALVGGVTVMASPGGFVEFSRQRGLAPDGRAKAFGAGADGTSFA
EGAGALVVERLS DAERHGH TVLAVVRGSAVNSDGASNGLSAPNGPSQERVIRQALANAKLTPADVDAVEAHGTGTRL
30 GDPIEAQALLATY GQDRATPLLLGSLKSNIGHAQAASGVAGI IKMVQAIRHGELPPTLH ADEPSPHVDWTAGAVELL
TSARPWPGTGRPRRAAVSSFGVSGTNAHI ILEAGPVKAGPVEAGPVPAAPPSAPGEDLPLLVSARSPEALDEQIGRL
RTYLDTRPGVDRAAVAQTLARRTHFAHRAVLLGDTVITTSPSHQADELVFVYSGQGTQHPAMGEQLAAAFPVFAETW
HDALRRLDDPD PDPHDPTRSQHTLFAHQAA LTALLRSWDITPHAVIGHSLGEITAAYAAGILSLDDACTLITTRARLMH
TLPPPGAMVTVLTGEEEARQALRPGVEIAAVNGAHSVVLSGDEDAVL DVAQRLGIHHRLPAPHAGHSAHMEPVAAEL
35 LATTRRLRYDRPHTAIPNDPTTA EYWAEQVRNPVLFHAHTQQYPDAVFVEIGPGQDLSPLVDGIALQNGPANEAHAL
RTALARLFSRGATLDWPLVLGGASRHDPDVPSYAFQQRPYWIESARLAELPDADRD TALSTLVMDATAAVLGHADAS
EIGPTTTFKDLGIDSLTAIELRNRLAEATGLRLSATMVFDHPTPRVLAAKL

40

SEQ ID NO: 28

EPLAIVGMACRLPGGVTSPEDLWRLVASGTDAITEFPTDRGWDIDRMFDPDPDAPGKTYVRHGGFLSEAAGFDAAFF
GISPREAWAMPDQQRVILETVWEAFENAGIVPDTLRGSDTG VFMGAFSHGYGAGVDLGGFGATATQNSVLSGRLSYF
FGMEGPAVTIDTACSSSMVALHQAAQSLRDGECSLALAGGVTVMP TPLGYVEFCRQRGLAPNGRAKAF'AE GADGTSF

5 SEGAGVLVVERLSDAERNGHTVLALVRSSAVNQDGASNGISAPNGPSQQRVIRQALDKAGLTPADVDDVVEAHGTGTP
LGDPIEAQAI IATYGQDRDTPLYLGSVKSNIGHTQTTAGLAGVIKMMAMRHGLLPKTLHVDEPSSHVDWSAGAVEL
LTEARPWPDSDRPRRAGVSSLGISGTNAHVILEGVAESSVRSGGSSGLVPLPVSARTESSLALQVERVGEYVRGGAD
LGAVADGLVRGRAVE'DRRAVLLGESTVAGVAVEGARTVFVFPGQGSQWVGMGRELMGASEVFAARMRECAAALEPHT
GWDVLDVLGEAVVADRVEVLQPASWAVAVSLAALWQAHGVVPDAVIGHSSQGEIAAACVAGALSLEDAARVVALRSQT
IAARLGHGAMASIALPASAVEVAEGVWIAARNGPSTVVAGDPGAVERVLARYEAAGVRVRRRIAVDYASHTPHVEAI
EEQLADV LGGITSSAPDISWWSTVDSGWVTEPVGDDYWYRNLRQPVAMDTAISELDGSLFIECSAHPVLLPALDQEH
TVASLRTDDGDWDRFLTALAQAWTQGAPVDWTTLIEPAPHRDLPTYPFDHKRYWIEAAARLAGHTAAEQRRVMQEV
VLRQAAAVLAYGLGEQVAADRPFRLGFDLSLTAVDLNRNRLAAETGLRLPTTVVFSHPTAEALATHL

10
SEQ ID NO: 29
EPIAIVAMACRLPGGVTSPEELWRLVESGTDAITMAPGDRGWDLDALYDPDPDAVGKAYNLRGGFLEGAAEFDAAFF
DISPRESLGMDPQQRL LLETAWEAIERGRINPASLHGREIGVYVGAAAQGYGLGAEDTEGNAITGGSTSLLSGRLAY
VLGLEGPSVTVDTACSSSLVALHLACQGLRLGECELALAGGVSVLSSPAAFVEFSRQRGLAADGRCKSFGSGADGTT
15 WAEGVGVLVLERLSDAERLGH TVLAVVRGSAVTSDGASNGLTAPNGLAQQRVIRKALAAAGLTAADVDLVEGHGTGT
RLGDPVEADALLATY GQNRQEPVWLGLSLKSNIGHATAAAGVAGVIKTVQAIGAGTMPRTLHADEPSPAVDWTAGRVS
LLTGNRPWPDDERARRAAVSAFGLSGTNAHVILEQHRPEPVAPRPPREEPRPLPWVLSARTPAALRAQAARLRDHLA
AVPDADPLDIGYALATSRARFTHRAAVVATSSDEFRAGLDSVADGVEAPGVVGGTARERRVAF LFDGQGAQRVGMGR
ELHGRFPVF AA AWDEVSDAFGKHLEHSPTDVFHGEHGD LAHDTLYAQVGLFTLEVALLR LLEHWGVRPDVLVGH SVG
20 EVTAAYAAGVLT LADATALIVARGRALRALPPGAMTAVDGSPA EVGAFTGLDIAAVNGPSAVVLTGSPDDVTAFERE
WAAAGRRAKRLDVGHAFHSRHVDGALDDFRTVLESLSFGAARLPVVSTTTGRDAAGDLATPEHWRHRARRPVLFADA
VRELADLGVMFVAVGPSGALASAASENTGGSAGTYHAVLRARTGEENAALTAVAELHAHGAPVDLAAVLAGGRPVD
LPVYFPQHRSYWLAPDDLTVAEIVRRRAAALLGIADPGDVDADTTFFALGFDSLAVQRLRNQLTAATGLDLPTAVLF
DHDTPSALTAYL

25
SEQ ID NO: 30
EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDVENLYDPDPDASGKSYCVQGGFLDAAAGFDAGFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGTD TG VFIGAYPGGYGAGAGTELEGYGTTSGPSVL SGRVSY
FFGLEGPAITVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPDVFTEFARQRGLAADGRSKAFSDSADGAG
30 FSEGIGVLLVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRV IQAALGNAGLT TAEVDVVEGHGTGT
TLGDPIEAQALLATY GQDRERPLLLGSLKSNIGHTQAAAGVSGVIKMMALRHGLVPRTLHVDEPSSHVDWTAGAVE
LVTANQPWPDADRPRRAGVSSFCVSGTNAHVILESAPSTQAVDDVRPVETPVVGSELVPLVL SAKTLPALSGYEDRL
RAYLAGSPGVDLRAVASTLAVTRSVFEHRVLLGDDTVTGTAVTDPRVVFI FPGQGSQRAGMGEELAAAFPVFARIH
QQVWDLLDVPDLEVNETGYAQPALFALQVALFGLLESWGVPDAVVGH SVGELAAAYVSGVWSLEDACTLV SARARL
35 MQALPPGGVMVAVPVPEDEARAVLGEGVEIAAVNGPSSVVL SGDEAAVLRAAATLGKWMRLATSHAFHSARMEPMLD
EFRAVAERLTYQTPHLTMAAGEQVTT PDYWVRQVRDVVRFG EQVASFEDAVFVELGADRSLARLVDGVAMLHGAHEA
QAAISALAHLYVNGVTVDWPAVLGDVPGRVLDLPTYAFQH QRYWLEGWLAALTPAEREKALLKLVS DGAATVLGHAD
TSTIPVTGAFKDLGINSLTAVELRNSLAKATELRLPATLVFDYPTPATLAARLD

40
SEQ ID NO: 31
EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDVENLDSAGKSYRAEGGFLDAAAGFDASFFGISPR
EALAMDPQQRLVLEVSWEAFERAGIEPGSLRGSDTGVMGAYPGGYGIGADLGGFGATAGATSVLSGRVSYFFGLEG

PATENT
50869-016WO2

PAFTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQTFVEFSRQCGGLASDGRCKAFADAADGTGWAEGVG
VLLVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALSNAGLTAEVDVVEAHGTGTTLGDP
EAQALLATYGQDRERPLLLGSVKSNLGHTQAAAGVSGVIKMVMALRHGLVPRTLHVDEPSRHVDWSTGAVELVTENQ
PWPETGRPRRAGVSSFGISGTNAHVILESAPSAQVVENTVVESAPEWVPLVVSARTQSALADYEDRLRAYLAGSPGV
5 DLRAVASTLAVTRSVFEHRAVLVGDDTVTGSASVSDPRVVVFVFPQGGSQRAGMGEEELAAAFPLFAQIHQQVWDLLDVP
DLEVNETGYAQPALFALQVALFGLLESWGVRPDAVIGHSVGELAAGYVCGVWSLEDAC TMVSARARLMQALPAGGVM
VAVPVSEDEARAVLGEGVEIAAVNGPLSVILSGDEAAVLRAAATLGKWTRLATSHAFHSARMEPMLEKFRAVAEGLT
YRTPRLTMAAGDQVATAEYWVRQVRDVVRFGGEQVASFEDAVFLELGADRSLARLVDGIAMHLHGDHEAQAAISAL AHL
YVNGMAVDWPAVLGDVGRVLDLPTYAFEHQRYWLEGWLAVLAPAEREKALLKLVRDSAALVLGHADASTIPVAAAF
10 KDLGIDSLTAVELRNSLAKATGLRLPNTTVFDYPTPAILAARL

SEQ ID NO: 32

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWD AESLYDADPDAPGKSYCVEGGFLDNASSFDAGFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSIRGTD TGVMGAYAGGYGAGADLGGFAATASATSVLSGRVSYF
15 FGLEGP AITVDTACSSSLVALHQAGYALRQGECSLALVGGATVMATPQSFVEFSRQRGLASDGRCKAFADAADGTGW
AEGVGVLLVERLSDARRNGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALSNAGLAAHEVDVVEAHGTGTT
LGDP IEAQAVLATYGQDRERPLLLGSLKSNIGHTQAASGVSGVIKMVMALQHHTVPRTLHVNEPSRHVDWSAGAVEL
VRENQSWPEGDRPRRAGVSSFGVSGTNAHI ILESAPAQSAEEVQPVEVPVVASDVLPLVVS AKTHSALTEAEDRLRA
YLTASPEADMPAVASTLAVTRSVFEHRAVLLGDDTVTGTGTAMSDPRVVVFVFPQGWQWLGMGSALRESSV VFAERM
20 AECAAALSDFVDWDLFTVLD DPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGH SQGEIAAACIAGAVSLRD
AARIVTLRSQAIARGPAGRGAMASIALPAQEIELADGAWIAAHNGPASTVIAGTPEAVDLVLT AHEAQGTRVRRITV
DYASHTPHVELIRDELLHITAGIGSQVPVVPWLSTVDGTWVEGPLDAEYWYRNLREPVGFAPAISQLQAQGETVFIE
VSASPVLLQAMDDDAVTVATLRRDDGDATRILTALAQAYTHGVTVDWPA ILGTTTTTRALDLPTYAFQH QRYWLNRL
TGRTSVEQHRVMLELVLGEAASVLGHGSPDAIATDTSFKDLGMDSLTAIELRNRLMAETGLQLPATMVFDYPTANAL
25 ATHL

SEQ ID NO: 33

EP IAIVAMACRVPGGVSSPEGLWRLVESGTDVISGFPTDRGWDVEGLFDPDPDAPGKSYCVQGGFLDTAADFDAPFF
GISPREALGMDPQQRL LLETTWEAIERARIDPKSLRGRDVG VYGGA AQGYGVGVDQQRDNCITGSSVSLLSGRVSY
30 ALGLEGP GVTVDTACSSSLVALHLASQALRQRECSLALVSGV SVMSSPAMFVEFSRQRGLSSDGRCKSF AASADGTI
WSEGVGVLVVERLSDARRLGHRFLAVVRGSAVNSDGASNGLTAPNGASQQRVIRQALAGAGLTASDVDVVEAHGTGT
KLGDPIEAEAILATYGQERSTPAWL GSLKSNIGHTMAASGVLCVIKMVEAMRHGSLPRTLHVDDPSPHVDWTS GSVA
LLTEHQ PWPDDAKPRRAGVSSFGLSGTNAHVVLEQYQAPAPSVTPVTPVTPVTPVTPNEPRPLAWVLSAQSPKALRE
QAGRLYASLAEAPEWNSLDIGYSLATTRSDFAHRAVAVGSGREFLRALSKLADGASWPGLTTATAKARRVAFLEDGQ
35 GAQRLGMGKELYDSSPVFARAWDTV SACFDKHL DHSLTDVYFGE GGSTTAELVDDTLYAQACIFAMEVALFGLLEDW
GVRPDFVAGHSIGEATAAYASGMLSLEHVTTLIVARGRALRATPPGAMVALRAGEEEVRAFLDQTGAALDLAAVNSP
EAVVVAGEPDAVAGFEA AWAASGREARKLRVRHAFHSRHVEAVLDEFRTTLES LKFSAPALPVVSTVTCQLIEPDEM
GTPEYWLRQVRQPVRFQDAVRELAEAGVGTFVEIGPSGALASAGMECLGGDASFHAVLRPRSPEDVCLMTAIAE LYA
GGTAIDWAKVLSGGRAVDLPVYPFQHQSYWLAPAEP SYADEPRTMLELVHMEVASVLGMTDPGVILDDSSFLELGFD
40 SLSAVRLRNRLSKATGLDLPSTLLFEHPTSAELASHLD

SEQ ID NO: 34

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDVEGLFDPDPDASGKSYCVRGGFLDSVGGFDASFF
GISPREALAMDPQQRL LLEVSW EAFERAGIEPGSVRGSDTG VFMGGFPGGYGAGADLE'GFGATAGAASVLSGRVSYF'
FGLEGPAITVDTACSSSSLVALHQAGYALRQGECSLALVGGVTVMATPQSFVEFSRQRGLASDGRCKAFADAADGTGW
5 AEGVGVLLVERLSDAQAKGHQVLGVVRGSAVNQDGASNGLSAPNGPSQQRVIRAALS NAGLT TAEVDVVEAHGTGTT
LGDPIEAQAVLATY GQDREQ PLLLGSLKSNIGHAQAAAGVSGVIKMMALRHGLVPRTLHVDEPSRHVDWSAGAVEL
VTENQSWPVTGRPRRAGVSAFGVSGTNAHVILE SAPAQASEEAQPVVTPVVTPVVASELVPLVVS AKTESALAEVEG
RLRAYLAVSPGVDLRAVGSTLAVARSVFEHRAVLLGDDTVTGTVTGTAVSDPRVV FVFPGQGWQWLGMGSALRCASV
VFAERMAECAALGEFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWEAAGVRPDAVVGHSQGEIAAACVAG
10 AVSLRDAARIVTLRSQVIAGLAGRGAMASVALPAHEIELVEGAWIAACNGPASTVIAGEPDAVDRVLAVHEARGVRV
RRITVDYASHTPHVELIRDELLNITAGIGSQAPVVPWLSTVDGTWVEGPLDAEYWYRNLREPVGFDSAVGELRAQGD
TVFVEVSASPVLLQAMDDD VVS VATLRRDDGGAARMLTALAQA FVEGVTVDWPAVLGNAPGRVLDLPTYAFEHQRYW
LKSRWLARLAPVEREKALLKVVCDGAATVLGHADASTIPAAGAFRDLGVDSL TAVELRNRLAKATGLRLPATLVFDY
PTPTALAARL

15

SEQ ID NO:35

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AVSGFPTDRGWDVEDLFGPAAGDSYRLRGGFLDAAGGFDASFFGIS
PREALAMDPQQRLVLEVSW EAFERAGIEPGSVRGTD TG VFMGAYPGGYGIGADLGGFGTTAGAVSVLSGRVSYF'F'GL
EGPAFTVDTACSSSSLVALHQAGYALRQGECSLALVGGVTVMATPQTFAEFARQGGLAGDGRSKAFADSADGAGFSEG
20 VGVLLVERLSDARRNGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRV IQAALNNAGLT TAEVDVVEAHGTGTTLGD
PIEAQALLAAYGQDRERPLLLGSVKS NLGHTQAAAGVSGVIKMMALRHGLVPRTLHVDEPSRHVDWSEGAVELVTE
NQSWPDTGRPGRAGVSSFGISGTNAHVILE SAPSAQTVENTVVESAPEWVPLVMSARTQSALADYEGRLRAYLAGSP
GVDLRAVASTLAVTRSVFEHRAVLMGDDTVTGSAVSDPRVV FVFPGQGSQRAGMGEELAAAFPVFAQIHQQVWDL LD
VPDL DVNETGYAQPALFALQVALFGLLESWGVGPDAVVCHSVGELAAAYASCVWSLED ACTLV SARARLMQALPAGG
25 VMVAVPVSEDEARAVLGEGVEIAAVNGPSSVVL SGDEAAVLR AAAGLGK WTRLATSHAFHSARMEPML EEF'RAVAER
LTYQTPHLTMAAGEQVTT PDYWVRQVRDVVR FGEQVASFEDAVFLELGADRSLARLVDGIAM LHGDHEAQDAISAMA
HLYVSGVAVDWPAVLGDVRGRVLDLPTYAFQHERYWLEGRWLAALAPAEREKALLKLVSDGAATVLGHADASTVPVS
AVFRDLGVDSL TAVELRNRLAKATGLRLPATLVFDYPTPTALAARL

30 SEQ ID NO: 36

EPLAIVGMACRLPGGVASPEDLWRLVESGTD AVSGFPTDRGWDVEDFDSAGKSYRAEGGFLDAAAGF'DASFF'GISPR
EALAMDPQQRL LLEVSW ETFERAGIEPGSVRGTD TG VFMGAYPGGYGIGADLGGFGATAGATSVLSGRVSYFFGLEG
PAFTVDTACSSSSLVALHQAGYALRQGECSMALVGGATVMATPELTFTEFSRQGGLASDGRCKAFADSADGTGWAEGVG
VLLVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRV IQAALS NAGLAAYEVDVVEAHGTGTTLGDPI
35 EAQAVLATY GQDRERPLLLGSLKSNIGHTQAASGVSGVIKMMALQRGLVPRTLHVDEPSRHVDWSAGAVELVRENQ
SWPDTEGPRRAGVSSFGVSGTNAHVILE SAPAQPAEEAQPVVTPVVASELVPLVVS AKSQSALTEAEGRLRAYLAAS
PGVDTRA VGATLAVARSVFEHRAVLLGDDTVTGTGTAMSDPRVV FVFPGQGWQWLGMGSALRDSSVVFAERMAECAA
ALSDFVDWDLFTVLDDPAVVDRVDVVQPASWAVMVSLAAVWEAAGVRPDAVIGHSQGEIAAACIAGALSRLRDAARIV
SLRSQVIAGLAGRGAMASIALPAQDVELAEGAWIAAHNGPASTVIAGAPEAVDRVLAVHEARGVRVRRITVDYASHT
40 PHVELIRDELLHITAGIGSQAPVVPWLSTVDGTWVEGPLDAEYWYRNLREPVGFAPAIRQLQDQGETVFIEVSASPV
LLQAMDDD VVS VATLRRDDGGAARMVTALAQA YVQGVTVDWPAVLGNVPGRVLDLPTYAFEHQRYWLKSWLAALAPA
EREKALLKVVCD SAAVVLGHADARSIPAAGAFKDLGVDSLMAVELRNRLVKATGLRLPATLVFDYPTPAALAARL

SEQ ID NO: 37

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDVSGFPTDRGWDLEDLFDPDPEAAGKSYCVQGGFLDAAAGFDAGFF
GISPREALAMDPQQRLLEVSWEAFERAGIEPGSVRGSDTGVFIGA FVPVGYGVGFDREGYGATSGPSVLSGRVSYFF
5 GLEGPAITMDTACSSSLVALHLAAQALRNGECSMALAGGVTVMATPEVFTEFARQRGLASDGRCKAFADSADGAGFS
EGAGLLLVERLSDARRNGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRV IQAALINAGLT TAEVDVVEAHGTG TTL
GDPIEAQAVLATY GQGRERPLLLGSLKSNIGHTQAASGVSGVIKMMVMALQRGLVPRTLHVDEPSRHVDWSAGAVELV
RENQSWPDSEGPRRAGVSSFGVSGTNAHVILESAPAQPAEEAQPVVTPVVAS ELVPLVVS AKTESALTEVEGR LRVY
LAASPGVDTRAVASTLAVTRSVFEHRAVLLGDDTVTGTGTAVSDPRVVFVFP GQGQWLGMGSALRDSSV VFAERMA
10 ECAAALSEFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGH SQGEIAAACVAGVLSLRDA
ARIVTLRSQAIAGLAGRGAMASIALPAQDVELVEGAWVAAHNGPASTVIAGAPEAVDRVLAVHEARGVRVRR IAVDY
ASHTPHVELIRDEL LDITAGIGSQAPVVPWLSTVDGTWVEGPLDAEYWYRNLREPVG FAPAVSQ LQVQGETV FVEVS
ASPVLLQAMDDD VVSVATLRRDDGGAARMLTALAQAYTQGVAVDWP AVLGTTT AQVLDLPT YAFQHRRY WVEWLAAL
APEEREKALLRVVCDGAATVLGHADVGSIPVTAAFKDLGVDSL TAVELRNRLAKATGLRLPATLAFDYPTPTAL AAR
15 L

SEQ ID NO: 38

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDVEHLYDPDPDAPGKAYCVQGGFLDSAGGFDASFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSLRGTD TGVMGAYPGGYGIGADLGGFGATAGAVSVLSGRVSYF
20 FGLEGPAVTVD TACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQS FVEFSRQRGLAGDGRCKAFADAADGTGW
AEGVGVL LVERLSDAQAKGHQVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLT TAEVDVVEAHGTG TT
LGDPIEAQALLATY GQDRERPLLLG SVKSNLGH TQAAGVSGVIKMMVMALRHGLVPRTLHVDEPSRHVDWSEGA VEL
VTENQPWP DADRPRRAGVSSFGISGTNAHVILESAPSTQAVDDVRPVEAPVVASEWVPLVVSARTLPALVEYEGR LR
AYLAGSPGVD MRAVGSTLAVTRSVFEHRAVLMGDDTVTGS AVS GPRVVFVFP GQGSQRAGMGEELAAAFPVFARIHQ
25 QVWDL LDVPDLEVNETGYAQPALFALQVALFGLLESWGVGPDAVIGH SVGELAAGYVSGLWSLEDACTLV SARARLM
QALPPGCV MVAVPVSEEEAKAVLCEGVEIAAVNGPSSVVLSGDETAVLR AAAALGKSTRLATSHAFHSARMEPMLDE
FRAVAERLT YQTPRLPMAAGEQVTT PDYWVRQVREPVR FGEQAASCGDAVFVELGADRSLARLVDGVAMLHGDHEAQ
AAISALAHLYVNGVTVDWP AVLGDVPGRVLDLPT YAFQHQR YWLEGWLAALAPEERAKALLKVVC DTAATVLGHADA
RTIPMTGAFRDLGIDSLTAVELRNGLAKATGLRLPATLVFDYPTPTVLAARL
30

SEQ ID NO: 39

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDAESLYDPDPDAPGKSYCVEGGFLDN AASFDAGFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGTD TGVMGAYAGGYGAGADLGGFAATASATSVLSGRVSYF
FGLEGPAFTVD TACSSSLVALHQAGYALRQGECSLALVGGATVMATPQS FVEFSRQRGLASDGRCKAFADAADGTGW
35 AEGVGVL LVERLSDARRNGHQVLAVVRSSAVNQDGASNGLSAPNGPSQQGVIRQALANAGLT PAEVDVVEAHGTG TT
LGDPIEAQAVLATY GQDRERPLLLGSLKSNIGHTQAASGVSGVIKMMVMALQHHTVPRTLHVNEPSRHVDWSAGAVQL
VRENQSWPEGDRPRRAGVSSFGVSGTNAHI ILESAPAQSAEEVQPVEVPVVASDVLPLVVS AKTHSALTEAEDRLRA
YLTASPEADMPAVASTLAVTRSVFEHRAVLLGDDTVTGTGTAVSDPRVVFVFP GQGQWLGMGSALRDSSV VFAERM
AECAAALSDFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGH SQGEIAAACIAGALS LRD
40 AARIVTLRSQVIAGLAGRGAMASIALPAQEVELAEGAWIAAHNGPASTVIAGTPEAVDLVLT AHEAQGTRVRR IAVD
YASHTPHVELIRDEL LDITAGIGSQAPVVPWLSTVDGTWVEGPLDAEYWYRNLREPVG FAPAVRQLQDQGETV FIEV
SASPVLLQAMGDDAVTVATLRCDDGGAARMLTALAQAYTQGVAVDWP AVLGTTT ARVLDLPT YAFQRQRY WVEWLAG

LAPEERAKALLKVVCDTAATVLGHADARTIPLTGAFKDLGVDSLTAVELRNSLTAKATGLRLPATLVFDYPTPTALAV
RL

SEQ ID NO: 40

5 EPLAIVGMACRLPGGVSSPEDLWRLVESGTDVSGFPTDRGWDLEDLFDPDPEAAGKSYCAEGGFLDAAAGFDAGFF
GISPREALAMDPQQRLLEVSWEAFERAGIEPGSVRGSDTGVFIGA FPGVGYAAGAAREGYGATAAPNVLSGRLSYFF
GLEGPAITMDTACSSSLVALHLAAQAVRNGECSMALAGGVTVMATPEVTFTEFARQ RGLASDGRCKAFADSADGAGFS
EGAGLLLVERLSDARRNGHQVLAVVRGSAVNQDGASNGFTAPNGPSQQRVIIQQALANAGLT TAEVDVVEAHGTGTTL
GDPIEAQAVLATY GQDREQPLLLGTLKSNIGHTQAAAGVSGVIKMVMALQHDTVPR TLHVNEPSRHVDWTAGAVELV
10 TENQSWPVTD RPRRAGVSAFGVSGTNAHVILE SAPAPSVNNAQPVETPVVASELVPLVISAKTLPALTEHEDRLRAY
LAASPEADMPAVASTLAVTRSVFEHRAVLLGDDTVTGTGA AVSDPRVVVFVFPQGQWQWLGMGSGLRGSSVVF AERMA
ECAAALREFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWEAAGVRPD AVVGHSQGEIAAACVAGAVSLRDA
ARIVTLRSQVIAGLAGRGGMASVALPAHEIELVEGAWIAARNGPAATVIAGEPDAVDRVLAIHEAQGVRVRR IAVDY
ASHTPHVELIHDELLGVIAGVDSQAPVVPWLSTVDGTWVEGPLDAEYWYRNLREQVGFDPAVSQ LRAEGDTVFEVS
15 ASPVLLQAMDDDAATVATLRRDDGDAARMLTALAQA FVEGVTVDWPAILGTATPGVLDLPTYAFQHQR FWAERWLAR
LAPVEREKALLKVVC DGAATVLGHADASTIPATAAFKDLGIDSLTAVELRNGLAKATGLRLPATLVFDYPTPTALAA
RL

SEQ ID NO: 41

20 EPLAIVGMACRLPGGVSSPEDLWRLVESGTDVSGFPTDRGWDVGD LFGPAAGDSYRLRGGF LDAAAGFDASFFGIS
PREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGTD TGVFIMGAYPGGYGIGADLGGFGATASATSVLSGRVSYFFGL
EGPAITVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQT FVEFARQGGLAGDGRSKAFADSADGAGFSEG
VGVLLVERLSDAQAKGHQVLAMLRSSAVNQDGASNGLTAPNGPSQQRVIIQAALSNAGLAPHEVDVVEAHGTGTTLGD
PIEAQALLATY GQDRERPLLLGSVKSNLGH TQAAAGVSGVIKMVMALRNGLVPRTLHVDEPSRHVDWSVGAVELVTE
25 NQSWPDSGRPRRAGVSSFGISGTNAHVILESEPPAQVVENTVVEPAPEWVPLVMSARTQSALADYEDRLRAYLAGSP
GVDLRAVGSTLAVTRSVFEHRAVLLGDDTVTGTAVSDPRVVVFVFPQGQSQRAGMGEELAAAFPVFARIHQQVWDL LD
VPDLEVNETGYAQPALFALQVALFGLLESWGVGPD AVIGHSVGELAAGYVSGLWSLED ACTLV SARARLMQALPAGG
VMVAVPVSEEEAEAVLCEGVEIAAVNGPSSVVL SGDEAAVLRAAATLGKWTRLATSHAFHSARMEPML EEFRAVAEG
LTYRTPRLTMAAGDQIATAEYWVRQVRDVVRFGEQAASCGDAVFVELGADRSLARLVDGVAMLHGDHEAQAA ISALA
30 HLYVSGVAVDWP AVLGDVPGRVLDLPTYAFQHQR YWLEGRWLAALTPEERAKALVKVVCDSAATVLGHADASTIPVT
AAFRDLGVDSLTAVELRNSLTAKATGLRLPATLVFDYPTAGALAA RL

SEQ ID NO: 42

EPLAIVGMACRLPGGVFSPEDLWRLVESGTD AISGFPTDRGWD AENLFDPD PDAAAGKSYC LEGGFLETAANFDASFF
35 EISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFIMGAFPGGYGIGADLEGYGATSG LNVLSGRLSYFF'
GLEGPAVTVD TACSSSLVALHQAGYALRQGECSLALVGGVTVMATPHTFVEFSRQRGLASDGRCKAFADSADGTGWS
EGVGVLLVERLSDAQAKGHQVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLTIAEVDVVEAHGTGTTL
GDPIEAQALLATY GQDREQPLLLGSVKSNVGHTQAAAGVSGVIKMVMALRNGLVPRTLHVDEPSRHVDWSEGA VELV
TENQPWPETGRPRRAGVSSFGVSGTNAHVILE SAPPAQVVDNTVVESAPEWVPLVMSARTQSALADYEDRLRAYLAG
40 SPGVDLRAVASTLAVTRSVFEHRAVLMGDDTVTGTAVSDPRVVVFVFPQGQSQRAGMGEELAAAFPVFARIHQQVWDL
LDVPDLEVNETGYAQPALFALQVALFGLLESWGV RPD AVVGHSAGELAAAYVSGVWSLEDACALVSARARLMQALPA
GGVMVAVPVSEEEAEAVLCEGVEIAAVNGPSSVVL SGDEAAVLRAAAGLGKWTRLATSHAFHSARMEPML EEFRAVA

EGLTYRTPRLTMAAGDQVATAEYWVRQVRDVVRFGEQVASFEDAVFLELGADRSLARLVDGVAMLHGDHEAQAAISA
LAHLYVNGVTIDWPAVLGGVPGRVLDLPTYAFQHERRYWAEAWLAALAPAEREKALLKLVSDGAATVLGHADASTIPV
TAAFKDLGIDSLTAVELRNLSAKATGLRLPATLVFDYPTPTALAAARLD

5 SEQ ID NO: 43

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDALISGFPTDRGWDVENLYDPDPDAPGKSYSVRGGFLDAAANFDASFF
GISPREALAMDPQQRLMLEVSWEAFERAGIEPRSVRGSDTGVFIGAYPGGYGIGVDFEGFGATAGAASVLSGRVSYF
FGLEGPAFTVDTACSSSLVALHQAGYALRQGDCSLALVGGVTVMATPQTFVEFSRQRGLSADGRCKAFADSADGTGW
AEGVGVLLVERLSDAQAKGHQVLGVVRGSAVNQDGASNGLSAPNGPSQQRVIRAALSNAGLAPHEVDVVEAHGTGTT
10 LGDPIEAQALLATYGGGRGEPLLLGSLKSNIGHTQAAAGVSGVIKMMALQYGLVPRTLHVDEPSRHVDWTAGAVEL
VGENQPWPETGRPHRAGVSSFGISGTNAHVILESAPAQPAEEAQPVVTPVVASSELVPLVVSAKTESALTEVEGRRLRA
YLAASPGVDTRAVASTLAVTRSVFEHRAVLLGDDTVTGTGTAMSDPRVVFVFPQGQWQWLGMGSALRDSSVVFARM
AECAAALSDFVDWDLFTVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGHSQGEIAAACIAGAVSLRD
AARIVTLRSQAIAGLAGRGAMASIALPAQEIGLADGAWIAAHNGPASTVIAGAPEAVDRVLTAEHAQGARVRRIAVD
15 YASHTPHVELIRDELDDITAGIGSQAPVVPWLSTVDGTWVEGPLDAEYWYRNLRPEVGFAPAVRQLQAQGETVFVEV
SASPVLLQAMDDDAVTVATLRRDDGDATRMLTALAQAAYTHGVTVDWPAILGTTTTRALDLPTYAFQHERRYWAEAWLV
GLAPEERAKALLKLVSDSAAAVLGHADARGIPATGAFKDLGVDSLTAVELRNTLTATGLRLPATMVFDYPTPADLA
ARL

20 SEQ ID NO: 44

EPLAIVGMACRLPGGVSSPEELWQLVESGGDAISPFPDRGWDLETPYRGGFLTDPAAGFDAGFFGISPREAVAMDPQ
QRVLLEASWEAFERAGIKPDSLGRSDTGVFVGGFSQGYGTGADLGGFGATSTQTSVLSGRLSYFYGFEGPAFTVDTA
CSSLVALHQAASSLHIGECSLAVVGGVTVVATPGGFVEFARQGGALDGRCKAFADAADGIGLAEGVGVLLVERLS
DAQRNGHTVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTRLGDPIEAQAILAT
25 YGQDRDQPLLLGSLKSNIGHTQAAAGVAGVIKTMAMRHGTAPRTLHADEPSRHVDWSAGAVELLSENRLWPETDRP
RRAAVSSFCVSGTNAHVILESAPAESAEGPAGMGSESMGSESGPVVVVLSAKSASALAGQEERLRLAYLASGADVRAV
AAGLARRSVFEHRSVILGDSTVSGVAAGVPRVVFLEFPQGTQWAGMGADLLESSPVFAARMRQCAAELSKYTDWDLF
TALSDPALLDRVDVVQPVSWALMVSLAALWQHCGVQPDVIGHSQGEIAAACVAGALTQDQCARLITGRSALIAHLS
GRGTMASIALPADDLTLPDVCIAAVNGPATTIIAGPTPAIEHLLATYEASNIHTRRIPVDYPSHTPHVEDLHDPLL
30 AITHTLTPHTPTTPWLSTVDNTWIHTPPHPDYWYRNLRHPVQLAPAITTLTHPHPTHLEISTHPVLLPAIDTTTTL
TTTATLRRNHGTPHQLLTSLAHAHTHGATINWPALLGNPPTATTADLPTYPFQHKRYWLQDTERVAGLPAAEREQVV
VKAVCETAAVVLGHAHADDILATTLFKDLGVDSLIAVELRNRLAADAGLRLPATLVFDYPTPHALATWL

SEQ ID NO: 45

EPLAIVGMACRFPGGVSSPEDLWRLVESGGDAISDIPADRGWDLETPYRGGFLADAGGF'DAGFFGISPREALAMDPQ
QRVLLETWEALERAIEIEPGSLRGSDTGVFIGGF'SQSYGIGADLGGFGTTGIQTSVLSGRLSYFFGFEGPAFTVDTA
CSSLVALHQAASSALRQGECSLALVGGVTVLADPSGFVEFARQGGLAADGRCKAFADTADGTSLAEGVGVLLVERLS
DAQRNGHTVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTRLGDPIEAQAILAT
YGQDRDQPVLLIGSLKSNIGHTQAAAGVAGVIKMMAMRQGTVPRTLHVDEPSHHVDWTAGSVQPIQONQEWPOAGRV
40 RRAGVSSFGISGTNAHVIIIEGVPVAEPVVVADSGVVPLVLSARTPGALLEQEERLRLAYLACGADVRAVAAGLARRSV
FEHRSVLVGDTVSGTAADARLVLVFSGQGSQRAGMGEELAAARFPVFAEIHQRVWDLDDVGPGLDVDDTGYAQPALF
ALQVALFGLLESWGVRPDVLIGHSIGELAAACVSGVWSLQDACALVSARARLMQALPAGGVMAAVPVSEAEAEAVLR

EGVEIAAVNGPASIVLSGDEDAVLQAAASLGRFTRLSTSHAFHCARMDPMLDEFRQVAESIAYQPPRIAMAAGDQVI
TPDYWVRQVREPVRFGDQVAAHADAVFLEIGPDRHLARLIDGIPTLSVDEVQSAMTALGELHVRGIDVDWATLLGTT
PATPTDIPTYPFQHKHYWIDNRRISGLEPAERGQALLEIVREAAAVVLGHTDAREIAPTTAFRDLGIDSLTAIELRN
RVATETGLRLPATLVFDHPTPTTLATWI

5

SEQ ID NO: 46

EPLAIVGMACRLPGGISSPEDLWQLVQSGGDAITDLPTDRGWDLTHLYDNDAPPVYRGGFLTDAGDFDAAFFGISPR
EALAMDPQQRILLETWEAFERGGINPEAIRGSNTGVFIGGFSYGYGTGADLGGFGATSTQTSVLSGRLSYFYGFEG
PAVTVDTACSSSLVALHQASSALRQGECSLALAGGVTVMATPAGFEEFARQGGLAADGRCKAFSDTADGTGWAEGVG
10 VLLVERLSDAQRNGHTVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTRLGDPI
EAQAILATYGQDRDQPLLLGSLKSNIGHTQAAAGVAGIIKTMAMMRHGTAPRTLHADEPSRHVDWSAGAVELLSEN
LWPETDRPRRAAVSSFGVSGTNAHVII EQPPHTPAPEAERTTGLDVVPWLLSARTPAGLRAQAEQVSSLNEDFANIG
FSLATTRTPMEHRAVVVADVSGISEAAVFAGGGSPTDVVSGLANVRGKTVFVFPQGGAQWAGMGAELFATSPVFAER
MTECAAAFAALVDWSLIDVLQQREGAPSPDRVDVVQPLSFAMVSLAALWKSHGVVPDAVTGHSQGEVAAACVSGAL
15 SLSDAATVVALRSRVIAQLAGHGMVALPATEFAAEYWAGRLELA AVNGPASVVVAGEPEALEELLAENPNARRIPV
DYASHTSRVERIREELTGLLSGLAPRQPIVPFYSTVDNQWLDKPLDAEYWYRNLRQTVRFADAVHGLADAGFRAFVE
VSPHPVLTSSMRDILDERETTAVVTGTLRRDAHGVREFVRSLARLWVSGFSVDWSGLFGNGPRRIPLPTYPFQRNRY
WLQAE LDLVRTHAAAVLGHAGPEAVAADHPFRDLGVDSLIAVELRNRLAAETGLRLPATLVFDYPTPRALAAWLD

20

SEQ ID NO: 47

EPLAIVGMACRFPGGVSSPEDLWRLVETSGDAISDIPADRGWDLETPYRGGFLIGAAGFDAGFFGISPREALAMDPQ
QRLLEISWEALERAGINPESVRGSDTG VFGGSSYGYGVGADLGGFGATSTHISVLSGRVSYFFGFEGPAFTVDTA
CSSLVALHQASSALRQGECSLALVGGVTVMATPAGFEEFARQGGLAADGRCKAFSDTADGTSLAEGVGVLLVERLS
DAQRNGHTVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTTLGDP IEAQAILAT
25 YGQDRDQPV LIGSLKSNIGHTQAAAGVAGVIKMVMAMRQGTVPRTLHVDEPSHHVDWTAGSVQPI TQNQEWPOAGRV
RRAGVSSFGISGTNAHVII EGV PVAEPVVVADSGVVPLVLSARTPGALLEQEERL RAYLACGADVRAVAAGLARRSV
FEHRSVLVGDTVSGTAADARLVLFSGQGSQRAGMGEELAA RFPVFAEIHQRVWDL LDVGPGLDVDDTG YAQPALF
ALQVALFGLLESWGVRPDVLIGHSIGELAAACVSGVWSLQDACALVSARARLMQALPAGGVMAAVPVSEAEAEAVLR
EGVEIAAVNGPASIVLSGDEDAVLQAAASLGRFTRLSTSHAFHCARMDPMLDEFRQVAESIAYQPPRIAMAAGDQVI
30 TPDYWVRQVREPVRFGDQVAAHADAVFLEIGPDRHLARLIDGIPTLSVDEVQSAMTALGELHVRGIDVDWATLLGTT
PATPTDIPTYPFQHKHYWIDNTRISGLEPAERGQALLEIVREAAAVVLGHTDAREIAPTTAFRDLGIDSLTAIELRN
RVATETGLRLPATLVFDHPTPTTLATWI

35

SEQ ID NO: 48

EPLAIVGMACRLPGGISSPEDLWQLVQSGGDAITDLPTDRGWDLETPYRGGFLTDPAGEFDAGFFGISPREALAMDPQ
QRVLLEASWEAFERAGIKPDSL RGS DTGVFVGGFSQGYGTGADLGGFGATSTQTSVLSGRLSYFYGFEGPAVTVDTA
CSSLVALHQASSALRQGECSLALAGGVTVMATPAGFEEFARQGGLAADGRCKAFADTADGTGWAEGVGVLLVERLS
DAQRNGHTVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTRLGDPI EAQAILAT
YGQDRDQPLLLGSLKSNIGHTQAAAGVAGIIKTMAMMRHGTAPRTLHADEPSRHVDWSAGAVELLSENRLWPETDRP
40 RRAAVSSFGVSGTNAHVILESAPAESAEGPAGMGSESMGSESGPVVVVLSAKSASALAGQEERL RAYLASGADVRAV
AAGLARRSVFEHRSVILGDSTVSGVAAGVPRVVFLFPGQGTQWAGMGADLLESSPVFAARMRQCAAELSKYTDWDLF
TALSDPALLDRVDVVQPVSWALMVSLAALWQHCGVQPD AVIGHSQGEIAAACVAGALT LQDGARLITGRSALIAHLS

PATENT
50869-016WO2

GRGTMASIALPADDLTLPDDVCIAAVNGPATTIIAGPTPAIEHLLATYEASNIHTRRIPVDYPSHTPHVEDLHDPLL
AITTHLTPHTPTTPWLSTVDNTWIHTPPHPDYWYRNLRHPVQLAPAITTLTHPHPTHLEISTHPVLLPAIDTTTTL
TTTATLRRNHGTPHQLLTSLAHAHTHGATINWPALLGNPPTATTADLPTYPFQHKRYWLQDTERLTTQSSVEQHRLM
LDLVTSHAAAVLGHSSAAAITTDTPFRLDGFDSLTAVELRNRVAADTGLRLPATLVFNHPNADALTQYL

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SEQ ID NO: 49
DPIAIVAMACRLPGGVSSPEDLWRLVETGTDAIGPFPTDRGWDTELYPVPDAPGKTYCVEGGFLTGAAEFDAAFFDI
SPREALAMDPQQRLLLETSWEAVERARINPKSLCGKDVGVYVGAAAQGYGLGAGDQTEGTAITGGSTSLSSGRVSYA
LGLEGPAVTVDTACSSSLVAMHLAGQALRQGECSLALVGGVSVMASPALFVEFSRQRGLAADGRCKSFSDAADGTNW
10 AEGVGVLILERLSDAQRNHGPVLAVIRGSAINSDGASNGLTAPNGLSQQRVIRQALTAAGLRPEDVDAVEAHGTGTR
LGDPVEAEAILATYQONREQPLLLGSLKSNIGHAAAASGVAGVIKMOVQAMRNGVLPRTLHIDEPSQVDWTSGNVAL
LTESRPWPDEDKPRRAGVSSFGISGTNAHIVLEQYRAAEPEDRPGDGPGERRPVAVVLSGKSPAAVRAQAGRLRAHL
VGTQGWRPVDVGYALATTRADFAHRAVAVGSGPEFLHALEKLAEGASWPRLTTNRASARRVAFLEFDGQGTQRLGMGR
ELHQRFPFAFAEAWDTVDAEFAPYLDRLSTEVEFFSDGGSGLMDDTLYAQAGLFAVETALFRLLAGWGVRPDFVAGHSA
15 GEITAAHVAGVLSVTDVAVRLIVARGQALRLAPPGAMASVRSSAQEVRDFIAQSGLPVDLAAINSPGSVVVAGSPETI
AEFEGAWTASGRQAKRLAVRHAFHSRHVDGVLDEFRAALGGCRFGVAELPLVSTATGELASPDELGTPEHWLRHARQ
TVRFQDAIRALTEQGVDTFVEIGPSGTLASAGMECGGGTAAFHAVMRARQPEEVSLMTAVAELYAGGTPVEWSRVLD
GRSVVDLPVYPPQRQPYWLAPADELSQPEQQKALLELVKAEAAVLLGITDATAIEDDARFLELGFDSL SATRLRNQL
AKATGLALEQTLLFDFPTPAALAAHL

20
SEQ ID NO: 50
EPLAIVGMACRLPGGVSSPEDLWRLVESGGDVISDFPTDRGWDTTGEDSSFIRGGFLT DAGGFDAGFFGISPREAVA
MDPQQRVLVLETSWEVLERAGIEPGSLRGSDTG VFIGGFSQGYGAGADLGGFGATGTQTSVLSGRVSYLLGLEGPAVT
VDTACSSSLVALHQAAASALRQGECSLALVGGVTVMATTHSFVEFARQGGGLSSDGRCRSFADSADGTGWAEGVGVLV
25 ERLSDARRSGHPVLALVRGSAVNQDGASNGLSAPNGLSQQRVIRQALATAGLDAADVVEAHGTGTVLGDPIEAQA
ILATYQGQREEPLLLGSLKSNVGHTQAAAGVAGVIKMMAMRQGTVPRTLHVDEPSHHVDWTACRVELLTENRPWPQ
AGRVRRAGVSSFGISGTNAHVIIIEGVPVAEPVVVADSGVVPLVLSARTPGALLEQEERL RAYLACGADVRAVAAGLA
RRSVFEHRSVLVGDTVVS GTAADARLVLVFSGQGSQRAGMGEELAA RFPVFAEIHQRVWDL LDVGPGLDVDDTG YAQ
PALFALQVALFGLLESWCVRPDVLIGHSIGELAAACVSGVWSLQDACALVSARARLMQALPAGGVMAAVPVSEAEAE
30 AVLREGVEIAAVNGPASIVLSGDEDAVLQAAASLGRFTRLSTSHAFHCARMDPMLDEF RQVAESIAYQP PRIAMAAG
DQVITPDYWVRQVREPVRFGDQVAAHADAVFLEIGPDRHLARLIDGIPTLSVDEVQSAMTALGELHVRGIDVDWATL
LGTTPATPTDIPTYPFQHKHYWIDNTRISGLEPAERGQALLEIVREAAAVVLGHTDAREIAPTTAFRLGIDSLTAI
ELRNRVATETGLRLPATLVFDHPTPTTLATWI

35
SEQ ID NO: 51
EPLAIVGMACRLPGGISSPEDLWQLVQSGGDAITDLPTDRGWDLET PYRGGFLTDPAGFDAGFFGISPREALAMDPQ
QRVLLEASWEAFERAGIKPDSL RGSDTG VFGGFSQGYGTGADLGGFGATSTQTSVLSGRLSYFYGFEGPAVTVDTA
CSSSLVALHQASSALRQGECSLALAGGVTVMATPAGFEEFARQGG LAADGRCKAFADTADGTGWAEGVGVLVVERLS
DAQRNHGTIVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTRLGDPIEAQA I LAT
40 YGQDRDQPLLLGSLKSNIGHTQAAAGVAGIIKTVMMAMRHGTAPRTLHADEPSRHVDWSAGAVELLSENRLWPETDRP
RRAAVSSFGVSGTNAHVILESAPAESAEGPAGMGSESMGSESGPVVVVLSAKSASALAGQEERL RAYLASGADVRAV
AAGLARRSVFEHRSVILGDSTVSGVAAGVPRVVFLFPGQGTQWAGMGADLLESSPVFAARMRQCAAELSKYTDWDLF

TALSDPALLDRVDVVQPVSWALMVSLAALWQHCGVQPDVIGHSQGEIAAACVAGALTLDGARGLITGRSALIAHLS
GRGTMASIALPADDLTLPDDVCIAAVNGPATTIIAGPTPAIEHLLATYEASNIHTRRIPVDYPSHTPHVEDLHDPLL
AITTHLTPHTPTTPWLSTVDNTWIHTPPHPDYWYRNLRHPVQLAPAITTLTHPHPTHLEISTHPVLLPAIDTTTTL
TTTATLRRNHGTPHQLLTSLAHAHTHGATINWPALLGNPPTATTADLPTYPFQRRRFFWAERISGLEPAERGQALLEI
5 VREAAAVVLGHTDAREIAPTTAFRDLGIDSLTAIELRNRVATETGLRLPATLVFDHPTPTTLATWI

SEQ ID NO: 52

EPLAIVGMACRLPGGISSPEDLWQLVQSGGDAISDFPTDRGWDLTHLYDNDAPPVYRGGFLTDAGDFDAAFFGISPR
EALAMDPQQRLILETSWEVLERAGIEPGTLRGSETGVFVGGFTQGYGTGADLGGFGMTSGHSSVLSGRVSYFFGFEG
10 PAVTVDTACSSSLVALHQASSALRQGECSLALVGGVTVMASPOGFTEFSRQGGGLSPDGRCKAFADAADGTGWAEGVG
VLLVERLSDAQRNGHTVLA VVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTTLGDP
EAQAILATYQGDRDQPLLLGSLKSNIGHTQAAAGVAGVIKMMAMRHGTAPRTLHIDEPSRHIDWTTGSVALSTENQ
PWPETGHPRRAGVSAFGVSGTNAHVVLGVPVAGPPEEDVEPGVVPLLISAKSRPALMEQEQLRRTYLDGSQTDIRA
VAATLAHARSVFEHRSVLVGDTVVSAGTAADARLVLVFSGQGSQRAGMGEELAARFPVFAEIHQRVWDLDDVGPGLDV
15 DDTGYAQPALFALQVALFGLLESWGVRPDVLIGHSIGELAAACVSGVWSLQDACALVSARARLMQALPAGGVMAAVP
VSEAEAEAVLREGVEIAAVNGPASIVLSGDEDAVLQAAASLGRFTRLSTSHAFHCARMDPMLDEFRQVAESIAYQPP
RIAMAAGDQVITPDYWVRQVREPVRFGDQVAHADAVFLEIGPDRTLARLIDGVPLLSKEDEVQAALVALAELHVRG
VPLEWSTVIGGMTSIVDLPTYPFRRKRYWIESAERLTTQSSVEQHRLMLDLVTSHAAAVLGHSSAAAITTDTPFRDL
GFDSLTAVELRNRVAADTGLRLPATLVFNHPNAGDLARHL

20
SEQ ID NO: 53
EPLAIVGMACRLPGGISSPEDLWQLVQSGGDAITDLPTDRGWDLTHLYDNDAPPVYRGGFLTDAGDFDAAFFGISPR
EALAMDPQQRILLETWEAFERGGINPEAIRGSNTGVFIGGFSYGYGTGADLGGFGATSTQTSVLSGRLSYFYGFEG
PAVTVDTACSSSLVALHQASSALRQGECSLALAGGVVTMATPAGFEEFARQGGGLAADGRCKAFADTADGTGWAEGVG
25 VLLVERLSDAQRNGHTVLA VVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTPADIDVVEAHGTGTTLGDP
EAQAILATYQGDRDQPLLLGSLKSNIGHTQAAAGVAGIIKTMAMRHGTAPRTLHIDEPSRHVDWSAGAVELLSEN
LWPETDRPRRAAVSSFGVSGTNAHVILESAPAESAEGPAGMGSESMGSESGPVVVVLSAKSASALAGQEERLRAYLA
SGADVRAVAAGLARRSVFEHRSVILGDSTVSGVAAGVPRVFLFPGQGTQWAGMGADLLESSPVFAARMRQCAAELS
KYTDWDLFTALSDPALLDRVDVVQPVSWALMVSLAALWQHCGVQPDVIGHSQGEIAAACVAGALTLDGARGLITGR
30 SALIAHLSGRGTMASIALPADDLTLPDDVCIAAVNGPATTIIAGPTPAIEHLLATYEASNIHTRRIPVDYPSHTPHV
EDLHDPLLAITTHLTPHTPTTPWLSTVDNTWIHTPPHPDYWYRNLRHPVQLAPAITTLTHPHPTHLEISTHPVLLP
AIDTTTTLTTTATLRRNHGTPHQLLTSLAHAHTHGATINWPALLGNPPTATTADLPTYPFQHKRYWLQDTRLSALAP
AEREQALVKAVCETAAMVLGHADTREIAATTAFKELGLDSLTA VQLRDLAAETGRKLPATLVFDYPSQPQALAAWL

35 SEQ ID NO: 54
EPLAIVGMACRLPGGVASPEDLWRLVESGTDAITDFPTDRGWDLDEVADQSYCLQGGFLDNAAGFDAAFFGISPREA
LAMDPQQRLVLEASWEAFERAGIKPGSLRGSDTGVMGAYPGGYGTGADLGGFGATAGAVSVLSGRISYFFGFEGPA
MTVDTACSSSLVALHQAGYALRQGECSIALVGGVTVMATPQSFIIEFSRQRGLAADGRCKTFADAADGTGWAEGVGVL
LVERLSDARAKGHQILAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALVNAGLSPADVDDVVEAHGTGTTLGDP
40 QALLTTYGQGRSVPLLLGSKNLGHTQAAAGVTGVKMMALRHGVVPRTLHVDEPSRHVDWSAGAVELVTSNREW
PVVDRPGRAGVSSFGISGTNAHVILEAVPSDTPASTSTDAVLPLVVSARTAPAAEDLTARLRAYLSAAPETDQRAAA
ATLALTRSVFEHRAVVLGDELVSGQAVRDPVVVFVFSGQGSQRAGMGEQLAAVFPVFAEIHERVWALLDVPDGLDVD

DTGHAQPALFALQVALSGLLESWGVRPAAVIGHSIGELAAAYVSGVWSLEDACALVSARARLMQALPPGCGVMVAVPV
PEAEARAVLRDGVIEIAAVNGPSSVVLSGDEDAVLQAVSGFAKWTRLKTSHAFHSAHMDPMLDEFRAVAERLTYRRPS
VEMAAGDRVTTAEYWVRQVREAVRFGDQTTAYEDAVFVEIGPGRTLARLIDGITMLHGDTEREAALTGLSQLFVRGV
DVDWATVIEDTTARILDLPITYAFQHENYWLHWLSGLTPAEREQALLTAVRENAAAVLGHADARTVPVNSAFRDLGFD
5 SLTAIELRNSLAKATGLSLPATMAFDYPTPAVLATRL

SEQ ID NO: 55

EPLAIVGMACRLPGGVSSPEELWRLVESGVDAISGFPVDRGWDVENLFDPDFDAAGKSYCVQGGFLDSAAEFDAFF
GISPREALAMDPQQRLVLETSWEAFERAGIEPGSIKGSDTGVFMGAYQGGYGSGADLGGFGATAGATSVLSGRVSYF
10 FGFEGPAMTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQSFVEFSRQRGLAVDGRSKAFADAADGTGW
AEGVGVLVERLSDAQAKGHQILAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANASLTPADVVEAHGTGTT
LGDPIEAQAVIATYGQDRSTPLLLGSLKSNIGHTQAAAGVSGVIKMMALRHGVVPQTLHVDQPSRHVDWSAGAVEL
LTSNQWPSSERARRAGVSAFGVSGTNAHVILESAPAEPVVAEAGPVPVVSVDLPLVLSAKSAPALRALEQRLRAYD
GAAGRALATARATFDHRAVLIGDDTVTGAVPDPRVVFVFPQGQGWQWLGMGRELRGSSVVFMAERMAECAALSEFVD
15 WDLFAALDDPAVVDRVDVVQPCWAVMVSLAAVWQAAGVNPDAVVGHSSQGEIAAAVVAGSLSLRDGARVVALRSQLI
KGLAGRGAMASIALPADQIGLVEGAWIAALNGPSSSTVIAGTPEAVEQVLAQDARVRRIAVDYASHTPQVEAIRDEL
LELTAGVSSQPPTVPWLSTVDNTWVEGPLPADYWFERNLREQVGFAQAVVTLGDVAVFEVSGSPVLMQSMGDAVTVAS
FRRDDGSATRMVTSLAEAYVQGVNVNWAAVLGAGTERALDLPTYPFQRQHYWISLAALPPAERERALLKVVRDSAAV
VLGHADGRTVPATAAFKDLGLDSLTAVELRNSLRKATGLQLPATLVFDYPSVALAARL
20

SEQ ID NO: 56

EPLAIVGMSCRLPGGVSSPEDLWRLVESGVDAISGFPVDRGWDAEGLFDPDPDAAGKTYCVQGGFLEAAGEFDTAFF
GISPREALAMDPQQRVLLEASWEAFERAGIGADTVRGTDGTGVFIGAYPVAYGAGVDREGYGATAAPNVLSGRLSYFF
GLEGPAITVDTACSSSLVALHLAASALRNCECSLALAGGVTVMATPEVFTEFARQRGLAFDGRSKSFADAADGAGFS
25 EGAGLLVLERLSDARRNGHQVLAVIRGSAVNQDGASNGFTAPNGPSQQRVIEAALGNAGLTTAEVDVVEAHGTGTKL
GDPIEAQAVLATYQDRDLPLLLGSLKSNIGHTQAASGVAGVIKMMALRHGVVPQTLHVDEPSRHVDWSAGAVELV
TSNQWPSSERPRRAGVSAFGVSGTNAHVILESAPVEPVVAEAGPVPVVGDLPLVLSAKSAPALTVLEQRLRAYEA
ADEKAVAATLAAARATFGHRAVLLGGDTVTGAVPDPRVVFVFPQGQGWQWLGMGRELRGSSVVFMAERMAECAALSE
FVDWDLFTALDDPAVVDRVDVVQPCWAVMVSLAAVWQASGVNPDAVVGHSSQGEIAAAVVAGSLSLRDGARVVALRS
30 QLIKLAGRGAMASIALPAEIDLVEGSWIAALNGPSSSTVIAGTPEAVEQVLAVQDARVRRIAVDYASHTPQVEAIR
DELLELTGEVVSARKPDVPWLSTVDNAWIEGPLGADYWFERNLREQVGFAQAVVTLGDVAVFEVSASPVLMQSMGDAVC
VPSLRRDDGTATRMVTSLAEAYVQGVQVNWAAVLGAGTERALDLPTYPFQRQHYWALHWLRLSPAEREQALLKLVC
ESASVVLGHADAGAIPVTAAFKDLGVDSLTAVELRNSLATATGQRLPATAVFDYPTPAVLAARL

35 SEQ ID NO: 57

EPLAIVGMACRLPGGVSSPEGLWRLVVSGSDVISGFPADRGWGVEGLRGGLPGAADFAGFFGISPREALAMDPQQ
RLVLEASWEVLERAGIAPGSLRGSDTGVMGAYPGGYGIGADLGGFGATAGAVSVLSGRVSYFFGFEGPAMTVDTAC
SSSLVALHQAGHALRNSECSLALVGGVTVMASPTFVEFERQGGLAADGRSKAFSDGADGAGFSEGVGVLLVERLS
ARAKGHQILALVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANASLTVADVVEAHGTGTTLGDPIEAQALLATY
40 GQDRDRPLLLGSVKSNLGHTQAAAGVTGVIKMMALRHGVVPRTLHVDEPSRHVDWSAGAVELVTSNREWPVTDPRG
RAGVSSFGISGTNAHVILEAVPVVSAVSTGGEVQPLVVSARTAPAAEDLTARLRTYLADTPDQDQRAAATTLALTRS
VFEHRAVLLGDDTITGAAVPDPRVVFVFSGQGSQRAGMGEQLAAAFPVFAEIERVWALLDVPDGLDVDDTGHQAQPA

LFALQVALSGLLESWGVRPAAVICHSIGELAAAYVSGVWSLEDACVLVSARARLMQALPPGGVMVAVPVPEAEARAV
LRDGVEIAAVNGPSSVVLSGDEDAVLQAVAGFAKWTRLKTSHAFHSAHMDPMLDEFRAVAERLTYRRPSVEMAAGHG
VTTAEYWVRQVREAVRFGDQTTAYEDAVFVEIGPGRTLARLIDGITMLHGDTEREAALTGLSQLFVRGVDVDWPAVI
EDTTARILDLPTYFPQRQRYWLTFRWLAGMSPEDRRQALLRVVRDSAAVVLGHAEAGTIPPNAAFKDLGIDSLTAVE
5 LRNSLATATGLRLPATLVFDYPAPETLAARLD

SEQ ID NO: 58

EPLAIVGMACRLPGGVASPEDLWRLVASGTDALISGFPTDRGWDVEGLFDPDPDVAGKTYCVQGGFLDTAARFDAAFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSLRGS DTGVFMGAFFPGGYGLGADLEGYGVTTGGPNAVSGRLSYFF
10 GLEGPFTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMGTPQTFVEFSRQRGLAVDGRSKSFSDQADGTGWS
EGVGVLVVERLS DARAKGHQILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANASLTVADVDVVEAHGTGTTL
GDPIEAQALLATYQGDRDRPLLGSVKSNLGH TQAAAGVAGVIKVMALQHGIVPQTLHVSEPSRHVDWTAGAVELV
TSNQFPWPSSGRPGRAGVSAFGVSGTNAHVILEGVPSNTPVSTAAGDVLPLVVSARTAPAVEDLTARLR TYLADTPGT
DQRAAATTLALTRSVFEHRAVLLGEDTITGVAVPDSRVVFVFSGQGSQRAGMGEQLAAAFPVFAAIHERVWALLDVP
15 DGLDVDDTGH AQPALFALQVALSGLLESWGVRPDAVIGH SIGELAAAYVSGVWSLEDACALVSARARLMQALPSSGGV
MVAVPVPEAEARAVLRDGVEIAAVNGPSSVVLSGDEDAVLQAVAGFAKWTRLKTSHAFHSAHMDPMLDEFRAVAERL
TYRRPSVEMAAGDRVTTAEYWVRQVREAVRFGDQTTAYEDAVFVEIGPGRTLARLIDGITMLHGENEGHAALAALSH
LFVQGVVRVDWPAVLGTTAERVDLPTYFPQHEHYWARAEHWLAGLPADEREKALLKIVRDSAAAVLGHADGRTVASGA
VFKEGLDLSLTAVELRNSLGKATGLRLPSTAAFDYPTPAALATRL

20
SEQ ID NO: 59
EPLAIVGMACRLPGGVSSPEDLWRLVESGSDALISGFPTDRGWDVDGLFDPDPDAAGKSYCVQGGFLDSAAEFDAAFF
GISPREALAMDPQQRLLET SWEAFERAGIDPGSVRGS DTGVFVGAFPGGYGAGADIEGYGATAGPSVLSGRLSYFF
GLEGPFTVDTACSSSLVALHQAGHALRQGECSLALVGGVTVMASPVTFVEFSRQRGLAADGRCKAFGDGADGTGWS
25 EGVGVLLVERLS DAQAKGHQILAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAAALASAGLVTSDVDVVEAHGTGTTL
GDPIEAQAVLATYQDRSTPLLLGSLKSNIGHTQAAAGVSGVIKVMALRHGVVPQTLHADEPSRHVDWSAGAVELL
TSNRSWPSSERARRAGVSAFGVSGTNAHVILESAPVEPVVAVAGVPVVS DVLPLVLSAKSAPALTAEQRLRVYDG
AAGRALATARATFDHRAVLIGDDTVTGVAVPDPRVVFVFPQGQWQWLGMGRELRDSSVVFASRMAECAALSEFVDW
DLFTALDDPAVVDRVDVVQPCWAVMVSLAAVWQASGVNPD AVVGHSQGEIAAAVVAGSLSLRDCARVVALRSQLIK
30 GLAGRGAMASIALPAAEIDLVEGSWIAALNGPSSTVIAGTPEAVEQVLAVQDARVRRIAVDYASHTPQVEAIRDELL
ELTAEVESRRPDVPWLSTVDNTWVEGPLSADYWFRNLREQVGFAQAVVT LGDAVFVEVSASPVLQMOSMGDAVTVATL
RRDDGSALRMVTS LAEAYVQGVNVNWA AVLCAGTERALDLPTYFPQRQHYWVTAQSLAGLPAEDREKALLKIVRDSA
AQVLGHPDGRAVPAGAAFIELGVDSL TG VEMRNRLGGITGLRLPATMVFDYPTPAALAGRL

35 SEQ ID NO: 60
EPLAIVGMACRLPGGVSSPEELWRLVESGVDAISGFVDRGWDVENLFD PDPDAAGKSYCVQGGFLDTAAEFDAAFF
GISPREALAMDPQQRLVLETSWEAFERAGIEPGSLKGS DTGVYMGAFSGGYAADLEGFGATAGATSVLSGRVSYFFG
FEGPAMTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMAS PQSFVEFSRQRGLAADGRSKAFADAADGTGWAE
GVGVLLVERLS DAQAKGHQILAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANASLT PADIDVVEAHGTGTTLG
40 DPIEAQAVIATYQDRSTPLLLGSLKSNIGHTQAAAGVSGVIKVMALRHGVVPQTLHVDQPSRHVDWSAGAVELVT
SNQFPWPSSERPRRAGVSAFGVSGTNAHVILESAPAEPVVAEVGLVPVVS DVLPLVLSAKSAPALT VLEQRLRAYEAA
DERTVAATLATARATFDHRAVLIGTETVTGPLMTDPRVVFVFPQGQWQWLGMGRELRGSSVVF AERMAECAALSDF

VDWDLFTALDDPAVVDRVDVVQPVWCWAVMVSLAAVWQAAGVNPDAVVGHSSQGEIAAAVVAGSLSLRDGALVVALRSQ
LIKGLAGRGAMASIALPADQIGLVEGAWIAALNGPSSTVIAGSPEAVEQVLAAQDARVRRIAVDYASHTPQVEAIRD
ELLELTAGVSSQPPTVPWLSTVDNTWVEGPLPADYWFRNLREQVGFAQAVVTLGDAVFVEVSASPVLQMGMGDAVCV
PSLRRDDGSATRMVTSLAEAYVQGVNVNWA AVL GAGTERALDLPTYPFQQRQRYWAGHWLARLAPGERETALLKLVSE
5 SAAAVLGHADARSIPATAVFRDLGMDSLTAVEVRNSLAKTTGLRLPATLAFDYPTPAVLAARL

SEQ ID NO: 61

EPLAIVGMACRLPGGVSSPEGLWRLVVSGSDVISGFPADRGWGEGLRGGLPGAADF DAGFFGISPREALAMDPQQ
RLVLEASWEVLERAGIAPGSLRGSDTGVMGAYPGGYGIGADLGGFGATAGAVSVLSGRVSYFFGFEGPAMTVDTAC
10 SSSLVALHQAGHALRNSECSLALVGGVTVMASPTFVEFERQGGLAADGRSKAFSDGADGAGFSEGVGVLLVERLS
ARAKGHQILALVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANASLTVADVDVVEAHGTGTTLGDPPIEAQALLATY
GQGRSVPLLLG SVKSNLGHTQAAAGVTGVIKMMALRHGVVPRTLHVDEPSRHVDWSAGAVELVTSNREWPVVDPRG
RAGVSSFGISGTNAHVILEGIPSNTPVSTAAGAVLPLVVSARTAPAAEDLTARL RAYLSAAPETDQRAAAATLALTR
SVFEHRTVLLGDDTITGAAMPDPRVVFVFSGQGSQRAGMGEQLAAVFPVFAEIERVWALLDVPDGLDIDDTGHAQP
15 ALFALQVALSGLLESWGVRPDAVIGHSIGELAAAYVSGVWSLEDACALVSARARLMQALPPGGVMVAVPVSEAEART
VLRDGVEIAAVNGPSSVVLSGDEDAVLQAVSGFAKWTRLKTSHAFHSAHMDPMLDEFRAVAERLT YRRPSVEMAAGH
GVTTAEYWVRQVREAVRFGDQTTAYEDAVFVEIGPGRNLARLIDGITMLHGDTEREAALTGLSQLFVRGVDVDWATV
IEDTTARILDLP TYPFQHERYWLSWLVLGPPAERAKALLKTVRDSA AVVLGHQGT RAIPVDGAFRELGMDSLTAVEL
RNSLAKATGLSLSATLVFDYPTPKVLADHLD

20
SEQ ID NO: 62
EPLAIVGMACRLPGGVSSPEELWRLVESGSDAISGFPVDRGWDADGLFDPDPDAAGKSYCVQGGFLDTAAEFDAFF
GISPREALAMDPQQRLVLETSWEAFERAGIEPGSIKGS DTGVFIGAYPGGYGSGVELGGFGATSGAGSVLSGRVSYF
FGFEGPAMTVDTACSSSLVALHQAGYALRQGD CSMALVGGVTVMSTPHIFVEFSRQRGLAADGRCKAFGDGADGTGW
25 SEGVGVLLVERLS DARAKGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIHAALASAGLVTSDVDVVEAHGTGTT
LGDPPIEAQAVIATYGCQDRSTPLLLGSLKSNIGHTQAAAGVSGVIKMMALRHGVVPQTLHVDQPSRHVDWSAGAVEL
LTSNQWPWPSSERARRAGVSAFGVSGTNAHVILESAPVEPVVAEAGPVPVSDVLPLVLSAKSAPALRALEQRLRVYD
GAAGRALATARATFDHRAVLIGDDTVTGVAVPDPRVVFVFPQGQWQWLGMGRELRGSSVVF AERMAECAALSEFVD
WDLFAALDDPAVVDRVDVVQPVWCWAVMVSLAAVWQAAGVNPDAVVGHSSQGEIAAAVVAGSLSLRDGALVVALRSQLI
30 KGLAGRGAMASIALPATEISLVEGAWIAALNGPSSTVIAGSPEAVEQVLAVQDARVRRIAVDYASHTPQVEAIRDEL
LELTAGVSSQLPTVPWLSTVDNTWVEGPLPADYWFRNLREQVGFAAAVQELGESVFVEVSGSPVLIQSMGDAVT VAT
LRRDDGSATRMVTSLAEAYVQGVQVNWA AVL GAGSERALDLPTYPFQRDHFVWLSLAALPSAEREKALVKIVCESAA
AVLGHTDTS AVPAAA FKELG LDSLTAVDLRNRLRRATGLQLPATLVFDYPTPTAMAARL

35 SEQ ID NO: 63
EPLAIVGMSCRLPGGVSSPEDLWRLVESGSDAISGFPTDRGWDVDGLFDPDPDAAGKTYCVQGGFLEAAGEFDAAFF
GISPREALTMDPQQRVLLEASWEAFERAGIAPTSVRGTD TGVFIGA FPGYGAGADHEGYTATAGVGSVLSGRLSYF
FGLEGPAMTMDTACSSSLVALHLAASALRNGECSLALAGGV T VMATPEVFTEFARQRGLAADGRCKPFADAADGAGF
SEGAGLLVLERLS DARRNGHQVLAVIRGSAVNQDGASNGLTAPNGPAQQRVIRQALANAGLNSSDVDVLEAHGTGTT
40 LGDPPIEAQAVLATYGCQDRSTPLLLGSLKSNIGHTQAASGVAGVIKMMALRNGLVPRSLHLDEPSRHVDWSAGAVEL
LTSNQWPWPSSDRPRRAGVSAFGVSGTNVHVILESAPAEPVGAEAGPLPVVGDLPLVVS AKSAPALTALEQRLRAHV
AADERAAAATLATARATFDHRAVLIGAETVTGVA AVDP RVVFVFPQGQWQWLGMGRELRGSSVVF AERMAECAALS

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EFVDWDLFTALDDPAVVDRVDVVQPVCWAVMVSLAAVWQAVGVNPDVVGHSQGEIAAAVVAGSLSLRD GALVVALR
SQLIAGLAGRGAMASIALPADQISLVEGAWIAALNGPSSSTVIAGTPEAVEQVLAAQDARVRRIAVDYASHTPQVEAI
RDELLELTGEVVS RKPDVPWLSTVDNAWIEGPLGADYWFERNLREQVGFAQAVVTLGDAVFVEVSASPVLMQSMGDAV
CVPSLRRDDGTATRMVTS LAEAYVQGVQVNWAAVLGAGTERALDLPTYPFQRRERFWVLWLAGLAPQERETALLKLVC
5 DSAAVVLGHGDGQAIPDTTAFKDLGVDSLTAVEVRNRLAAATGLRLPATMVF'DYPTPTALAARL

SEQ ID NO: 64

EPLAIVGMACRLPGGVASPEDLWRLVESGTDAITGFPADRGWTTTEPGQGGFLADAAGFDAAFFGISPREALAMPQQ
RLLLETSWEAFERAGIAPLSLRGSDTGVIYIGAYPDGYGIGADLGGFGTTAGSPSVLSGRVSYFFGLEGPAITVDTAC
10 SSSLVALHQAGYALRNNECSLALVGGVTVMATPEVFSAFALQDGLAADGRSKAFSDGADGAGFSEGVGVLLVERLS
AQANGHQILALVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANASLTPADVDVIEAHGTGTTLGDP'IEAQALLATY
GQGRSVPLLLG'SVKSNLGHTQAAAGVTGVIKMMALRHGVVPRTLHVDEPSRHVDWSAGAVELVTSNREWPVTD
RPG RAGVSSFGISGTNAHVILEAVPVVSAVSTGGEVQPLVVSARTAPAAEDLASRLRTYLADTPD TDQRAAAATLALTRS
VFEHRTVLLGDDTITGAAMPDPRVVVFVSGQGSQRAGMGEQLAAVFPVFAE'IERVWALLDVPDGLDIDDTGHAQPA
15 LFALQVALSGLLESWGVRPDAVIGHSIGELAAAYVSGVWSLEDACALVSARARLMQALPPGGVMVAVPVPEAEARTV
LRDGVEIAAVNGPSSVVLSGDEDAVLQAVSGFAKWTRLKTSHAFHSAHMDPMLDEFRTVAERLTYRRPSVEMAAGHG
VTTAEYWVRQVREAVRFGDQTTAYEDAVFVEIGPGRTLARLIDGITMLHGDTEREAALTGLSQLFVRGVDVDWATVI
EDTTARILDLP'TYPFQHERYWAGRWLAGLAPDKRDAALLTMVRDSAARVLGHADGSAISPTATFRDLGVDSLTA
VEL RNRLARTAGLRLATTIVF'DYPTPTALAAHL

20
SEQ ID NO: 65
EPLAIVGMACRLPGGVASPEDLWRLVESGTDAITGLPTDRGWDLGAVAAESYCVEGGFLDGVAGFDAAFFGISPREA
LAMDPQQRLLETSWESLERAGIAPLSLRGSDTG'VFMGAYPGGYGAGADLGGFGTTSGAASVLSGRISYFFGLEGPA
MTVDTACSSSLVALHLAGQALRN'GECSLALVGGVTVMAAPDIFPEFARQ'RLASDGRSKAFADSADGTGWSEGVGV
25 LVERLSDAQANGHQILALVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANASLTPADVDVIEAHGTGTTLGDP'IEA
QALLATY GQGRSVPLLLG'SVKSNLGHTQAAAGVTGVIKMMALRHGVVPQTLHVDEPSRHVDWSAGAVELVTSNREW
PVTDRPGRAGVSSFGISGTNAHVILEAVPSDTPAPT'TTDAVLPLVVSTRTAPAAEDLTARLRAYLSAAPETDQRAAA
ATLALTRSVFEHRAVVLGEDTITGVAVPDPRVVVFVSGQGSQRAGMGEQLAAAYPVFAA'IERVWALLDVPDGLDVD
DTGHAQPALFALQVALSGLLESWGVRPAAVIGHSIGELAAAYVSGVWSLEDACVLVSARARLMQALPPGGVMVAVPV
30 PEAEARAVLRDGVEIAAVNGPSSVVLSGDEDAVLQAVSGFAKWTRLKTSHAFHSAHMDPMLDEFRAVAERLTYRRPS
VEMAAGDRVTTAEYWVRQVREAVRFGDQTTAYEDAVFVEIGPGRTLARLIDGITMLHGDTEREAALTGLSQLFVRGV
DVDWATVIEDTTARILDLP'TYPFQHEHYWLRRRAARTPAERAQELLKLVRDNAAAVLGHADGRTVPAAAAFRDLGVDS
LIAVELRNNLALATGLQLPTTIVF'DYPTASSLAERL

35
SEQ ID NO: 66
EPLAIVGMACRLPGGVESPEDLWRLVESGADAI SGFPTDRGWDADGLFDPDLAVGKTYCVQGGFLQTAAEFDPAFFG
ISPREALAMPQQRLVLETSWEAFERAGIEPGSLKGS'DTG'VFMGAYPGGYGMGADLGGFAATAGAGSVLSGRVSYFF
GFEGPAMTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMAS'PQSFVEFSRQRGLAADGRSKAFADAADGTGWA
EGVGVL'LLVERLSDAQAKGHRILAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANASLTPADIDVVEAHGTGTTL
40 GDPIEAQAVIATY GQDRSTPLLLGSLKSNIGHTQAAAGVSGVIKMMALRHGVVPQTLHVDQPSRHVDWSAGAVELV
TSNQPWPSSE'RRRAGVSAFGVSGTNAHVILESAPVEPVGA'EAGLVPVVADVLPWVVSAKSAPALRALEQRLRAYEA
ADERTVVATLATARATF'DHRAVLIGTETVTGPLMTDPRVVVFVFPQGWQWLGMGREL'RGSSVVF'AERMAECAALSE

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FVDWDLFTALDDPAVVDRVDVVQPVCWAVMVSLAAVWQAAGVNPDAVVGHSQGEIAAAVVAGSLSLRDGALVVALRS
QLIKGLAGRGAMASIALPADQIDLVEGAWIAALNGPSSSTVIAGTPEAVEQVLAAQDARVRRIAVDYASHTPQVEAIR
DELLELTAEVLSRKPDVPWLSTVDNTWVEGPLPADYWFRNLREQVGFAQAVVTLGDVAVFVEVSASPVLIQSMGDAVT
VATLRRDDGSATRMVTSLAEAYVQGVQVNWGAVLGAGTERALDLPTYPFQRQHYWALERLGERAGTERHRLMLEVVL
5 GHAASVLGHSSAAALEPDRPFKDLGMDSLTAIELRNHLVAETGLRLPATMVFDFTADALAGHL

SEQ ID NO: 67

EPIAVVSMACRLPGGVDTP EGLWRLVESGTD AISGFPTDRGWDLTDFYSADPQGGFLTGA AEF DAGFFGISPREALG
MDPQQRL LLETTWEA IERAQLDPRSLRGRDVG VYVGGA AQGYGVGFAGEPRDNA ITASSISLLSGRVSYALGLQGPG
10 VTVDTACSSSLVALHLACQALRQRECSLALVGGVSVIATPDVFAEFSRQNGLAADGRCKSF GAAADGTGWSEGVGML
VLERLSEATR HGHRI LAVVRGSAVN SDGASNGLTAPNGQSQQRVIRQALSNAGLAASD VDVVEAHGTGTRLGDPIEA
EAILATYGQDRAAPAWLGSLKSNIGHTMAASGVLGVIKMVEAMRHGTVPRTLHVDEPSPHVDWSAGR VALLTENQPW
PDGAKPRRAGVSSFGLSGTNAHV VLEQHPEPASPV PARETGVPVPWVLSAQSPKALQEQA GR LHAA LVSDPRWHPLDV
AFSLATTRSAFTHRTAVVASGRDLL EALSTLATSATATSTTARTRRVAFLFDGQGTQRAGM GRELYERHPAFARAWD
15 EVSAAFDKHLEHPLHAVYFGAGALDELVDDTGYAQAAIFTFEVALFELLHEWGVRPDFVAGHSIGEVA AAYVSGLFS
LADAAQLIVARGRALRSAPPGAMAALRAGETETREFLARTGTALDVA AVNSPEAVV VSGSPEAVAEFTA AWTA SGRR
ARRLNVNRAFHSRHVDGLLDDFRAVLES LTCRTDTVLPMVSTVTGRLIDPAELRTPQYWLSQVRD TVRFQDAVAELA
ANGVGVFVEVGPSSSLASAGTETLGDEAHFQALQHSRTPADPALLTALAGLHSGGVGVDWEKVLVGGRAVELPVYPF
QHRAYWLAPASTQEPATMLELVRFEVA AVLGM PDPAAVFEETS FLELGFD SLSAVRLRNRLTRSTGVELPATLLFDH
20 PTPAELAAHL

SEQ ID NO: 68

EPLAIVGMACRLPGGVASPEDLWRLVESGTD AISDFPTDRGWDVEGLYDPDPDVPGKSYAVKGGFLDAA GFDA AFFG
ISPREEAAMD PQQRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAMANGYGAGADLGGFGATAGAGSVLSGRISYFF
25 GLEGPAMTVDTACSSSLVALHQASFALRQGECSLALVGGVTVMPTPQLFVEFARQRGLAVDGRSKAFADAADGSGFS
EGVGVLVVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALDNAGLSSMDVDVVEGHGTGTRL
GDPIEAQAVISTY GQDRERPLLLGSLKSNIGHAQAAAGVSGVIKMVMALRHGVVPQTLHVDEPSRHVDWAAGAVELV
TENQPWPVAERARRAGVSSFGISGTNAHVILESAPAEAA SASEPVTPPSEVSVPVVASDVVPLVVS AKTPGALTDIE
ERLRGYLAAAPEADMQAVASTLAATRSVF EHRVLLGDDTITGIATPDPRVVFVFPQGQWQWLGMGSVLRETSPVFA
30 GRMAECAAAALREFVDWDLFSVLDDPTVVDRVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGH SQGEIAAACVAGAVS
LRDAARIVALRSKLIGARLGHGAMASIALPADAITLTDGAWIAAHNGPASTVIAGTPQAVDTVLAAYEAQGIRVRR I
TVDYASHSPQVEEIHTELLDATATVGSQTPAVPWLSTVDGAWVEGPLDADYWYRNLR EPVRFDQAVTHLQTQGETVF
IEVSASPALTPAMNDDAITVATLRRDDDSPTRILTALAEAFVQGVGVDWPAVTGATTARVLDLPTYAF'QRQRYWTLS
GLAAAERRQALAKLVRESAAVVLGHADPDSPAAA AFKDLGVDSLTAVELRNSLGRSTGLRLPATMVFDYPTPDALA
35 ARLD

SEQ ID NO: 69

EPLAIVGMACRLPGGVDSPEDLWRLVESGTD AISGFPTDRGWDLD SLYDPILGASGEFYSAQGGFLDRAADF DASF
GISPREALAMD PQQRLVLEVSWEALERAGIEASSVRGSDTG VFMGAMANGYGIGADFGAFGMTASAGSVLSGRVSYF
40 FGLEGPAMTVDTACSSSLVALHQAGYS LRQGECSMALVGGVTVMPTPQTFVEFARERGLAVDGRSKAFADAADGSGF
SEGVGVLVVERLS DARARGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLASADVDVVEAHGTGTR
LGDPIEAQAVIETY GQDRERPLLLGSLKSNIGHTQAAAGVSAVIKMVMALRHGVVPQTLHVDEPSRHVDW TAGAVEL

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ATEKLPWPASDRVRRAGVSSFGISGTNAHVILESVPAEVVSPSESSGPNLASDVVPLVVSAKTSGALVDIEERLRGY
LAAVPGVDLGAVASVLAGSRSVFGHRGVLVGGELVSGVALSGPRVVFVFSGQGSQCVGMGERLAGVFPVFAEVYGRV
WDLLDVPGSGLGVDDTG FVQPALFALQVGLFGLLESWGVRPEVVVGHSVGEVAAGYVAGLWSLEDACVLVSARARLM
QGLPGGGVMVSVSVSEERARAALVEGVEIAAVNGPSSSVVLSGDEAAVVGVAEGLGGRWRRLATSHAFHSARMDPMLD
5 EFRVVAEGLEYREPRIVMAGGAGVVSPEYWVRQVRD TVRFGDQVAAYQGDAVFVEVGPGGSLARLIDGVAVGDGEDE
VRAAVMAVAELFVRGVDVDWPAVVGT TATPVDLPTYPFQRQRYWTASWLVALEPEERGQALLRMVREGASVVLGHAD
ARAVEVDRAFRDLGVDSLTA VQVRNNLAKATGLRLPATMVFDYPTPAALAAARLD

SEQ ID NO: 70

10 EPLAIVGMACRLPGGVASPEDLWRLVESGTDVISGFPTDRGWDLDNLYDPDPAVGKSYCVQGYFLDDVADFDASFFG
ISPREALAMDPQQRLILEASWEAFERAGIEPGSVRGSDTG VFMGAFSSGYGIGADHSGFGMTAGAGSVLSGRISYLE
GLEGPAMTVDTACSSSLVALHQASSALRQGECSLALVGGVTVMPTPQTFLEFARQ RGLAADGRSKAFSDAADGSGFS
EGVGVLVVERLS DARARGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLSSADVDVVEAHGTGTRL
GDPIEAQAVIETYGQDRERPLLLGSLKSNIGHTQAAAGVSAVIKVMALRHGVVPQTLHVDEPSRHVDWTAGAVQLA
15 TEKQPWPASDRARRAGVSSFGISGTNAHVILESAPVHSVETDETAPMALASDVVPLVVSAKTSGALVDIEERLRGYL
AVAGSEVDLGAVASVLAGSRSVFGHRGVLVGGELVSGVALSGPRVVFVFSGQGSQCVGMGERLAGVFPVFAEVYGRV
WDLLDVPGSGLGVDDTG FVQPALFALQVGLFGLLESWGVRPEVVVGHSVGEVAAGYVAGLWSLEDACVLVSARARLM
QGLPGGGVMVSVSVSEERARAALVEGVEIAAVNGPSSSVVLSGDEAAVVGVAEGLGGRWRRLATSHAFHSARMDPMLD
EFRVVAEGLEYREPRIVMAGGAGVVSPEYWVRQVRD TVRFGDQVAAYQGDAVFVEVGPGGSLARLIDGVAVGDGEDE
20 VRAAVMAVAELFVRGVDVDWPAVVGT TAA PVDLPTYPFQRQRYWTQTWLTGLASEDRRQALLKVVRDSAATVLGHAD
AGMIPATAAFKDLGLDSLTA VELRNSLGKSTGLSLPATMVFDYPTPDALADRLD

SEQ ID NO: 71

EPLAIVGMACRLPGGVASPEDLWRLVESGTD AISDFPTDRGWDVEGLYDPDPA PGKSYAVKGGFLDAAGFDAAFFG
25 ISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAFAPAGYGGDREGFGATAGAGSVLSGRVSYFFGL
EGPAITVDTACSSSLVALHQAGYSLRQGECSLALVGGATVMATPQTFVEFSRQRGLSVDGRSKAFADAADGTGWAEG
VGVLVVERLS DAQAQKGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLSSADVDVVEAHGTGTKLGD
PIEAQAVIATY GQDRERPLLLGSLKSNIGHTQAAAGVSGVIKVMALQHGVVPQTLHVDEPSRHVDWAAGAVELVTE
NQPWPVAERARRAGVSSFGISGTNAHVILESAPAEAA SASEPVTPPSEASVPVVASDVVPLVVSAKTPGALTDIEER
30 LRGYLAAA SDVDMAAA STLAATRSVF EHRVLLGDDTITGIATPDPRVVFVFPGQGWQWLGMGSVLRETS PVFAGR
MAECAALGEFVDWDLFSVLDDPTVVD RVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGH SQQGEIAAACVAGAVSLR
DAARIVALRSKLIGARLGHGAMASIALPAGDVALVDGAWIAAHNGPASTVIAGTPQAVDTVLA AHEAQGIRVRRITV
DYASHSPQVEEIHAE LLDATAAVGSQAPAVPWLSTVDGAWVEGPLDADYWYRNLREPVRFDQAVTLLQTQGETVFIE
VSASPALTPAMNDDAITVATLRRDDDSPARIL TALAEAFVQGVGVDWPAVTGATT SRVDLPTYPFQHQR YWAWLAGL
35 APEARQALLKV VRESAAVVLGHTGADTVPVTA AFKDLGLDSLTA VELRNSLGRSTGLRLPVTAVFDYPTPAALAAAR
LD

SEQ ID NO: 72

EPLAIVGMACRLPGGVASPEDLWRLVESGRDVISDFPVDRGWDLDNLYDPDPAVGKTYCKRGGFLDAAAEFDAAFFG
40 ISPREEAAMPDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAFANEY GAGADFGAFGMTAGAGSVLSGRVSYLF
GLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMPTPQLFVG FARERGLAVDGRSKAFSDAADGAGWA
EGVGVLVVERLS DAQAARGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLSSADVDVVEAHGTGTRL

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GDPIEAQAVIATYGQDRERPLLLGSLKSNIGHTQAAAGVSGVIKMVMALRHSVVPRTLHVDEPSRHVDWAAGAVELV
TEKQPWPTSDRARRAGVSSFGISGTNAHVILESAPAQPLETDEALVPVVASDVMPPLVVS AKTPDALTDIEDRLRAHL
AAAPEADMQAVASTLAATRSVFEHRAVLLGDDTITGVAASGPRVVFVFPQGQWQLGMGSVLRETSPVFAGRMAECA
AALREFVDWDLFSVLDDPTVVDVRVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGHSQGEIAAACVAGAVSLQDAARI
5 VALRSKLIAGHLAGHMASIALPADAITLTDGAWIAAHNGTASTVIAGTPQAVDTVLATHEAQGIRVRRITVDYASH
SPQVEEIHTELLDATATVGSQTPAVPWLSTVDNTWISRPLD TDYWYRNLREPVRFDQAVTLLQTQGETV FIEVSASP
ALTPAMNDDAVTVATLRRDDDSPTRILTALAEAFVQGVGVDPAVTGATTT PVDLPTYPFQRQRYWTASWLAGLAPE
ARGQALLKVRESTAVVLGHVD TETVPATAPFKDLGLDSL TAVQVRNGLAKATGLRLPATMVFDYPTPAAL AARLD

SEQ ID NO: 73

EPLAIVGMACRLPGGVASPEDLWRLVESGTD AISDFPTDRGWDVEGLYDPDPDVPGKSYAVKGGFLDAAGFDAAFFG
ISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDIGVFMGAMANEYGAGADFGAFGMTAGAGSVLSGRVSYFF
GLEGPAMTVDTACSSSLVALHQAGSALRQGECSMALVGGVTVMPTPQTFVEFARQ RGLATDGRSKAFADAADGSGFS
EGVGVLVVERLSDARARGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLASADVDVVEAHGTGTRL
15 GDPIEAQAVIETYGQDRERPLLLGSLKSNIGHTQAAAGVSAVIKMVMALRHGVVPQTLHVDEPSRHVDW TAGAVQLA
TEKQPWPASDRARRAGVSSFGISGTNAHVILESAPVHSVETDETAPMALASDVVPLVVS AKTSGALVDIEERLRGYL
AAVPGVDLGAVASVLAGSRSVFGHRGVLVGGELVSGVALSGPRVVFVFSGQGSQCVGMGERLAGVFPVFAEVYGRVW
DLLDVPGSGLGVDDTG FVQPALFALQVGLFGLLESWGVRPEVVVGHSVGEVAAGYVAGLWSLEDACVLVSARARLMQ
GLPGGGVMVSVSVSEDRARAALVEGVEIAAVNGPSSVVL SGDEAAVVGVAEGLGGRWRRLATSHAFHSARMDPMLDE
20 FRVVAEGLEYREPRIVMAGGAGVVSPEYWVRQVRD TVRFGDQVAAYQGDAVFVEVGPGGSLARLIDGVAVGDGEDEV
RAAVMAVAELFVRGVDVDWPAVVGT TATPVDLPTYPFQRQRYWAWLTGLASEDRRQALLKVVRDSAATVLGHADARA
VEVDRAFRDLGVDSL TAVQVRNNLAKATGLRLPATMVFDYPTPAAL AARLD

SEQ ID NO: 74

EPLAIVGMACRLPGGVASPEDLWRLVESGTD AISDFPTDRGWDVEGLYDPDPDVPGKSYAVKGGFLDAAGFDAAFFG
ISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAFTNGYGTGADLDGFGATAGTGSVLSGRVSYFF
GLEGPAMTVDTACSSSLVALHQAGYSLRQGECSMALVGGVTVMPTPQTFVEFARQ RGLATDGRSKAFADAADGSGFS
EGVGVLVVERLSDAQARGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLASADVDVVEAHGTGTRL
GDPIEAQAVIETYGQDRERPLLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVVPQTLHVDEPSRHVDWSAGAVELA
30 RERQPWPVAGRARRAGVSSFGISGTNAHVILESAPVHSVETDETAPMALASDVVPLVVS AKTSGALVDIEERLRGYL
AAVPGVDLGAVASVLAGSRSVFGHRGVLVGGELVSGVALSGPRVVFVFSGQGSQCVGMGERLAGVFPVFAEVYGRVW
DLLDVPGSGLGVDDTG FVQPALFALQVGLFGLLESWGVRPEVVVGHSVGEVAAGYVAGLWSLEDACVLVSARARLMQ
GLPGGGVMVSVSVSEERARAALVEGVEIAAVNGPSSVVL SGDEAAVVGVAEGLGGRWRRLATSHAFHSARMDPMLDE
FRVVAEGLEYREPRIVMAGGAGVVSPEYWVRQVRD TVRFGDQVAAYQGDAVFVEVGPGGSLARLIDGVAVGDGEDEV
35 RAAVMAVAELFVRGVDVDWPAVVGT TATPVDLPTYPFQRQRYWAWLTGLASEDRRQALLKVVRDSAATVLGHADARA
VEVDRAFRDLGVDSL TAVQVRNNLAKATGLRLPATMVFDYPTPAAL AARLD

SEQ ID NO: 75

EPLAIVGMACRLPGGVDSPEDLWRLVESGTDVISGFPTDRGWDLDNLYDPDPAVGKSYCVQGYFLDDVADF DASFFG
40 ISPREALAMDPQQRLILEASWEAFERAGIEPGSVRGSDTG VFMGAFFSSGYGIGADHSGFGMTAGAGSVLSGRVSYLF
GLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGATVMPTPQTFVEFARQ RGLATDGRSKAFADAADGAGWA
EGVGVLVVERLSDAQARGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLSSADVDVVEAHGTGTRL

GDPIEAQAVIETYGQDRERPLLLGSLKSNIGHTQAAAGVSAVIKMMALRHGVVPQTLHVDEPSRHVDWTAGAVQLA
TEKQPWPASDRARRAGVSSFGISGTNAHVILESAPAQPLETDEPSAPIVASDVVPLVVS AKTLDALTDIEDRLRGYL
AAASDVDMAAVASTLAATRSIFEHRAVLLGDDTITGIATPGPRVVVFVFPQGQWQLGMGSTLRETSPVFAARMAECA
AALREFVDWDLFSILDDPTVVDRVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGHSQGEIAAACVAGAVSLQDAARI
5 VALRSKLIAGHLAGHGAMASIALPADAITLTDGAWIAAHNGTASTVIAGTPQAVDTVLATHEAQGIRVRRITVDYASH
SPQVEEIHTELLDATTTINPRTPAVPWLSTVDNTWISRPLD TDYWYRNLREPVRFDQAVTLLQTRGETV FIEVSASP
ALTPAMNDDAITVATLRRDDDDSPARILTALAEAFVQGVGVDWPAVTGATTARVLDLPTYAFQHORYWATAWLAGLAP
AERGEALLKVVSDTVARVLGHADGRTIPATAAFKELGVDSL TAVELRNRLSAATGLRLPATMVF DYPSPGALAGWL

10 SEQ ID NO: 76
QPLAIVGMACRLPGGVASPEDLWRLVESGTD AISDFPVDRGWDLEGLYDPASDEPGVLYCDQGGFLDAAAGFDAAFF
GISPREAAAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAMANGYGAGADLGGFGATAGAGSVLSGRISYF
FGLEGPAMTVDTACSSSLVALHQASFALRQGECSLALVGGVTVMPTPQTFVEFARQ RGLAADGRSKAFSDAADGAGW
AEGVGVLVVERLSDAQAKGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLSSAEVDVVEAHGTGTR
15 LGDPIEAQAVIATY GQDRERPLLLGSLKSNIGHAQAAAGVSGVIKMMALRHGVVPQTLHVDEPSRHVDWAAGAVEL
VTENQPWPVAERARRAGVSSFGISGTNAHVILESAPAEASASEPVTPPSEASVPVVASDVVPLVVS AKTPGALTDI
EERLRGYLAAAPEADMQAVASTLAATRSVFEHRAVLLGDDTITGVAASGPRVVVFVFPQGQWQLGMGSVLRETSPVF
AGQMAECA AALREFVDWDLFSVLDDPTVVDRVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGHSQGEIAAACVAGAV
SLRDAARIVALRSKLIGARLGHGAMASIALPAGAITLTDGAWIAAHNGPASTVIAGTPQAVDAVLAAYEAQGIRVRR
20 ITVDYASHSPQVEEIRAELLDATATVGSQAPVVPWLSTVDGAWVEGPLDADYWYRNLREPVRFDQAVTLLQTQGETV
FIEVSASPALTPAMNDDAITVATLRRDDDDSPARILTALAEAFVQGVGVDWPAATGATT SRVDLPTYPFQHORYWTQT
LSGLAAAERRQALAKLVRESAAVVLGHADPDSVPAAAAFKDLGVDSL TAVELRNSLGRSTGLRLPATMVF DYPTPDA
LAARLD

25 SEQ ID NO: 77
EPLAIVGMACRLPGGVDSPEDLWRLVESGTD AISGFPTDRGWDLDSLYDPILGASGEFYSAQGGFLDRAADF DASFF
GISPREALAMDPQQRLVLEVSWEALERAGIEASSVRGSDTG VFMGAFSSGYGTGSDFGAFGATSSAGSVLSGRISYF
FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGITVMSTPLTFAEFARQ RGLAPDGRSKAFSDAADGAGF
SEGVGVLVVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLASADVDVVEAHGTGTR
30 LGDPIEAQAVIATY GQDRERPLLLGSLKSNIGHAQAAAGVSGVIKMMALRHGVVPQTLHVDEPSRHVDWAAGAVEL
VTENQPWPVAERARRAGVSSFGISGTNAHVILESAPAEASASEPVTPPSEASVPVVASDVVPLVVS AKTPGALTDI
EERLRGYLAAASDVDMAVVASTLAATRSVFEHRAVLLGDDTITGVAASGPRVVVFVFPQGQWQLGMGSVLRETSPVF
AGRMAECA AALREFVDWDLFSVLDDPTVVDRVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGHSQGEIAAACVAGAV
SLRDAARIVALRSKLIGARLGHGAMASIALPADAITLTDGAWIAAHNGPASTVIAGTPQAVDAVLAAYEAQGIRVRR
35 ITVDYASHSPQVEEIRAELLDATATVGSQAPVVPWLSTVDNTWISRPLD TDYWYRNLREPVRFDQAVTLLQTQGETV
FIEVSASPALTPAMNDDAITVATLRRDDDDSPARILTALAEAFVQGVGVDWPAVTGATTARVLDLPTYPFQRQRYWAW
LTGLASEDRRQALLKVV RDSAATVLGHADARAVEVDRAFRDLGVDSL TAVQVRNNLAKATGLRLPATMVF DYPTPAA
LAARLD

40 SEQ ID NO: 78
EPLAIVGMACRLPGGVASPEDLWRLVESGTDVISGFPTDRGWDLDNLYDPDPAVGKSYCVQGYFLDDVADFDASFFG
ISPREALAMDPQQRLILEASWEAFERAGIEPGSVRGSDTG VFMGAFSSGYGIGADHSGFGMTAGAGSVLSGRISYLF'

GLEGPAMTVDTACSSSLVALHQASSALRQCECSLALVGGATVLATPYGFVEISRQRGLAADGRSKAFSDAADGMSFS
EGAGVLVLERLSDAQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIIQQALANAGLASADVDVVEAHGTGTRL
GDPIEAQAVIATYGQNRERPVLGSLKSNIGHTHAAAGVSGVIKMMALQHGVPRTLHVDAPSRHVDWAAGAVELV
TENQPWPVAERARRAGVSSFGISGTNAHVILESAPAQPLETGEPSAPIVASDVVPLVVS AKTPDALTDIEDRLRAHL
5 AAPEADMQAVASTLAATRSIFEHRAVLLGDDTITGIATPDPRVVFVFPQGQWQWLGMGSTLRETSPVFAARMAECA
TALREFVDWDLFSILDDPTVVDRVDVLQPACWAVMVSLAAVWQEAGVSPDAVIGHSQGEIAAACVAGAVSLQDAARI
VALRSKLIHLAGHGAMASIALPADAITLTDGAWIAAHNGPASTVIAGTPQAVDTVLATHEAQGIRVRRITVDYASH
SPQVEEIRAELLDATATVGSQAPVVPWLSTVDGAWVEGPLDADYWYRNLRFPVRFDQAVTLLQTQGETV FIEVSASP
ALTPAMNDDAVTVATLRRDDDSPTRILTALAEAFVQGVGVDWPAVTGATTTPVDLPTYPFQRQRYWTIASDRLSGRTS
10 GDQHRIMLELVLGHAASVLGHGAADAVAADKPFKDLGMDSLTAIELRNHLVAETGLRLPATTAFDHPTADDLARRL

SEQ ID NO: 79

EPIAIVSMACRAPGGVDSPDGLWRLVESGTD AISGFPTDRGWDVADLYSPDPAGYKSYCVQGGFLDTAADFDAAFFG
ISPREALGMDPQQRLLLEASWEAIERARIDPRSLRGRSVGVFVGGASQGYGAGADDQQQSNAITGGSISLLSGRVSY
15 ALGLEPGVTVDTACSSSLVALHLASQALRQRECSLALVSGVSVMATPDVFVEFSRQRGLAPDGRCKSFSAADGTG
WSEGVGVLVLERLSEATRLGHRVHAVVRGSAVNSDGASNGLTAPNGASQQKVIRQALANAGLAASEVDAVEAHGTGT
KLGDP IEAEAILATYGQDRAAPVWLGSLKSNIGHTMAASGVLGVKMMVESMRHG LLPRTLNVDEPSPHVDWASGDVA
LLTENQPWPADVGPRRAAVSSFGISGSNAHVVLEQYGEPA GPDLSDLTNTRAVNAADAPDRRQPVPLMLSARSQRAL
REQAGRLHAALAGAPDWRPLDIGYSLATTRSHFTHRAVAVGSGRELLRALSKLADGADWPALTTRI AKSRRVAFLED
20 GQGTQRLGMGSGLYAGFPVFAGVWDQVSAAFDKHLDHSLTDVFLGRDDRPAAAELVDDTLYAQAGLFTLEVALFRLL
EEWGVRPDFLAGHSIGEAAAAYAGGMFSLEDVTALIVARGEALRLAPPGAMLALRASEEEVREFLGRTGAELDLAAV
NGPASVVVSGASEAVADFRARWTAAGRKARELNVSRAFHSRHVEAGLGRFREVLES LTFGTPVLP IVSTVTGQLVDP
VEMSTPEYWLRQVRQPVLFQDALRELSGQGVNTFVEIGPSGTLASAGLECLGGDASFHAVQQPRSPQDVGLMTAVAE
LHAGGTAVDWAKALAGGRATDLPVYPFQHESYWLAPADYAYPEEPGTMLELVRLEAAKVLGITEPDTILEETSFLDL
25 GFDSLGTMLRLRNRLSEVTELDLPATLLFDNPSPAELAAYLD

SEQ ID NO: 80

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISHFPTDRGWDLDNLYDPDPDAPCKGYRVQGGFLDAAGFDAAFFG
ISPREAQAMDPQQRLVLEASWEAFERAGIDPGAMRGSH TGVMGAMANGYGAGADLGGFGATAGAVSVLSGRVSYLF
30 GLEGPAMTVDTACSSSLVALHQAAYS LRQCECSLALVGGVTVMPTPQMFEVEFARQRGLAADGRSKAFADAADGAGFS
EGVGVLVVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANARLAPNEIDVVEAHGTGTTL
GDPIEAQALIAAYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMMALQHGVPRTLHVDSPSRHVDWTAGAVELV
TENQPWPAIDRARRAGVSSFGISGTNAHVILESAPAQP VVE'EEVPAPPVVASDMMPLVISAKTPSALVEFEGR LRA
YLTSTPGVDMRAVASTLAGTRSVFEHRAVLLGDET VTGPGTGAGSGVAVSDPRVVFVFPQCQSQRAGMGEQLAAVFP
35 VFAEIHQQVWDLLDVPDPGLD TDETG YAQPSLFALQVALFGLLESWGVRPQAVIGHSVGEIAAGYVAGLWSLRDACT
LVSARARLMQTLPTGGAMVAVPVSEKQAQAALTDGVEIAAVNGPSSVVL TGDETAVLETAALGRSTRLT TSHAFHS
ARMEPVLDEFRTVAETLDYRTPHIPMAAGDAVVTPEYWVRQIRDTVRF GDQVAAHENAVFVEIGPDRTLSRLTDGIA
MLHGDNETQTAITATLHTHG VNIHWP AVIGATTARVLDMP TYAFQHQR YWTTWLAGLAPEERKQALLKVVRDSAA
AVLGHAGADTVPVTA AFKDLGLDSL TAVELRNSLGKSTGLRLPATMVFDY PNPTTLAARLD
40

SEQ ID NO: 81

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDIENLYDPDPDAPGKGYRVQGGFLDRAAEFDASFF

GISPREAQAMDPQQRLVLETSWEAFERAGIEPCAMRGSDTGVFMGAMANGYGTGADLCAFCMTSAAVSVLSGRVSYL
F'GLEGPAMTVDTACSSSLVALHQAAYSLRQGECSLALVGGVTVMPTPQTF'VEFARQRGLAADGRSKAF'SDAADGAGF'
SEGVGVLVVERLSDARAKGHHVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALDNAGLSSTDVDVVEAHGTGTT
LGDPIEAQALIAAYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMMALQHGVPRTLHVDSPSRHVDWTAGAVEL
5 VTENQPWPAIDRARRAGVSSFGISGTNAHVILESAPDLPVVETEETPAPVVTSDMMPLVISAKTPAALADMEGRLRS
YLTSMPGVDMRAVASTLAGTRSVF'EHRVLLGDETVTGPGTGVAVSGPRVVFVFPQGGSQRAGMGEQLAAVF'PVFAE
IHQQVWDLLDVPDPGLGADETGFAQPSLFALQVALFGLLESWGVRPQAVIGHSVGEIAAGYVAGLWSLRDACTLVSA
RARLMQTLPTGGAMVAVPVSEKQAQAALTDGVEIAAVNGPSSVVLTGDETAVLETAALGKSTRLTTSFAFHSARME
PVLDQFRTVAETLDYRTPHIPMAAGDAVVTPEYWVRQIRDTVRFGDQVAAHENAVF'VEIGPDRTLSRLTDGIAMLHG
10 DNETQTAITALATLHTHGVNIHWPAVIGATTTTPVDLPTYAFERQRYWAWLAGLAPEERKQALLKTVRDNAAKVLGHA
DARDIAVNTAFRDLGLDSLTA VQVRNSLAKATGLRLPTTTTFDYPNPTALATHLD

SEQ ID NO: 82

EPLAIVGCMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWDLDNLYDPDPDTPGKAHNVQGGFLDAAGFDASFFG
15 ISPREAQAMDPQQRLVLETSWEAFERAGIDPASVRGSDTGVFMGAFSGSYGTGADLGFGATAGAVSVLSGRVSYLF
GLEGPAMTVDTACSSSLVALHQAASSALRQDECSLALVGGVTVMPTPQTFVEFARQRGLAADGRSKAFADAADGAGFS
EGVGVLVVERLSDARAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQSALDNAGLSSTDVDVVEAHGTGTTL
GDPIEAQALIAAYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMMALQHGVPRTLHVDEPSRHVDWTAGAVELV
TENQPWPAIDRARRAGVSSFGISGTNAHVILESAPDLPVVETEEVPAPPVVASDLMPLVISAKTPSALADMEGRLRA
20 YLTATPGVDMRAVASTLAGTRSVFEHRVLLGDDTVTGPGVAVSGPRVVFVFPQGGSQRAGMGEQLAAVFPVFAEIH
QQVWDLLDVPDPGLDIDETGFAQPSLFALQVALFGLLESWGVRPQAVIGHSVGEIAAGYVAGLWSLRDACTLVSARA
RLMQTLPTGGAMVAVPVSEKQAQAALTDGVEIAAVNGPSSVVLTGDETAVLETAALGKSTRLTTSFAFHSARMEPV
LDQFRTVAETLDYRTPHIPMAAGDAVVTPEYWVRQIRDTVRFGDQVAAHENAVF'VEIGPDRTLSRLTDGIAMLHGDN
ETQTAITALATLHTHGVNIHWPTIVGTTTTPVLDLPTYAFQHORYWTSWLAGLAPEERKQALLKTVRDSAAAVLGHVG
25 TDTVPATAAFKDLGLDSLTA VELRNSLGKSTGLRLPATMVFDYPNPTALAAARLD

SEQ ID NO: 83

EPLAIVGCMACRLPCGVSSPEDLWRLVESGTD AISGFPTDRGWDIENLYDPDPALGRITYTVQCGFLDIAGFDAAFFCI
SPREAQAMDPQQRLVLEASWEAFERAGIEPGSMRGSDTGVFMGAFSSGYCAEHEGFGATAGAVSVLSGRVSYFFGLE
30 GPALTVDTACSSSLVALHQAAGYSLRQGECSLALVGGVTVMPTPQTFVEFSRQRMVVDGRSKAFADAADGAGWAEGV
GVLVVERLSDARAKGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLSSADVDVVEAHGTGTRLGDP
IEAQAVLATY GQDREQPLLLGSLKSNIGHAQAAAGVSGVIKMMALQHGVPRTLHVDSPSRHVDWTAGSVELVTEN
QPWPVLERARRVGVSSFGISGTNAHVILESAPDPDVAVVEVEETPAPPVVVISAKTPSALADMEGRLRAYLAARPGV
DVRVAVASTLAGTRSVFEHRVLLGDDTVTGSTGTGSGAAVSGVAVSGPRVVFVFPQGWQWLGMGCGLRETSAVFA
35 GR LAEC AAALSEFVDWDL LTVLDDPSVVD RVDVLQPACWAVMVSLAAVWQEAGVVPDAVIGH SQGEIAAACVAGALT
LRDAARIVALRSRLIARLAGQCAMASIALPAHEIVLCDGAVVAARNGPAATVVAGTARAVERVLAVHEKECARVRI
TVDYASHSPQVEEIRTEL LDILATTGSRTPVVPWLSTVDGTWTEQPLDPDYWYRNLREPVG FHPAVDTLRSMGETVF
IEISASPTLTPAMDDATTVATLRRDNDTPQQILTALAEAH THGVNIHWPAIIGTTTTTPARVDLPTYAFQHORYWTSW
LAGLAPEERKQALLKMVRDSAAAVLGHAGADTVPVTA AFKDLGLDSLTA VELRNSLGKSTGLRLPVTMVFDYPNPTT
40 LAARLD

SEQ ID NO: 84

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDIENLYDPDPDAAGTTYTVQGGFLDIAGFDASFFG
ISPREALAMDPQQRLVLETSWEAFERAGIEPSSMRGSDTGVFMGAF'TNGYGAGVDF'GAF'GGASAAVSVLSGRVSYFF'
GLEGPAITVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMPTPQLFVDFS RQRGLAADGRSKAFADPADGAGFS
5 EGVGVLVVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALDNARLAPNEIDAVEAHGTGTTL
GDPIEAQALIATYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVPRTLHVDSPSRHVDWTAGAVELV
TENQPWPAIDRARRAGVSSFGISGTNAHVILESAPDPDVPVVEETEETPPPPVVVISAKTPSALADMEGRLRAYLAAT
PGVDVRAVASTLAGTRSVFEHRAVLLGDDTVTGTSTGTGSGAAVSGVVVSGPRVVFVFPQGQGWQLGMGCGLRETS
VFAGRLAECAAALSEFVDWDLTTLVDDPSVVD RVDVLQPACWAVMVSLAAVWQEAGVVPDAVIGHSQGEIAAACVAG
10 ALTLRDAARIVALRSRLIARLAGQGAMASIALPAHEIALGDGAVVAARNGRAATVIAGTARAVDRVLAVHEKEGARV
RRITVDYASHSPQVEEIRTEL LDILATTGSRTPVVPWLSTVDGTWTEQPLDPDYWYRNLREPVG FHPAVDTLRSMGE
TVFIEISASPTLTPAMDDATTVATLRRDNDTPQQILTALAEATHGVNIHWPAIMGATTTRVDLPTYAFQH QRYWTS
WLAGLAPEERKQALLKVVRDSAAKVLGHAGADTVPVTA AFKDLGLDSL TAVELRNSLGKSTGLRLPATMVF DYPNPT
TLAARLD

15
SEQ ID NO: 85

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDIENLYDPDPDAPGKGYRVQGGFLDRAAEFDASFF
GISPREAQAMDPQQRLVLETSWEAFERAGIEPGAMRGSDTGVFMGAMANGYGTGADLGAFGMTSAAVSVLSGRVSYL
FGLEGPAMTVDTACSSSLVALHQAA YSLRQGECSLALVGGVTVMPTPQTFVEFARQ RGLAADGRSKAFSDAADGAGF
20 SEGVGVLVVERLSDARAKGHHVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALDNAGLSSTDVDVVEAHGTGTT
LGDPIEAQALIATYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVPRTLHVDSPSRHVDWTAGAVEL
VTENQPWPAIDRARRVGVSSFGISGTNAHVILESAPAQPVVETE EVPAPPVVASDMMPLVISAKTPSALVEFEGR LR
AYLTSTPGVDMRAVASTLAGTRSVFEHRAVLLGDDTVTGPDTGTGAGSGVAVSDPRVVFVFPQGQSQRAGMGEQLAA
VFPVFAEIHQQVWDLLDVPDPGLGADETGF AQPSLFALQVALFGLLESWGVRPQAVIGHSVGEIAAGYVAGLWSLRD
25 ACTLV SARARLMQTLPTGGAMVAVPVSEKQAQAALTDGVEIAAVNGPSSV VLTGDETAVLETA AALGKSTRLTTS HA
FHSARMEPVLDQFRTVAETLDYRTPHIPMAAGDAVVTP EYWVRQIRD TVRFGDQVA AHENAVFVEIGPDRTLSRLTD
GIAMLHGDNETQTAITALATLH THGVNIHWP AVIGATTARVLDLPTYAFERQRYWAWLAGLAPEERKQALLKVVRDS
AAAVLGHADARDIAVNTAFRDLGLDSL TAVQVRNSLAKATGLRLPTTTVF DYPNPTALATHLD

30
SEQ ID NO: 86

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWDLDNLYDPDPDTPGKAHNVQGGFLDAAGF'DAAFFG
ISPREALAMDPQQRLVLETSWEAFERAGIDPASVRGSDTGVFMGAFGSGYGTGADLGGFGATAGAVSVLSGRVSYLF
GLEGPAMTVDTACSSSLVALHQASSALRQDECSLALVGGVTVMPTPQTFVEFARQ RGLAADGRSKAFADAADGAGFS
EGVGVLVVERLSDARAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALDNAGLSSTDVDVVEAHGTGTRL
35 GDPIEAQALIATYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVPRTLHVDSPSRHVDWTAGAVELV
TENQPWPAIDRARRVGVSSFGISGTNAHVILESAPAQPVVETE EVPAPPVVASDMMPLVISAKTPSALVEFEGR LR
YLTSTPGVDMRAVASTLAGTRSVFEHRAVLLGDDTVTGPDTGTGAGSGVAVSDPRVVFVFPQGQSQRAGMGEQLAAV
FPVFAEIHQQVWDLLDVPDPGLD TDETGYAQPSLFALQVALFGLLESWGVRPQAVIGHSVGEIAAGYVAGLWSLRDA
CTLVSARARLMQTLPTGGAMVAVPVSEKQAQAALTDGVEIAAVNGPSSV VLTGDETAVLETA AALGRSTRLTTS HAF
40 HSARMEPVLDDEFRTVAETLDYRTPHIPMAAGDAVVTP EYWVRQIRD TVRFGDQVA AHENAVFVEIGPDRTLSRLTDG
IAMLHGDNETQTAITALATLH THGVNIHWP AVIGATTARVLDMP TYAFQH QRYWTTWLAGLTPEERKQALLKTVRDS
AAAVLGHADARDIAVNTAFRDLGLDSL TAVQVRNSLAKATGLRLPTTTVF DYPNPTALATHLD

SEQ ID NO: 87

EPLAIVGMACRLPGGVSSPEDLWQLVESGTD AISHFPTDRGWDIDNLYDPDPDTPGKTYCVQGYFLDGIAEFDASFF
GTSPREALAMDPQQRLVLETSWEAFERAGIDPASVRGSDTGVMGAFSSGYGTGADLGGFGATAGAGSVLSGRVSYL
5 FGLEGPAMTVDTACSSSLVALHQAGYSLRQGECSLALVGGVTVMPTPQAFVEFSRQRGLAADGRSKAFADAADGAGW
AEGVCVLVVERLS DARAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRSALDNARLAPNEIDVVEAHGTGTR
LGDPIEAQALIAAYGQDREQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVPRTLHVDEPSRHVDWTAGAVEL
VTENQPWPAIDRARRAGVSSFGISGTNAHVILESPPAQPVVETEEVPAPPVVASDMMPLVISAKTPSALADMEGRRLR
AYLAARPGVDVRAVASTLAGTRSVFEHRAVLLGDDTVTGTSTGTGSGAAVSGVVVSGPRVVFVFPQGQWQWLGMGCG
10 LRETSAVFAGRLAECAAALSEFVDWDL LTVLDDPSVVD RVDVLQPACWAVMVSLAAVWQEAGVVPDAVIGH SQGEIA
AACVAGALT LRDAARIVALRSRLIARLAGQGAMASIALPAHEIALGDGAVVAARNGPAATVIAGTPRAVD RVLAVHE
KEGARVRRITVDYASHSPQVEEIRTEL LDILATTGSRTPVVPWLSTVDGTWTEQPLDPDYWYRNLREPVGFHPAVDT
LRSMGETV FIEISASPTLTPAMDDATTVATLRRDNDTPRQILTA LAEAH THGVNIHWPTVIGTTTTTPARVDLPTYAF
QHCRYWTSWLAGLAPAERDEALLKMVRDSAALVLGHAGGRTIPVAAAFKDLGVDSL TAVELRNRLSAATGLRLPATL
15 VFDYPNPAALAGWL

SEQ ID NO: 88

QPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWDIENLYDPDSPGEGEAYS AQGGFLDAA GFDAAFFG
ISPREAQAMDPQQRLVLEASWEAFERAGIDPGAMRGSH TGVMGAMANGYGAGADLGGFGATACAGSVLSGRISYLF
20 GLEGPAMTVDTACSSSLVALHQAA YSLRQGECSLALVGGVTVMATTQT FVEFARQRGLAADGRSKAFADAADGAGWA
EGVGVLVVERLS DARAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRSALDNAGLSSADVDVVEAHGTGTTL
GDPIEAQALIAAYGQDREQPVLLGSLKSNIGHAQAAAGVSGVIKMVMALQHGVPRTLHVDSPSRHVDWTAGAVELV
TENQPWPVTERARRAGVSSFGISGTNAHVILESAPDPDVPV VETEKVPAPPVVVISAKTPSALVEFEGRRLRAYLAAR
PGVDVRAVASTLAGTRSVFGHRAVLLGDDTVTGTSTGTGSGAAVSGVVVSGPRVVFVFPQGQWQWLGMGCGCLRETS A
25 VFAGRLAECAAALSEFVDWDL LTVLDDPSVVD RVDVLQPACWAVMVSLAAVWQEAGVVPDAVIGH SQGEIAAACVAG
ALT LRDAARIVALRSRLIARLAGQGAMASIALPAHEIALGDGAVVAALNGPAATVIAGTPRAVD RVLAVHEKEGARV
RRITVDYASHSPQVEEIRTEL LDILATTGSRTPVVPWLSTVDGTWTEQPLDPDYWYRNLREPVGFHPAVDTLRSMGE
TVFIEISASPTLTPAMDDATTVATLRRDNDTPQQILTA LAEAH THGVNIHWPTVMGATTTRVDLPTYAFQHCRYWTS
WLAGLAPEERKQALLKVVRDSAAAVLGHAGTDTPVPTAAFKDLGLDSL TAVELRNSLGKSTGLRLPATLVFDYPNPT
30 TLAARLD

SEQ ID NO: 89

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPTDRGWDIENLYDPDPDAPGTGYRVQGGFLDRAAEFDASFF
GISPREALAMDPQQRLVLETSWEAFERAGIEPGSVRGSDTGVMGAFSSGYGTGADFGAFGATSAAVSVLSGRVSYF
35 FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMSTPLTFAEFARQRGLAADGRSKAFADAADGAGF
SEGVGVLVVERLS DARAKGHRVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLSSADVDVVEAHGTGTR
LGDPIEAQAVLATY GQDREQPLLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVPRTLHVDSPSRHVDWTAGAVEL
VTENQPWPVLERARRAGVSSFGISGTNAHVILESAPDPDLPVVEVEETPAPVVAVISAKTPSALVEFEGRRLR TYLTA
RPGVDVRAVASTLAGTRSVFGHRAVLLGDDTVTGTGP GAAVSGVVVSGPRVVFVFPQGQWQWLGMGCGCLRETS AVFA
40 GR LAECAAALSEFVDWDL LTVLDDPSVVD RVDVLQPACWAVMVSLAAVWQEAGVVPDAVIGH SQGEIAAACVAGALT
LRDAARIVALRSRLIARLAGQGAMASIALPAHEIALGDGAVVAARNGPAATVIAGTPRAVD RVLAVHEKQGARVRI
TVDYASHSPQVEEIRTEL LDILATTGSRTPVVPWLSTVDGTWTEQPLDPDYWYRNLREPVGFHPAVDTLRSMGETVF

IEISASPTLTPAMDDATTVATLRRDNDTPQQILTALAEATHGVNIHWPTVMGATTTTPVRVDLPTYAFERQRYWAWL
AGLTPEERKQALLKTVRDSAAAVLGHTDARDIAMNTAFRDLGLDSLTAVQVRNSLAKATGLRLPTTTTVE'DYPNPTAL
ATHLD

5 SEQ ID NO: 90

EPLAIVGMACRLPGGVSSPEDLWQLVESGTDASHFPTDRGWDIDNLYDPDPDTPGKTYCVQGYFLDGIAEFDASFF
GISPREAQAMDPQQRLVLETSWEAFERAGIDPASVRGSDTGVMGAFGSGYGTGADLGGFGMTAGAGSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQASSALRQGECSLALVGGTTVLATPYGLVEISRQRGLAADGRSKAFSDAADGMGF
SEGVGVLVVERLSDARAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRSALDNAGLSSADVVDVVEAHGTGTR
10 LGDPIEAQAVLATYQDREQPLLLGSLKSNIGHTHAAAGVSGVIKVMALQHGVVPRTLHVDEPSRHVDWTAGAVEL
VTENQPWPAIDRARRAGVSSFGISGTNAHVILESPPAQPVEVEETPAPPVVASDMMPLVISAKTPSALADMEGRRLR
AYLAARPGVDVRAVASTLAGTRSVFEHRAVLLGDDTVTGTSTGTGSGAAVSGVVVSGPRVVFVFPQGQWQWLGMGCG
LRETSAVFAGRLAECAAALSEFVDWDLTLVDDPSVVDRVDVLQPACWAVMVSLAAVWQEAGVVPDAVIGHSQGEIA
AACVAGALTLRDAARIVALRSRLIARLAGQGAMASIALPAHEIALGDGAVVAARNGRAATVIAGTARAVIDRVLAVHE
15 KEGARVRRIAVDYASHSPQVEEIRTELLEDILATTGSRTPVVPWLSTVDGTWTEQPLDPDYWYRNLREPVGFHPAVDT
LRSMGETVFIEISASPTLTPAMDDATTVATLRRDNDTPRQILTALAEATHGVNIHWPTVIGTTTTTPARVDLPTYAF
QHORYWTSDRNLNGRTGLEQHRVMLELVLGHAASVLGHSAPDAIAADRPFKDLGMDSLTAIELRNHLVAETGLRLPAT
TAFDHPTADDLAKRL

20 SEQ ID NO: 91

EPPIAIVSMACRVPGGVDSPEGLWHLVESGTDASIDFPTNRGWDVANLYSPDPAGYTSYCVQGGFLDSAADFDTFFG
ISPREALGMDPQQRLVLEASWEAIERAQIDPRSLRGSNVGVFVGGASQGYGASANEQQQSNAITGGSSSLLSGRVTY
ALGLEGPAVTVDACSSSLVALHLASQSLRQRECSLALVSGVSVMATPDVFVEFSRQRGLAPDGRCKSFSASADGTG
WSEGVGVLVLERLSEATRLGHRVLAVVRGSAVNSDGASNGLTAPNGASQQRVIRQALANAGLTASQVDAVEAHGTGT
25 TLGDPIEAALLATYQQRSTPAWLGLKSNIGHTMAASGVLGVKMEAMRHGLLPRTLHVDEPSPHVDWASGDIA
LLSESRPWPDCSTPRRAGVSSFGISGTNAHVVLEQYRDPAGPDPTGTGSDTQTCPETTTEHGPLPLMLSARSPKALRE
QAGRLHAALVEAPRWRPLDIGYSLATTRSSFHRAVAVGSDRELLRALSQADGGTSPALVTATAKAGRVAFLEDGQ
GTQRLGMGSGLYERFPARTWDLVSAAFDKHLNHSITDVFLGRSGSVTAELVDDTLYAQAGIFTMEVALFELLDEW
GIRPDFLTGHSIGEAAAAYGAGMLSLEDVTTLIVARGQALRLSPPGAMVALRASEEEVREFLDRTGAALDLAAVNSP
30 TSVVVSGAPDAVSDFRATAWTESGREARALNVRHAFHSRHVEAGLGRFREVLDSLTFRAPVLPVVSTVTGRLVEPAEM
STPEYWLRQVRQTVRFHDALRELSGRGVGTTFVEIGPSGTLASAGLECLGGDAAFHAVQRPRSAEDVCLMTAVAEHA
CGTAVDWTKVLAGGRRTDLPVYPFQHEAYWLTPAEPSYAEELTTLELVCSEAANVLGITEPGILLEDSSFLDLGLD
SLGAMRLRNRLSELTELDLPATLLFDNPNPTDLAAYLD

35 SEQ ID NO: 92

EPLAIVGMAARFPGGVASADDLWRLVVSGGDAIGGFPTDRGWDLDLYDPDPAATGRSYVREGGFLSDATTFDASFF
RIGPREAKAMDPQQRLLETSWEAFEHAGIRPETLRGTATAVFAGISLQDYGVLAGSDPELEGYAGTGNAPSVLSGR
LSYFYGLEGPAVTIDTACSSSLVALHLAQSLRRDECTLAVVGGVTVMPSPNVFVEFSRQRGLAPDGRCKPFAAAD
GTGWSEGAGVLVVERLSDARRNNRRI LAVVRGSAVNQDGASSGLTAPHGPSQQRVIRAALAAAGLTAGDVDVVEAHG
40 TGTTLGDPPIEAQGVLATYGDRKGAPVRLGSVKSNLGHTQAAAGVAGVIKMQALRHGVMPSRLHIDEPSPHVDWTAG
RVELLTSNLPWPASERPRRAAVSSFGISGTNAHVILEQAFFPATEPEPPFTPVVSGPELPLIFSAKDPDALAAQTRVT
DGPGVAYALATSRSMDHRTVRLGDMTVTGIAVTDPEVVVFVFPQGTQWAGMGRDLMEASPVFAERMNECAALEPY

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50869-016WO2

LDLWAAIDAPDHVETLQPASWAMMVSLAAVWQAAGVQPAAVIGHSQGEIAAACVSGAISLQDAAAVVALRSKAIAAS
LGKGAMASIPLPADAIELTGEVWVAALNGPSSSTVVAGVPEAVELVRARYEGRRIAVDYASHTPHVEALRGQVVSVP
QAPVIPWFSTVDSGWVEGPLDDDDYWFRNLRQPVQFGPAAAGFDNAVFIIEVSARPVLIPALEASVTVP
SLRRDDGGPE
RMLASLAQAFVAGVPVDWTTIVAPAPFVELPTYPFQGERYWIDPRTLDEVLAVVRDSAATVLGHTDPTAITPDRSFK
5 DLGFDSLAAVQLRNHLLTATGVRLSATAVFDFPTPVVLAGEV

SEQ ID NO: 93

EPIAVVGMACRLPGDVSSPEDLWRLVSEGRDAVGPFPPADRGWEPGDAAYARVGGFVTGATGFDAGFFGISPREAQAM
DPQQRLLLEVAWEAFERAGIAPDELRGSDTGCVFVGTYGQGYGELAVDGDAGEYVGIGNSGSVVSGRVSYFFGLEGPA
10 VTVDTACSSSLVALHQAQALRQGECSLALVGGVTVMSSPLIFQEFARQGGLAADGRCKAFADGADGTGWGEGVGVL
VVERLSEAQRRGHTVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRAALASAGLGVGDVDLVEAHGTGTALGDPIEA
QALLATYGS DGSPVWLGSLKSNIGHTQAAAGVAGVIKAVEAMRHGVMPRTLHVDQPS SHVDWSAGAVELLTANRPWD
SGGRPRRAAVSSFGISGTNAHVILEESPSAPVPPEPGTAPLLLSARSPAALAQFESRTAGLRPSRDLASTLSRRALF
DHRAVVLPDGD TVRGGVGDAPLVFVFAGQGSQRADMG SRLAEFPVF AAAYERVWSLLDVDESLEVDHTGFAQPALF
15 AFEVALAELLGVRPDAVIGH SVGELAAAYVAGAMSLEDACRLVSARARLMQALPSSGGVMVSVRVSEEAARTVLRDGV
EIAAVNGPQAVVLSGDEDAVLAAAELGEFKRLRTSHAFHSARMEPMLEEFRAVASTVAFDEPQIALSFVPSAEYFV
RQVRET VRFGEQVA AFAPGTLFVEVGPDGSL SRLTGGSAAEPMKALAYLWVRGVGVWDTPYIGDGRLLDDAPTYPFQ
PERYWPEQRRRARHGDFLALVTATAAVVLGHPEGTDIPADTPFQSLGLDSL SAVDLRNQLAQATGVRLSPTAVFDYP
TPRALAERL

SEQ ID NO: 94

DP IAI VGMACRYPGGVATADDLWDLVAEGGDAVGPFPPVDRGWDLAALYDPDPEAAGKSYVREGGFLGGAADFDAFF
GISPREALAMDPQQRLLLETAWAEFEHAGIDPLDLRRSDTGCVFVGTM AQEYGGLVTD SAHGLEGWIGTGNSQSVMSG
RLSYFFGLQGP AVTVDTACSSSLVALHQAQALRN GECALAVVGGVTVMSSPRTFQEF SRQRGMAPDGRCKPFAAAA
25 DGTGWSEGVGV LVVERLSEARRNGH AVLAVVRGTAVN QDGT SNGLTAPNGPAQQQVIRAALERAGLGVGDVDVVEAH
GTGTALCDPIEAQA ILD TYGSRTGGEPVRLG SVKSNL GHTQAAAGVAGVIKMVQAMRHATMPRSLHIDEPSPHVDWA
SGAVELLTAERGWPATDRPRRAAVSSFGISGTNAHVIVEGVADPELSREASPGGPLPFVLSAPTAEALSAQETR LRR
FRVERPDVDERDIAITLAGRTGFAHRTVLIGDLTVSGVAVADRRVVFVFPGQGTQWAGMGRDLMAASPVFAERMNEC
AAALEPYLDLWEAIDSPDRVETLQPASWAVMVSLAAVWQAAGVQPAAVIGH SQGEIAAACVSGAISLQDAAAVVALR
30 SKAIGASLGKGAMASIPLPADAIELIDEVWIAALNGPSSSTVVAGAPEAVEQIRARYDGRRIAVDYASHTPHVEALRG
QVVSVP SRAPAIPWFSTVDSAWVEDPLDEDYWFRNLRQPVQFGPAAAGFDNAVFIIEVSARPVLIPALEDAVTVP TLR
RDDCGIDRLHASVAQAWTAGADV DWAALLPAGGRRIALPPYAF THERFWPRRPTAACQDLLTVVRTAAATVLGHRDA
ARVPADRAFKELGFDSL SAVQLRNELLTATGVRLSATAVFDHPTAAALAEAL

SEQ ID NO: 95

EPIAI VGMACRLPGDVSSPDELWELVEAGRDAVGPFPPADRGWNLSTLFDPPDPAPGKSYVREGGFLTGAGLFDADFF
GISPREALAMDPQQRLLLEMAWEAFERAGIAPDELRGSDTG VYVGTYAQGYGELAAATAGEG FVGIGNSGSVVSGRV
SYFLGLEGPAVTVD TACSSSLVALHQAQALRLGEC SMALVGGVTVMASPLMFQEF SRQRGLSPDGRCKAFAESADG
TGWGEGVGVL VVERLSEARRRGHTVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRAALASAGLTVGDVDLVEGHGT
40 GTALGDPIEAQALLATYGSAGSPVWLGSLKSNIGHTQAAAGVAGVIKMVQAMRHGVMPRTLHVDQPS SHVDWSAGAV
ELLTANRPWD SGGRPRRAAVSSFGISGTNAHVILEGVPAP EPAAGDAETAPLVLSARTAPALTDLEARVSARPSSPD
LAATLAGRASFDHRAVVLPDGEVVRGRAGAAPVVLV FAGQGSQRADMASRLAGEFPVF AAAYERVWSLLDVDEALDT

DQTGFAQPALFAYEVALAELLNVRPDAVIGHSIGELAAAYTSGSLSLEDACRLVSARARLMQALPPGGAMVSVRVSE
EVAREVLRDGVIEIAAVNGPQAVVLSGDEDAVLAAAAKLGEFKRLRTSHAFHSARMEPMLLEEFRAVALTVEFREPEVA
LSFVPSAEYFVGQVRETVRFGEQVASFEPGTLFVEVGPDGSLSRLTGGVSAAEPLTALAYLWVHGVAIDWVPYLGGG
RLDLGAPTYPFQHERYWPARALAQLPPARRGRALLDLVQNRVAKTLGLVRPADPGRAFTDLGFTSLTALELRNSIAE
5 ETGLPMPASLVFDHPNARSLAGYLD

SEQ ID NO: 96

EPLAIVGMACRLPGGISSAEELWRLVAEGGDAIGPFPGDRGWDVDALYDPDPAAGHTYTRSGGFLPGATDFDAAFFG
ISPREAQAMDPQHRQLLETSWEALEHAGIDPAGLRGRDVGVFAGFSGQDYIAEMGVGPAEAGGYQVTGRAASVLSGR
10 LSYFYGLEGPAVTVDTACSSSLVALHLAGQSLRDGESSLALVGGVTVMSSPGLFVEFSRQRGLAPDGRCKAFSADAD
GTGWSEGVGVLVVERLSDARRNGHRILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALAQSGLSVADVVDVVEAHG
TG TALGDPIEAQAVLATYGGRAGGEPVRLGSLKSNIGHTQAAAGIASLIKMVQAIRYGVMPTLHVSEPSPLVDWAS
GRVELLTSDIPWPDGVRRAAVSAFGISGTNAHVILEEAPAPAAVPSIRPVVSGPALPLVFSARDPSALAAQTRVTDG
PGVAYALATSRTMLDHRTVRLNDVTVTGIAVTDPEVVVFVFPQGGSQWAGMGRDLMGSSPVFAERMNECAALEPYLD
15 LWAAIDAPDRVETLQPASWAVMVSLAAVWQAAGVQPAAVIGHSSQGEIAAACVSGAISLQDAAAVVALRSRAIAASLG
KGAMASIPLPADAIELADEVWVAALNGPSSTVVAGALEAVEQVRARYEGRRIAVDYASHTPHVEALRGQVVSVPSPA
PAIPWFSTVDSGWIEGPLDDDYWFRNLRQQVQFGPAAAGFDNAVFIEVSARPVLIIPALDASVTVP SLRRDDGGPERM
LASLAQAFVAGVPVDWTTIVPPAPHVELPSYPFQRQRHWIDMERLGQLPPGDRDRFLDLVRDAAA AVLGHGSRETV
PASAAFKELGFDSLIAVQLRNAVSAATGVRLPATVTFDHPTPQALAAALL
20

SEQ ID NO: 97

EPLAIVGMACKFPGGVDSPERLWEMLEAGEDVIGPFPDDRWDVDGGYDPDPEKAGSWYARAGGFLAGAADFDAFF
GINPREALAMDPQQRLLEVAWEAFERSGIAPDSL RGTDTGVFVGTGQGYGRLVSAGAPGLEAYS GTGNTG SVASG
RLSYVFGLEGPAVTVDTACSSSLVALHQASQSLHRGEC SLALVAGVTVMSTPDSFVEFSRQRGLSPDGRCKAFAAAA
25 DGTGFSEGAGVLVVERLSDAQRNHQILAVVRGSAVNQDGASNGLTAPHGPSQQRVINTALTDADLT TTDIDLVEAH
GTGTTLGDP IEAQAILATYGNRTTGNPVHLG SVKSNLGH TQAAAGVAGVIKVIQAMRHATMPKSLHIDQPSPHVDWT
AGRVELLTGNRPWPATDRPRRAAVSSFGVSGTNAHVILEERAAAEQPPAVDGPVPLVLSARTPEALTAQEEAVRGL
STDDRHRVAPALALGRAALPHRAVLLGDSVIRGTASADDGRPVFLFPGQGAQWAGMGRELMAASPVFAERMRECAVA
LAGFVDWDLFAVLDDAEALRRTEIVQPASWAVMVSLAALWESWGVH PAAVVGHSQGETAAAVVACAIGLRD GARLSA
30 TRSRVLALLAGHGALASIALPAAEVEVVDGVSVA AVNGPRATLISGDPAGVEAVTARYEASGVRVRRI PADVASHSP
HVERAEETLLTALAGIEARVPGVPWLSTATGDWITEPVDERYWYRNLRSPVLFHPAITTLRDRGHRLFLEISTHPQL
LPAMEDDLLTVGSLRRDDGGPDRMHTALAEAWAGGADV DWPVAVLGAGPVRALDLPTYPFQRRRFWPEAALPPVERDR
ALVEIVRDQAAAVLGHPDAGALTPGTAFRDLGFDSLTA VQLRNHLATATGLTLPATVIFDHPTPRALATFLD

35 SEQ ID NO: 98

EPLAVVGMACRLPGGVASPDQLWDLVVSGGDGIGPFPADRGWPTDDIFDPDPDAPGKTYVREGGFLDGAGEFDAAFF
GISPREALAMDPQQRLLETSWEAFEHAGIDPAGLRGGDTGVFVGGFTQAYGVGTADLEGYAATGTVGSVLSGRLSY
FYGFEGPAVTVDTACSSSLVALHQAGQALRQGECTLAVVGGVTVMPTPVVFQEF SRQRGLATDGRCKAFAD EADGTG
FAEGAGVLLVCRLSDARRDGRRILAVVRGSAVNQDGASNGLTAPHGPSQQRVIRAALANARLGPGDVLDLIEGHGTGT
40 TLGDPIEAQALLATHGSGASPVRLGSLKSNIGHTQAAAGVAGVIKVIQALRNGLMPRTLHAGTPSSRV DWSAGNVEL
LTSNLPWPAADRPRRAAVSSFGISGTNAHVILEEAPAAA VPTISPVVSGPALPLVFSARDPSALAAQTRVTEGP GV
AFALATTRSMFEHRAVRIGDFS VSGAAVADRRVVFVFPGQGTQWAGMGRDLMSASPVFAERMNECAALEPYLDLWE

AIDSPDRVETLQPASWAVMVSLAAVWQAAGVQPAAVIGHSQGEIAAACVAGSITLQDAAAVVALRSRAIAASLGKGA
MASIPLPAEQIELAGEVWVAALNGPSSTVVAGLPEAVEQVRARYEGRRIAVDYASHTPHVEALRGQVVSVP SRAPAI
PWFSTVDSGWIEGPLEDEDYWFRNLRQPVQFGPAAGRFD DAVFIEVSARPV LIPALEDAATVP SLRRDDGGGDRMLAS
LAQAFVAGVPVDWTTIIPPAPFVELPSYPFQHRRYWIDSS EDALRDLVREQAAAVLGYPDPSRITPGVAFRDLGFDS
5 LTAVQLRNALSAATGLRLSATVAFDHPTPAALAAAL

SEQ ID NO: 99

EPIAIVGMACRLPGGVSSPDELWELVESGRDAIGPFPADRGWNLDELYDPDPDAAGRSYVREGGFLTGAADF DAGFF
GINPREALAMDPQQRLVLEVAWEAFERAGIAPDSL RGTDTGVFLGAFAGGYLTLVNGAADLEGYAGTGNSVSVLSGR
10 LSYVLGLEGP AVTVDTACSSSLVALHQA AQALRLGEC SLAVVGGVTVMSTPDSHVEFSRQRALSPDGRCKAFADGAD
GTGWAEGAGVLVVERLSEARRRGHTVLA VVRGSAVNQDGASNGLTAPNGPSQQRVIRAALASAGLGVDVDLVEGHG
TG TALGDPIEAQALLATY GSDGSPVWLGS LKSNIGHTQAAAGVAGVIKAVESMRRGVMPQTLHVGT PSSHVDWAAGA
VELLTANRAWDSVERPRRAAVSSFGISGTNAHVILEGVPAP EPAAGSAESAPLLLSARSAAALAQFESLTSGLRPSR
DLASTLSRRAFFDHRAVVLPGGDVVRGRVGDAPVVLVFAGQGSQRADMASRLTAEFPVF AAAHERVWSLLDVDEGLG
15 IDQTGFAQPALFAYEVALAE LLDVRPDAVIGH SIGELAAAYVAGAVSLEDACRLVSARARLMQALPPGGAMVSVRVS
EEAARAVLRDGVEIAAVNGPQAVVLSGDEDAVLAAA AELGEFKRLRTSHAFHSARMEPMLDEFRAVALTVEFREPEV
ALS FVPSAEYFVRQVRET VRFGEQVA AFAPGTLFVEVGP DGSLSRLTGGVSAAEPLTALAYLWVRGVGV EWTPTYVGG
GILDQGAPTYPFQRERYWVRPRLAGRTTDERDALLIDLVRDDVASVLGHSGRRRLETDRPLLELGFDSL TALRLNR
LAAATDVALPATLIFDYPNIQAI AVHL

20
SEQ ID NO: 100
EPLAVVGMACRYPGGVASADDLWRLVAAGGDAVGPF PDDRGWELES LVDPDPEAVGRSTTGQGGFLADAAGFDAAFF
GISPREATAMDPQQRL LLEVSWAALEHAGLRADALRG SATGVFMGSNGQDYAGLLAGAPELEGWIGTGVSASV VSGR
LSYFYGFEGPAVTVD TACSSSLVALHLAAQSLRTGESS LALVGGVTVMTSPTVFRSFSRQRGLAPDGRCKAFSAGAD
25 GTGWSEGVGV LVVERLSDAQRN GHQILAVVRGSAVNQDGASNGLTAPHGPSQQRVINTALTDADLTTT DIDLIEAHG
TGTTLGDP IEAQAILATYGNRTTGNPVHLG SVKSNLGH TQAAAGIAGI IKAIQAMRHATMPRTLHIDEPSPHVDWTA
GRVELLTSNLPWPATGRPRRAAVSSFGVSGTNAHVILEEAPAPA AVPSIRPVVSGPALPLVFSAKDPDALAEFQSHT
PAGEGVAYALATS RSTLDHRSVRIGDVTVTGIAVTDPEVVFVFP GQGTQWAGMGRDLMSASPVFAERMNECAALEP
YLDLWAAIDAPDRVETLQPASWAMMVSLAAVWQAAGVQPAAVIGH SQGEIAAACVSGAISLQDAAAVVALRSKAIAA
30 SLGKGAMAS IPLPADAIELTGEVWVAALNGPSSTVVAGVPEA VELVRARYEGRRIAVDYASHTPHVEALRGQVVSVP
SQAPVIPWFSTVDSGWVEGPLDDDYWFRNLRQPVQFGPAAAGFDNAV FIEVSARPV LIPALDASVTVP SLRRDDGGP
ERMLASLAQAFVAGVPVDWTTIVPPAPHVDLP SYPFQHQRFWIEGRVTAAAGAERLRIMLEV VLAETATVLGHCGAA
AIGPGRAFQDLGFDSL TAVELRNRLAAATGLTLPTTLVFNHPTPEALAAHL

35 SEQ ID NO: 101
EPVAIVGMACRLPGDVESPEDLWRLVAEGRDAVGPFPSDRGWN LGTLDDPDAGRSYVKEGGFLAGAAHFDPAFFGI
GPREALGMDPQQRILLEIAWEALEHARIA PGDLRGSETGVYVGAAAQGYGVDA PLEGNLLTGGSTSAMSGRVAYALG
LHGPAVTVD TACSSSLVALHLAAQALRHGECTLALAGGVAVMASPVLFTEFSRQRGLAPDGRCKAF AAAADGTGWSE
GAGLVVLERLSDAERHGH RVLA VIRGSAVNSDGASNGLTAPNGTAQRRVIRSALRAAGLGAGDVDVVEAHGTGTTLG
40 DPVEADALIATYQ RSDTPPVRIGSLKSNIGHTVAAAGVAGVIKMVEAMRHGTMPRTLHVDRPTPHVDWSAGAAELL
TGELPWPRGDRPRRAAVSAFGLSGTNAHLILEDVAAA AEPPAGDDSGSGSETVPLLLSADDLP AVRDQAARLRAHLL
AHPELMRDVA YALATTRTARPHRAAVTATERELLRELALLAAGDQGP GTQLGEAVPHRRVAF'LF DGQGTQRHGMGR

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50869-016WO2

ALHQRHPVFAAAWDEVCAALDPLLDRGVAEVYFAEAGRDLADDPLYTQAGLFALEVALYRLLTSWGVTPDAVAGHSV
GEVAVAHVAGVLSLPDAASLLAARGAALRQLPPGAMAAIRASEDDTRGVLPDLDVAAVNGPEMTVVSGAEEAVDRF'
VAEQAGAGRQVRRRLRVGRAYHSRHVDAVLAEFGATLSALTFHEPTLPVVSTVTGRPAGAGDLTTPEYWLRHARRPVR
FGAALASLSELGMDSFVEVGPSGSLSSMAGETVAGTFHPLLDRRVPDEIGAAAAAGELFTAGMALDWTAVLAGGRP I
5 DLPVYPERREFYWL GARYDLMAAAVRRDALLDLVRVQVALLGRADAIGVRDNTSFLDVGLDSL GASRLRNRLAAAT
GLTLPGGLA F'DHPTPARLADHLD

SEQ ID NO: 102

EPLAIVGMACRLPGGVWSPEDLWHLVASGTD AISDFPADRGWDVEKLFDPDPDAPGKTYCVQGGFLEATAAFDAAFF
10 GISPREALAMDPQQRLMLEVSWEAFERAGIEPGSVRGSDTG VFLGAYPGGYGAGAGADLGGFGATGGAGSVLSGRVS
YFFGLEGPAMTVDTACSSSLVALHQAAYS LRQRECSLALVGGVTVMGTPHMFVDFS RQRGLSVDGRCKAFADAADGT
SWSEGVGVLLVERLSDAQAKGHRVLAVVKGS AVNQDGASNGLTAPNGPSQQRVIRQALANADLAPHEVDVVEAHGTG
TTLGDPIEAQALLATY GQDREQPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHGVVPRTLHVDEPSRHVDWSAGAV
ELVTQNQPWPSSDRPRRAGVSSFGVSGTNAHI ILESAPAQPLAPSTPITGLVPLVISAKTAPALTA FEARLRSYVTA
15 DADLTAIAATLATRSTFEHRAVLLGDDTVTGIATPDPRVVFVFPQGQGWQLGMGSALRETSVVFKERMAECAAALS
EFVDWDLFSVLDDPAVVDRVDVVQPACWAVMVSLAATWQAAGARPD AVVGHSQGEIAAACVAGAI SLQD GARVVALR
SQLIARLAGHGAMASIALPADQITLTDGVWIAARNGPAATVIAGAPEAVDSVLA AHQDARVRRITVDYASHTPHVEK
IRDELLPMLADIDSQTPLVPWLSTVDGLFIEGPLKADYWYRNLREQVGFD TAVNQLPDSIFIEVSASP VLLPGMGDA
LTVATLRRDEGGQERLVTALAEAYVQGVAVDWAAVIYNTTALVDLPTYPFQHEHYWLDSTRLMGLAAEERDKALVAV
20 VRESAAVVLGHADARAIPATAAFRELGVDSL TAVQLRNSLAKATGLRLPTTLAFDYPTPAVLAARL

SEQ ID NO: 103

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDLPTDRGWDLDNLYDPDPGAPGKSYCVQGGFLDTVADFDPAFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGSDTG VFMGAFGNGYGIDTDGGGFGATAGTGSVLSGRVSYF
25 LGLEGPAMTVDTGCSSALVALHQARYALRQGD CSLALVGGVTVMASPYTFVEFS RQRGMAADGRCKAFADAADGTGW
AEGVGVLLVERLSDAEAKGHQVLAVVRGSALNQDGASNGLTAPNGPSQQRVIQAALANAGLVSADVDVVEAHGTGTT
LGDPIEAQAVLATY GQDRERPLLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVVPRTLHVDEPSRHVDWSAGAVEL
VTENQPWPSPVDRPPRAGVSAFGISGTNAHV ILEAVPAPPFEPTPTVTGPVPLVISAKTRPALTA FEARLRAYVTADA
DLTAIASTLATRSIFEHRAVLLGDDTVTGI AVPDPRVVFVFPQGQGWQLGMGSALRESSV VFAERMAECAAAALSDY
30 VDWDLF SVLDDPAVVDRVDVVQPACWAVMVSLAATWQAAGVRPDAVIGHSQGEIAAACVAGAI SLRDAAQIVALRSQ
LIAGLAGHGAMASIALSADQITLTDGAWIAARNGPAATVIAGAPAAVDSVLA AHEDARTRRITVDYASHTPHVEQIR
TELLDLTTDLDSRAPVIPWLSTVDVTWVEGPLDADYWYRNLREPVGFDTAVENLPDSVFIEVSANPVLLPAMGDALT
VATLRRDAGGQTRLLTALAEAYVQGVAVDWVTVIGATPARVDLPTYAFQH QRYWVADRLHDRPSAEQHRLMRELVQR
HAATVLGHASPD TIAADRPFKDLGLDSL TAVELRNHLVAETGLRLSATTA FDHPTADDLAGHL

35
SEQ ID NO: 104
EPIAIVAMACRAPGGVSSPEGLWRLVESGTDATSGFPTDRGWDVDNLFDPDPDAAGKTYSVRGGFLETAADF DAAFF
GISPREALGMDPQQRL LLETSWEAIERAQIDPKSLRGRDVG VYVGGA AQGYGIGATDQQQENLITGSSISLLSGRVS
YALGLEGPVTVDTACSSSLVALHLASQALRQRECSLALVSGVSVMATPDVFVEFS RQRGLAADGRCKSF SAAADGT
40 TWSEGVGVVLVLQRLSEAVREGHRVLAVVRGS AVNSDGASNGLTAPNGVSQQRVIRQALAGAGLTASEVDVVEAHGTG
TKLGDPIEA EAILATY GQDRDAPAWLGSLKSNIGHTMAASGVLGVIKMVQAMRHGLLPRTLHVDEPSPHVDWARGDI
ALLTENQPWPDGTRPRRAGVSSF'GLSGTNAHV VLEEYPAPVAAAPPVTPARGGPLPWVLSAQSPNALREQAARLYAA

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LAEDPDWHPLDIGYSLATTRPCGFPHRAVAVGSDREDFQRALSKLADGAGWPGLITATAAKDRRVAFLEFDGQGTQRLG
MGRGLHRRFPVFARAWDAVSAAFAKHLDSLTDIYLGESSPTNTDLADDTLYAQAGIFTLEVALVELLQDWGVRPDF'
VTGHSIGEAAAAYVAGVLSLEDVTALIVARGKALRLTPPGDMVALRAGEADVDFLNRTGAALDLAAVNSPEAVVVS
GTPDAVADFRAAWTASGGQARNLTVRHAFHSRHVESALDEFRTTLETLTFRAPKVPLVSTATGRLVGPAELGAPEYW
5 LRQVRQTVRFEDALRDLSGRGVGTFVEIGPSGSLATAGLECLGDDASFHAVQRPRSPEDVCLMTAVAE LHAGGTTVD
WAKVLAGGRTVDLPVYPFQHRPYWIAPASYPDEPRMTRELVRLEVAGILGLSDPSVILDDSSFLELGFDSLSSLRLG
NRLATVTGLDLPSTLLFDYATPAALATHLD

SEQ ID NO: 105

10 EPLAIVGMACRLPGGVSTPEDLWRLVESGVDAISDFPADRGWDVANLFDPDAPGKTYSVRGGFLDTAADFDAAFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPSSVRGSDTGVMGAFSAGYGTELEGFGATAGAVSVLSGRVSYFFG
LEGPAMTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMASPOSFVEFSRQRGLSVDGRCKAFADAADGTGWAE
GVGVLVVERLSDAEAKGHRIQAMVRSSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLTGADV DVVEAHGTGTTLG
DPIEAQALLATYQGDRQPLLLGSLKSNVGHTQAAAGVSGVIKMMALQHGVPRTLHVDEPSRHVDWSAGAVELVT
15 QNQPWPSFDRPRRAGVSSFGVSGTNAHIILESAPAQPLAPSTPIPGLVPLVISAKTAPALTA FEARLRDYLTA DADL
TAIAATLATRSTFEHRAVLLGDDTVTGIAAPDPRVVFVFPQGQWQWLGMG SALSCESSVVFASRMAECAALSEFVD
WDLFSVLDDPAVVDRVDVVQPACWAVMVSLAATWQAAGVHPDAVVGH SQGEIAAACLAGAISLQD GARVVALRSQLI
ARLAGHGAMASIALPADQIALTDGAWIAARNGPAATVIAGAPEAVDSVLA AHGDARVRRITVDYASHTPHVEQIRAE
LLAILADIDS RPPSIPWLSTVDDALVEGPLKADYWYRNLREPVGFDTAVSALQDAVFIEVSANPVLLPAMGDAATVA
20 TLRRDDGGQDRLLTAVAEAYVQGVAVDWA AVIGATGARVLDLPTYAFQHQRFWARAASAAGLAPEALLKV VQDSAAQ
VLGYADPGAIAVTA AFKDLGIDSLTAVEMRNTLAKKTGLRLPATLVFDYPTPGVLAGRL

SEQ ID NO: 106

EPLAIVGMACRLPGGVSSPEDLWRLVESGGDAISDFPADRGWDIENLFDPDPAAGKTYSVRGGFLDAAAGFDAAFF
25 GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTGVMGAYPGGYGTGADVGGFGATAGAVSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGHALRQGECSLALVGGVTVMATPHTFIEFSRQQGLASDGRSKAFADAADGAGF
SEGVGVLVVERLS DARAKGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTGADV DVVEAHGTGTT
LGDPIEAQAVLATYQDRQKPLLLGSLKSNVGHTQAAAGVSGVIKMMALQHGVPRTLHVDEPSRHVDWSAGAVEL
VTENQPWPSVDRPRRAGVSSFGISGTNAHVILESVPVQLPVPSAGLAPLMISAKTAPALGDAEARLRGYLTADADLP
30 AIASTLATRSMFEHRAVLLGDTTITGTAAADPKVVFVFSGQGSQRAGMGEQLAFFPVFADIHRRVWDL LDVPDLDVD
QTGYAQPALFALQVALAGLLESWGVRPQAVIGH SVGELAAGYVAGLWSLED ACTLV SARARLMQALPPGGVMVAVPV
SEDQARAALLEGVEIAAVNGPSSVVLSGDETAVLQVAAGLGKWTRLSTSHAFHSARMEPML EEFRAVAEQVTYRTPV
ITMAAGAATPDYWVRQVRD TVRF'GDQVA AFEGATFVEIGPDRTLARLVDGIAM LHGDDEVEAALTGLARLF'VQGV PV
AWDNGARVLDLPTYPFQHQR YWLDARRAASAGGDLK MVRDNAALILGHTNPGA ISETTAFRDLGVDSLTA VQLRNS
35 LAKATGLRLPATLVFDYPTPSVLAGRL

SEQ ID NO: 107

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPADRGWDVDNLFDPDAPGKTYSVQGGFLDAAAEFDAAFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTGVMGAYSGGYGAGADLDGF'GATAGAGSVLSGRISYF'
40 FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLAVVGGVTVMATPDLFVEFSRQRGLAADGRCKAFGDAADGTGW
AEGVGVLLVERLSDAEAKGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIRSALATAGLAPQD VDVVEAHGTGTT
LGDPIEAQAVLATYQDRERPLLLGSLKSNVGHTQAAAGVSGVIKMMALQHGVPRTLHVDEPSRHVDWSAGAVEL

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VTQNQPWPDVDRPRRAAVSAFGVSGTNAHVILESVPAVPPVPSAGPAPLMISAKTAPALGDAEARLRDYLTDADALT
AIASTLATRSTFEHRSVIFENHTITGTAAPDPRVVFVFSGQGSQRAGMGEQLAATFPVFAEIHRRVWDLLDGPDLDD
VDQTGYAQPALFALQVALVGLLESWGVRPEAVIGHSVGELAAGYVSGLWSLEDAC TLVSARARLMQALPPGGVMVAV
PVPEDQARAALVEGVEIAAVNGPSSSVVLSGDEAAVLQVAAGLGKWTRLATSHAFHSARMEPML EEFRGVAEQLT YRT
5 PVISMAAEVATPDYWVRQVRD TVRFGDQVAEFEGATFVEIGPDRTLARLIDGIAM LHGDDEVEAALNGLARLFVQGV
PVAWDNGGRVLDLPTYPFQRQRYWAVSPEALLKAVRDSAAMILGHADPSA ISETAAFRDLGVDSL TAVELRNSLAKA
TGLRLPATLVFDYPTPAVLAARL

SEQ ID NO: 108

10 EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWD AASLFDPD PDAAGK TYSVQGGFLDAAADFDAFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGTD TGVMGAFSAGYGARLEGFGATAGAVSVLSGRVSYLFG
LEGPAMTVDTACSSSLVALHQAAYSLRQGECSLALVGGVTVMATPQIFVDFSRQRGLAPDGRCKAFGDNADGTGWAE
GVGVLVVERLSDAQAKGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTSADV DVVEAHGTGTTLG
DPIEAQAVLATY GQDRDRPLLLGSLKSNIGHTQAASGVSGVIKMVMALQHGVVPPTLHADQPSQHVDWSTGAVELVT
15 QSQPWPSVDRPRRAGVSSFGISGTNAHVILESVPAQPPVPSAGPAPLMISAKTAPALGEAEARLRDYLTDADLPAI
ASTLATRSTIFEHRAVLLGDTTITGTAAADPKVVFVFSGQGSQRAGMGEQLAFPVFADIHRRVWDLLDVPDLDVDQT
GYAQPALFALQVALAGLLESWGVRPQAVIGHSVGELAAGYVAGLWSLEDAC TLVSARARLMQALPPGGVMVAVPVSE
EQARAALTEGVEIAAVNGPSSSVVLSGDETAVLQVAAGLGKWTRLSTSHAFHSARMEPML EEFRAVAEQLT YRTPTIT
MTEEVTTPDYWVRQVRD TVRFGDQVAAFEGATFVEIGPDRTLARLIDGIAM LHGDDETEAALTGLARLFVQGV PVTW
20 DNKARVLDLPTYPFQRQRYWAGWLAGLAAEERDKALVTVVRDSVA AVLGYADSRKIPVSAAFKDLGVDSL TAVELRN
SLAKTTGLRLPATLVFDHPTLATLAARL

SEQ ID NO: 109

EPLAIVGVACRLPGGVSSPEALWQLVESGTD AISGF PADRGWDVDNLFDPDPEASGKTYCVQGGFLDAVAEFDASFF
25 GISPREALAMDPQQRLILEVSWEAFERAGIEPGSVRG SNTGVFMGAFGSGYGS DLEGFSATAGAGSVLSGRISYFFG
LEGPAMTIDTACSSSLVALHQAAGYALRQGECSLALVGGATVMATPQT FIEFSRQRGLAADGRCKSF GDNADGTGWSE
GVGALLVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLAPQDVDVVEAHGTGTRLG
DPIEAQAVLATY GQDRERPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHGVVPQTLHVDEPSRQVDWSAGAVELVT
ENQPWPDVDRPRRAAVSAFGVSGTNAHVILESAPAQP VAPSTPATGLTPLVISAKTAPALTASEARLRDYLTDADL
30 TAI AATLAATRS AFEHRAVLLGDDT VTGIAAPDPRVVFVFPGQGWQLGMGSALRDSSVVF AERMAECAALSDYVD
WDLFSVLDDPAVVDRVDV VQPACWAVMVSLAATWQAAGVRPDAVVGHSQGEIAAACVAG AISLRDGAKIVALRSQLI
ARLAGHGAMASIALPADQITLTDGVWIAARNGPAATVIAGAPEAVDSVLSAHGDARVRR IAVDYASHTPHVEQIRTE
LLPILADIDSQTPRIPWLSTVDDTWIEGPLGADYWYRNLREQVGFD TAVEHLQDSVFIEVSASPVLLPAMGDAITVA
TLRRDEGGQDRLVTALAEAYVQGV PVDWAAVIDNTTARVLDLPTYAFQHQRFWVANLTPEALLKAVRDSAATVLGHA
35 DPGTIPETA AFKDLGIDSLTAVELRNSLAKTTGLRLPATLVFDYPTPGVLAARL

SEQ ID NO: 110

EPLAIVGMACRLPGGVSSPEDLWRLVESGGDAISDFPVDRGWDVDNLFDPD PDAAGK TYSVQGGFLDTAAEFDAAFF
GISPREALAMDPQQRLVLEASWEVFERAGIEPGSVRGSDTGVMGAYPGYYGIGADLDGF GATAGAGSVLSGRVSYF
40 FGLEGPAMTVDTACSSSLVALHQA GSALRQGECSLALVGGVTVMATPQTYVEFSRQRGLASDGRSKAFADAADGAGF
SEGVGVLLVERLSDARRHGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIRQALATAGLSPHEVDVVEAHGTGTT
LGDPIEAQAVLATY GQDRDRPLLLGSVKSNIGHTQAAAGVSGVIKMVMALQHGVVPPTLHVDEPSRHVDWSAGAVDL

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50869-016WO2

VTENRPWPDLDPRRRAGVSSFGISGTNAHVILESVPAVPPVPSAGPAPLMISAKTAPALGEAEARLRDYLTDADLP
AIASTLASTRSTFEHRAVIFQNHTITGTAAADPRVVFV'FSGQGSQRAGMGEQLAATFPVFKDIHRRVWDLDDVPDLD
VDQTGYAQPALFALQVALFGLLESWGVRPEAVIGHSVGELAAGYVAGLWSLEDAC TLVSARARLMQALPPGGVMVAV
AVSEEHAQAALIKGVEIAAVNGPSSSVVLSGDETAVLQVAAGLGKWTRLSTSHAFHSARMEPMLEKF'RAVAEQLT YRT
5 PVITMAAEVTTTPDYWVRQVRD TVRFGDQVA AFEGATFVEIGPDRTLARLVDGIAM LHGDDEVEAALTGLARLFVQGV
PVTWDNGGRVLDLPTYAFQRQRYWATSTRWLAGLTPQERENALLKVVRD NAAVVLGHAGAGAI PATAAFRDLGVDSL
TAVELRNSLATTITGLRLPATMVFDYPTPAAVAARL

SEQ ID NO: 111

10 EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWDVESLFD PDPDAAGKTYSVRGGFLDAAASFDA AFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPSSVRGSDTG VFMGAFSAGYGTELEGFGVTAGAVSVLSGRVSYFFG
LEGPAMTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMAS PQSFVEFSRQRGLSVDGRCKAFADAADGTGWAE
GVGVLVVERLSDAQAKGHRVLAVVRSSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLTGADVDVVEAHGTGTTLG
DPIEAQAVLATY GQDREQPLLLGSLKSNIGHTQAAAGVSGVIKMVMALQHGVVPRTLHIDEPSQHVDWSAGAVELVT
15 QNQPWPGNDRPRRAGVSSFGVSGTNAHVILESAPTQPALPSVTATGPVPLVISAKTAPALTA FEARLRDYLTDADL
TAIAATLATTRATFDHRAVLLGDDTVTGAVPEPRVVFVFP GQGQWLGMGSALS ESSVVF AERMAECATALDEFVD
WDLFSVLDDPAVVDRVDVVPACWAVMVSLAATWQAAGVHPDAVIGH SQGEIAAACVAGAI SLRDGARIVALRSQLI
ARLAGHGAMASIALPADQITLTDGVWIAARNGPAATVIAGDPAAVDSVLA AHQDARVRRITVDYASHTPHVEQIRAE
LLAILSDIGSQTPVIPWLSTVDGEWVEGPLGNDYWYRNLRET VGFDTAVGLLPDSVFIEVSASPVLLPAMGDAVTVA
20 TLRRDDGGLTRLLTALAEAWVQGVAVDWAIGATTARVLDLPTYAFQH QHYWAVTGTGLTPEALLKVVDSTAQVLGY
TDAAAI AVTA AFKDLGIDSLTAVEMRNTLAKATGLRLPATLVFDYPTPSLLAGRL

SEQ ID NO: 112

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWDVESLFD PDPDAAGKTYSVRGGFLDAAAGFDAAFF
25 GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAYPGGYGTGVDVGGFGATAGAVSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGHALRQGECSLALVGGVTVMATPHTFIEFSRQQGLASDGRSKAFADAADGAGF
SEGVGVLVVERLSDAQAKGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIRQALADAGLVSADVDVVEAHGTGTT
LGDPIEAQAVLATY GQDREHPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHGVVPRTLHVDEPSRHVDWSAGAVNL
VTENLPWPSLDRPRRAGVSSFGISGTNAHVILESVPAQPPVSSTGPAPLVISAKTGPALTA FEARLR TYLAAASEVD
30 LGAVAATLATTRSVFEHRAVLLGEETIAGTAAVDPRVVFV'FSGQGSQRAGMGEQLADAF PVFADIHRRVWDLDDVPD
LDVNQTGYAQPALFALQVALFGLLESWGVRPAAVIGH SIGELAAGYVSGLWSLEDAC TLVSARARLMQALPPGGVMV
AVPVSEEQARGVLVEGVEIAAVNGPSSSVVLSGDEAVVLQV ASGLGKWTRLSTSHAFHSARMEPMLEEFQAVAEQ LTY
RTPAIEMAAGEEVTTTPDYWVRQVRD TVRFGEQVAAFSDAVFVEVGPDRTLARLIDGVAM LHGDDEPSAALTGLATLF
VQGV PVDWSAVVSGTEARVLDLPTYAFQH QRYWLDRKAARRAASAGGDLLKMVRGNAALILGHADPSAIAATTA FRE
35 LGVDSLTAVQLRNSLAKATGLRLPATLVFDYPTPAVLAGRL

SEQ ID NO: 113

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPPDRGWDVENLFD PDPDAPGKTYSIHGGFLDTAAEFDA AFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVQGS DTGVFMGAYSAGYGAGADLDGF'GATAGAGSVLSGRISYF
40 FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMATPDLFVEFSRQRGLATDGRCKAFADTADGTGW
AEGVGVLVVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLAPHEVDVVEAHGTGTT
LGDPIEAQAVLATY GQDREQPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQQGVVPQT LHVDEPSQHVDWSAGAVNL

VTQNQPWPDIDRPRRAAVSAFGVSGTNAHVILESVPASPPVPSTGPAPLVISAKTVPALTAFEARLRITYLAAVPEVD
LGAVAATLATTRATFEHRAVLLGEETIAGTAAVDPRVVFVFSGQGSQRAGMGEQLAAAF'PVFADIHHRVWELLDIPD
LDVDQTGYAQPALFALQVALFGLLESWGVRPAAVIGHSVGELAAGYVSGLWSLEDACTLV SARARLMQALPPGGVMV
AVPVSEEQARAVLVEGVEIAAVNGPSSVVLSGDEAVVLQVASGLGKWTRLSTSHAFHSARVEPMLEEF RVIAGQLTY
5 RTPVIEMAAGEQVTSPDYWVRQVRD TVRFGEQVAAFSDAVFVEIGPDRTLARLIDGVALLHGDD ETEAAMAGLARLF
VQGV PVDWSAVLGGTEARVLDLPT YAFQH QRYWAALTPEALLKVVRDSAAMVLGHADPSAISGTAAFRDLGLDSLTA
VELRNSLAKATGLRLPATLVFDYPTPSVLAGRL

SEQ ID NO: 114

10 EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPPDRGWD TASLFD PDPDAAGK TYSVQGGFLDAVAEFDAGFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGTD TGVMGAFSAGYGAHLEGFGATAGAVSVLSGRVSYLFG
LEGPAMTVDTACSSSLVALHQAA YSLRQGECSLALVGGVTVMATPQIFVDFSRQRGLAADGRCKAFADDADGTGWAE
GVGVLVVERLSDAQAKGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTSADV DVVEAHGTGTTLG
DPIEAQAVLATY GQDREQPLLLGSLKSNLGHTQAAAGVSGVIKMVMALQHGIVPRTLHVDQPSQHVDWSAGAVELVT
15 ENQPWPSLDRPRRAGVSSFGISGTNAHVILESVPASPPVPSTGPAPLVISAKTGPALTAFEARLRITYLAATPDADLP
TIASTLATTRSVFEHRAVLLGEETIAGTAAVDPRVVFVFSGQGSQRAGMGEQLADAFPVFADIHRRVWDL LDVPDL D
VNQTGYAQPALFALQVALFGLLESWGVRPAAVIGHSIGELAAGYVSGLWSLEDACTLV SARARLMQALPPGGVMVAV
PVSEEQARGVLVEGVEIAAVNGPSSVVLSGDEAVVLQVASGLGKWTRLSTSHAFHSARMEPMLEEFQAVAEQLTYRT
PAIEMAAGEEVTTPDYWVRQVRD TVRFGEQVAAFSDAVFVEVGPDRTLARLIDGVAMLHGDD EPSAAGTALARLHVQ
20 GVPVDWSAVLGGTGARVLDLPT YAFQ RQRYWAGWLAGLAAEERDKALVTVVRDSVA AVLGYADSRKIALSASFKELG
VDSLTAVELRNNLAKTTGLRLPATLVFDHPTLAAMAARL

SEQ ID NO: 115

EPLAIVGVACRLPGGVSSPEALWRLVESGTD AISGFPADRGWDVDNLFDPDPEASGKTYCVQGGFLDTVAEFDASFF
25 GISPREALAMDPQQRLILEVCWEAFERAGIEPGSVRGSDTGVMGAFGSGYGS DLEGFSATAGAGSVLSGRISYFFG
LEGPAMTVDTACSSSLVALHQAGYALRQGECSLALVGGATVMATPQTFIEFSRQRGLAADGRCKSF GDNADGTGWSE
GVGALLVERLSDAQAKGHRVLAVVRGS AVNQDGASNGLTAPNGPSQQRVIRQALANAGLAPHEVDVVEAHGTGTRLG
DPIEAQAVLATY GQDRERPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHSVVPQTLHVDAPSRQVDWSAGAVELVT
QNQPWPETGRARRAAVSAFGVSGTNAHVILESAPAQPPAPSTPVTGPVPLVISAKTASALGQAEARLRITYLADKPDA
30 DLAAIAATLATTRSTFEHRAVLLGDETIRGVAVPDPRVVFVFPGQGWQWLGMGSALRESSVVF AERMAECNAALSDY
VDWDLFSVLDDLAVVDRVDVVQPACWAVMVSLAATWQAAGVRPDAVIGH SQGEIAAACVAGAI SLRDAAQIVALRSQ
LIAGLAGQGAMASIALPADQITLTDGVWIAARNGLAATVIAGDPAAVDGVLA AHQDARVRRITVDYASHTPHVEQIR
TELLDLTTDISSRTPAIPWLSTVDSTWIEGPLD TDYWYRNLREPVGFD TAVNLLPDSVFIEVSASPVLLPAMGDAAT
VATLRRDDGSQTRLLTALAEAYVQGV AIDWTIGATTARVLDLPT YAFQHQRFWVANALTPEALLKVVRDSAATVLGH
35 ADPGTIPETA AFKDLGVDSLTAVELRNSLAKATGLRLPATLVFDYPTPSVLAGRL

SEQ ID NO: 116

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPADRGWDIENLFDPDPDAPGK TYSVQGGFLDTAAEFDAGFF
GISPREALAMDPQQRLVLEASWEVFERAGIEPGSVRGSDTGVMGAYPGYYGIGADLDGFGATAGAGSVLSGRVSYF
40 FGLEGPAMTIDTACSSSLVALHQAGSALRQGECSLALVGGVTVMATPQTYVEFSRQRGLASDGRSKAFADAADGAGF
SEGVGVLLVERLSDARRHGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIGSALANAGLAPHDVDVVEAHGTGTA
LGDPIEAQAVLATY GQDREQPLLLGSVKSNLGHTQAAAGVSGVIKMVMALQHGIVPRTLHVDEPSRHVDWSAGAVEL

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VTENQPWPEHDRPRRAGVSSFGISGTNAHVILESVPAQPPVSSTGPAPLVISAKTASALGQAEARLRTYLTVDADLP
AIAATLATTRAVFEHRAVLLGDDTTITGVAADPRVVFVFSGQGSQRAGMGEQLAAAFPVFADTHRRVWDLLDVPDLDV
DQTGYAQPALFALQVALFGLLESWGV RPEAVIGH SVGELAAGYV SGLWSLEDACALVSARARLMQALPPGGVMVAVA
VSEEQARTALVEGVEIAAVNGPGSVVLSGDEAVVLQVASGLGKWTRLATSHAFHSARMEPML EEFRAVAEQ LTYRTP
5 AIEMAAGEQVTTTPDYWVRQVRD TVRFGEQVAAFGDAVFVEIGPDRTLARLIDGVAMLHGDD ETEAAMAGLAKLFVEG
IPVDWSAVLGGNAARVDLPTYAFQRQRYWAASLLAGLTPEERGNALLKVVRD NAAVILGHAGAAAIPATAAFRDLGV
DSLTAVELRN SLATSTGLRLPATMVFDYPTPAAMAARLD

SEQ ID NO: 117

10 EPLAIVGMACRLPGGVFSPEDLWHLVESGTD AISGFPADRGWDVEKLFDPDPDAPGKTYCVQGGFLEATAAFDAAFF
GISPREALAMDPQQRLMLEVSW EAFERAGIEPGSVRGS DTGVFLGAYPGGYGAGAGTDLGGFGATGGAGSVLSGRVS
YFFGLEGPAMTVDTACSSSLVALHQAAYS LRQRECSLALVGGVTVMGTPHMFVDFSRQRGLSVDGRCKAFADAADGT
SWSEGVGVLLVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLAPHEVDVVEAHGTG
TTLGDPIEAQAVLATY GQDREQ PLLLGSLKSNVGH TQAAAGVSGVIKMVMALQRGVVPQTLHVDQPSRHVDWSAGAV
15 DLT TENRPWPDTDRPRRAGVSSFGVSGTNAHVILESAPAQPPTPSTPVTGPVPLVISAKTASALGQAEARLRDYLTA
DADLT AIAATLAI TRSTFEHRAVLLGDDTITGVATPDPRVVFVFPQGQWQWLGMGSALRESSVVF AERMAECAALD
EFVDWDLFSVLDDPAVVDRVDVVQPACWAVMVSLAATWQAAGVRPDAVIGH SQGEIAAACVAGAI SLRDGAKIVALR
SQLIAGLAGQGAMASIALPADQITLTDGVWIAARNGPAATVIAGTPSAVDSVLA AHQDARVRRITVDYASHTPHVEQ
IRTELLGILADIDSQTPLIPWLSTMEGTWVEGPLHSDYWYRNLREPVGFDTAVSLLPDSVFIEVSASPVLLPAMGDA
20 LTVATLRRDEGGQNRMTALAEAYVQGVAVDWAAVIGATTARVLDLPTYAFQHEDYWLDSTRLMGLAAEERDKALVT
VVRESAAVVLGHADARAIPVTAAFRELGVDSLTA VQLRNSLAKATGLRLPTTLAFDYPTPAVLAARL

SEQ ID NO: 118

EPLAIVGMACRLPGGVLSPEDLWRLVESGTD AISGLPTDRGWDIDNLYDPEPGAPGKSYCVQGGFLDTVADEFDPAFF
25 GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGS DTGVFMGAFGNGYGIDTDGGGFGATAGTGSVLSGRVS YF
LGLEGPAMTVDTGCSSALVALHQARYALRQGDCSLALVGGVTVMASPYTFVEFSRQRGMAANGRCKAFADAADGTGW
AEGVGVL LVERLSDAEAKGHRVLAVVRGSALNQDGASNGLTAPNGPSQQRVIQAALANAGLVSADVDVVEAHGTGTT
LGDPIEAQAVLATY GQDREH PLLLGSLKSNIGHTQAAAGVSGLIKVMALQHGVVPQTLHVDEPSRHVDWSAGAVEL
VTENRPWPSVDRPRRAGVSAFGISGTNAHVILESAPPSPAPSTPVTGLVPLVISAKTAPALGQAEARLRDYLTA DVD
30 LTAIAATLVTTTRSTFEHRAVLLGDDTVTGVAVPDPRVVFVFPQGQWQWLGMGSALRESSVVF AERMAECASALSDYV
DWDLFTVLDDPAVVDRVDVVQPACWAVMVSLAATWQAAGVRPDAVIGH SQGEIAAACVAGAI SLRDAAQIVALRSQ L
IAGLAGHGAMASIALPADQITLTDGVWIAARNGPTATVIAGNPQAVDSVLA AHQDARVRRITVDYASHTPHVEQIRT
ELLDLT TDVGSRTPAIPWLSTVDGEWVEGPLD TDYWYRNLREPVGFDTAVGMLPDSVFIEVSASPVLLPAMGDAATV
ATLRRDDGGQTRLLTALAEAYVQGVAVDWAVGATTARVLDLPTYAFQHQR YWVADRLHDRPGVEQHRLMRELVL RHA
35 ATVLGHDSPDAIAADHPFKDLGLDSLTA VELRNHLVAETGLRLSATTAFDHPTADDLARHL

SEQ ID NO: 119

EPIAIVSMACRAPGGVSSPEGLWRLVESGTDATSGFPTDRGWDVENLFDPD PDAAGKTYSMRGGFLETAADF DAPFF
GISPREALGMDPQQRL LLETAW EAIERAQIDPKSLRGQDVGVYVGGA AQGYGIGATDQQQENLITGSSISLLSGRVS
40 YALGLEPGVTVDTACSSSLVALHLAGQALRQRECSLALVSGVSVMATPDVFVEFSRQRGLAADGRCKSFAASADGT
TWSEGVGVVLVLQRLSEAVRQGHRVLAVVRGSAVNSDGASNGLTAPNGVSQRRVIRQALASAGLAASEVDVVEAHGTG
TKLGDPIEA EAILATY GQDRAAPAWL GSLKSNIGHTMAASGVLGVIKMVEAMRHGLLPRTLHVDEPSSHVDW ERGDV

ALLTENQPWPDSTRPRRAGVSSFGLSGTNAHVLEEYPAPAAADPPVTPACGGGPLPWVLSAQSPNALREQAARLYAA
LAEDPDWRPLDIGYSLATTRAGFPHRAVAVGSDREEFQRALSKLADGTGWPGELITATAAKDRRMAFLFDGQGTQRLG
MGKGLHRRFPVFARAWDAVSAAFAKHLDHSLTDIYLGFPSSPASAE LADDTLYAQAGIFTMEVALVELLEDWGV RPDF
VAGHSIGEAAAAYTAGMFSLEDVTALIVARGRALRLTPPGEMVALRGGEADVRELLQRTGAALDLAAVNSPEAVVVS
5 GAPDAVAEFRAAWTASGRRARDLTVRHAFHSRHVESVLDEF RATLAALTFRAPALPVVSTMTGRLADPAEMGTPEYW
LRQVRQTVRFEEAVRELSGQGVGTFVEIGPSGALATAGLECLGGDATFHAVQRPRAPEDVCLMTAVAE LHAGGTAVD
WTKILAGGRPVDLPVYPFQHRPYWIA PAPSYPDEPRTMRELVRLEVAGILGLSDPSVILDDSSFLELGFD SLSSMRL
GNRLATVTGLDLPSTLLFEYATPAALATHLD

10 SEQ ID NO: 120
EPLAIVGMACRLPGGVE SPDDLWRLVASGTD AISGFPRDRGWDVDNLYDPDPDAPGKTYTVLGGFLDSVAGFDASFF
GISPREALAMDPQQRLVLEVAWEAFEHAGIAPRSVRGTD TGVMGAFSSGYDAELEEFGMTGDAVSVLSGRVSYFFG
LEGPAMTVDTACSSSLVALHQASSALRQGECSLALVGGVTVLATPKTFVEFSRQRGLAGDGRSKAFADAADGAGWSE
GVGVLLVERLS DARAKGHHVLGVVRGSAVNQDGASNGLSAPNGPSQQRVIRQALAGAGLSPHEVDVVEAHGTG TKLG
15 DPIEAQAVIATY GQDRDQPALLGSLKSNVGHTQAAAGVAGVIKMVMALQHATVPATLHVDAPTRHVDWTAGAVELVT
ENRPWPETGRARRAAVSSFGISGTNAHVILESAPAAPEETEPVAPVVASDRVPLVISAKTPAALTSTEDRLRAYLA
AHPGTDPRAVASTLATTRS VFEHRAVLLGENTVTG SVAGADPRVVFVFPQGQWQRLGMGRELLAASPVFAGRMAECA
TVLREFVDWDLFTMLDDPAVVDRIEVVQPCWAIMVSLAAVWQAAGVRPDAVIGH SQGEIAAACVSGAVSLRDAARI
VTFRSDMIARMTGHGVMASVALHADDIPLVEGAWVAARNGPAATVVAGTPEAVDQVLAACEERGARVRRITAGVASH
20 TPLAEHVRGELLDATGGLPSRVPDIPWLSTVDGTWVEKPLDPAYWFRNMREPVGFAPAVDLLRAQGDHVFLEISASP
VLLPSMDDAVTVATLRRDDGSADRMLAALAEATHGVVDWPRVLGTAGRVRGLPTYAFQHQR YWAVSRPAVLTPDA
LLKVVRDSAATVLGYTDADSITVTTAFRDLGVDSLSAVELRNNLAKSTGLRLPATLVFDYPTPADLATHL

SEQ ID NO: 121
25 EPLAIIGMACRLPGGITS PEDLWRLVASGSDAISDFPDDR GWDVGNLYDPDPDAPGRSTTVRGGFLDEVAGFDASFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGTVRGSD TGVMGAYPGGYGVGADLGGFGTTAVSGSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGHALRQGECSLALVGGVTVMPTPNIFVEFSRQRGLAADGRCKPFADAADGTGF
SEGAGVLLVERLS DAQTNGHHILAVVRASAVNQDGASNGLTAPNGPSQQRVIRSALANAGLTTADV DVVEAHGTGTT
LGDPIEAQAVIATY GQDRAQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALRN GTVPRTLHVDEPSRHIDWTAGAVEL
30 ATENRPWPETERPRRAGVSSFGISGTNAHVILESTPTQPVEPSTPAAHPLPLPISAKTPPALA ALEARLRAYLTSET
DLAAVASTLASTRAVFEHRAVLLGDETIVGVAALDPRVVFVFSGQGSQRAGMGEQLAAVFPVFAQI HREVLDLLDIP
DLDIDQTGHAQPALFAFQVALAGLLDSWGV RPDVIGHSIGELAAAYIAGLWSLEDACTLV SARARLMQALPSCGAM
VAVQATEEQARAVLIDGVEIAAVNGPSSSVLSGDETAVLQVAAELGGKSARLKTSHAFHSARMEPMLDQFRQVAEQL
TYRSPVIEMAAGTTS DYWVRQVRD TVRFQDQVRVHQGSVLVEIGPDRTLARLIDGIATSHGDDEVRAVMTALAE LHV
35 RGVAVDWPGTTSARVLDLPTYAFQHERYWLANTA AE LTAADLLKAVRDSA AVVLGHADADSIPATTA FKDLGFD SLT
AIELRNRLAKDIGLRLPATMAFDYPTPAALAARL

SEQ ID NO: 122
EPLAIVGMACRLPGGVTS PEDLWRLVASGTD AITEFPTDRGWDVGNLYDPDPDAPGKSTTVHGGFLEGVAGFDASFF
40 GISPREALAMDPQQRLVLEVSWEAFERAGIEPGAVRGSD TGVMGAYPGGYGVGADLGGFGTTAGAGSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGHALRQGECSLALVGGVTVMPTPNIFVEFSRQRGLSADGRCKPFADAADGTGW
SEGVGVLLVERLS DARANGHRILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTTADV DVIEAHGTGTT

LGDP IEAQAVIATY GQDRTQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHDTV PASLHVDEPSRHVDW TAGAVEL
ATESRPWPKTGRAHRAGVSSFGVSGTNAHVILESAPTQPEEPSTPAPHPLPLPVSAKTS AALTDLED RIRAYLT PET
DLAAVASTLASTRAMFEHR AVL LGDETITGVAAPDPRLV FVFSGQGSQRAGMGEQLAAVFPVFAQIHREVL D LLDVP
DL DIDQTGHAQPALFAFQVALAGLLDSWGV RPD AVIGHSIGELAAAYVAGLWSLQDACALVSARARLMQALPPGGAM
5 VAVAVPEEQARAVLIDGVEIAAVNGPSSVVLSGDETAVLQVAAELGGKSTRLRTSHAFHSARMEPMLDQFRQVAEQL
TYRSPVIEMAAGTTPDYWVRQVRD TVRFGDQVRVHQGSVLVEIGPDRTLARLIDGIATSHGDDEVRAAMTALAELHV
RGVAVDWPGTTSARVLDLPTYAFQHRRYWVAPARRAAGRPADLTPEGLLT TVRDSAAVVLGHADASAIPATAAFQAL
GVDSLIAVELRNNLAKNTGLRLPATLIFDYPTPVDLATHL

SEQ ID NO: 123

EPLAIIGMSCRLPGGVTS PEDLWRLVASGTDAITGF PADRGWDLENLYDPDPDAPGR TTTVQGGFLDDVAGFDASFF
GISPREAVAMDPQQRLALEASWEAFERAGIEPGSVRGSDTGVMGAYPGGYGIGADLGAFMLTGRAGSVLSGRLSYF
FGLEGPAMTVDTACSSSLVALHQASYALRQGECSMALVGGVTVMPTPVMFVEFSRQRNLADDGRCKAFADGADGTGW
SEGVGVLLVERLS DALAKGHRIMAVVRGSAVNQDGASNGLTAPNGPSQQRVIQSALDSAGLTTADVDVIEAHGTGTT
15 LGDP IEAQAVIATY GQDRAQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQNGVVPRTLHVDEPSRHVDW TAGAVEL
ATENRPWPEVGRARRAAVSSFGFSGTNAHVILESAPAQPATPSAPVAHLLPLPISAKTPPALADLEARLRAYLTPEA
DLPVASTLASTRAVFEHR AVL LGDETIVGIAALDPRVVFVFSGQGAQRAGMGEQLAAVFPVFAQIHREVL D LLDIP
DL DIDQTGHAQPALFAFQVALAGLLESWGV RPD AVIGHSIGELAAAYIAGLWSLEDACALVSARARLMQALPSSGGAM
VAVQATEDQARAVLIDGVEIAAVNGPSSVVLSGDETAVLQVAAGLGGKSTRLRTSHAFHSARMEPMLDQFRQVAEQL
20 TYRSPVIEMAAGVTPDYWVRQVRD TVRFGDQVRVHQGSVLVEIGPDRTLARLIDGIATSHGDDEVQAAMTALAELHV
RGVAVDWPGTTSARVLDLPTYAFQHORYWTVSWLAGLTPEEREGALVKVVRDSAAVVLGHADAGTIPVTAAFKDLGL
DSLTAVELRNSLARSTGLRLPATMVFDYPTLGALAARLD

SEQ ID NO: 124

EPLAIVGMACRLPGGVTS PEDLWRLVESGTD AVSAFPADRGWDADALYDPDPEAAGKTYCVRGGFLDGVAGFDASFF
GISPREALAMDPQQRLILEASWEAFERAGIEPGSVRGSDTGVMGAFFPGSYGVDADLGGFGMTGGAASVLSGRVSYF
FGLEGPAMTVDTVCS SSSLVALHQAGHALRQGECSLALVGGVTVMSTPDTFVEFSRQRGLAADGRCKAFGDGADGTGW
AEGAGVLLVERLS DAQAKGHRILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRSALANAGLSSADVDVVEAHGTGTK
LGDP IEAQAVLD TYGQDRERPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHCVVPRTLHADVP SRQVDW TAGAVEL
30 VTENRSWPEADRPRRAAVSSFGLSGTNAHVILESPPDQPTTASAPTTGPVPLPISAKTPAALADLETRLRAYLT PET
DLPVAATLAVNRS LF EHR AVL I GDDTITGTASTEPRVVFVFPGQGWHWLGMG SALLASSAVFADRM AE CNAALSEF
VDWDLFTALDDPAVFDRVDVVQPTCWAVMVSLAAVWQHAGVRPDAVLGHSQGEIAAACFAGAI SLQDAARIVALRSR
LIGRLAGRGAMASVSLPPDEIPLIDGVTVAVLNGPSAVIAGAPDAVDAVLADCEARGARVRKINVDYASHTPHVEQI
RTELLDITAGITAETPTVPWLSTVDGTWIDRPLDTEYWYRNLREPVGFGATI ELLQAQGDTIFIEVSASPVLLQAID
35 DSIAIPTLRRDDGTPTRLLTALAEAHVHGVTIDWAKLLGSTASPVNLPTYAFQRQRYWAASAAACRPAELTPEHLLK
VVRDSAAVVLGHTDAGAIPATAAFQALGVDSLIAVELRNNLAKSTGLRLPATLIFDYPTPADLATHL

SEQ ID NO: 125

EPLAIIGMACRLPGGITSPEDLWRLVESGSDAISDFPDDR GWDVDRLE' DPDPDAAGKTYTTQGGFLSEVAGFDASFF
40 GISPREAVAMDPQQRLVLEVAWEAFERAGIEPGTVRGSDTGVMGAYPDGYGSGTDLAGFGVTAGAGSVLSGRVSYF
FGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMPTPRTFVEFSRQRGLAADGRCKPFADAADGTGF
SEGAGMLVVERLS DAQTNGHHILAVVRASAVNQDGASNGLTAPNGPSQQRVIQSALAGAGLV SADIDVIEAHGTGTT

LGDP IEAQAVIATY GQDRSQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHDTV PATLHVDEPSRHVDWTAGAVAL
VTENQPWPRNGHARRAGVSSFGVSGTNAHV IIEEAPAEPPVEPVPAADV VVPLVVSARDAIPLGDQAARLAALVEAP
DGPVLPALADALLTRRTTFAQRAVVVAGSRDDAAAGLRALATGTAHPALVTGAAGTSGRVVLMFPGQGSQWDGMGAQ
LIGASPVFAARIADCAAALQPWIDWDLQDVL RGNAPTDLLE RVDVVQPASFV MVGLAAVWESVGV RPD AVLGH SQG
5 EIAAAYVAGALT LADAAKV VAVRSRLIAARLGRGGMASVALSPQDAAARRGRAELA AVNSPASVVLGASEALDETL
AALEADGVRVRRVAVDYASHTGHVEELEQDLAEALADVRSQAPLVGFRSTVTGEWVTEAGALDGGYWYRNL RQQVRF
GPAVAALAEDGYSVFVEASAHPVLVQPVTETLDR TDAVV TGSLRRQDGGLSRLLTSVAEVFVGGVPVDWAGLLPAGA
GRSWVDLPTYAFDHQHYWLPAGGTRGRSEAE LLELVRGRAAAVLGHTDAGSIPATAAFKDLGLDSL TAVELRNSLAK
STGLRLPATMVFDYPTPAAVAARL

10

SEQ ID NO: 126

EPLAIVGMACRLPGGITS PEDLWRLVASGSDAISDLPVDRGWTVDGHFQGGFLDEVAGFDASFFGISP REAVAMDPQ
QRLVLEVAWEAFERAGIEPGSVRGTDAGVFMGAYADGYGMGTDLGGFGMTSVAVSVLAGRISYFFGLEGPAMTVDTA
CSSLVALHQAGHALRQGECSLALVGGVTVMPTPQT FVEFDRQRGLAADGRCKAFADAADGTSFSE GAGMLVVERLS
15 DALANGHHILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRSALANAGLTTADVDVVEAHGTGTTLGDP IEAQAVIAT
YGQNRQRPLLLGSLKSNIGHTQAAAGVSGVIKMVMALRNGTV PATLHVDEPSRHIDWTAGAVALVTENQPW PETERP
RRAGVSSFGISGTNAHVILESTPTPPATLSAQVAHPLPLPISAKTPPALADLEARL RAYLTPEADLA AVASTLSTR
AVFEHRAVLLGDETIVGVAALDPRVVFVFSGQGSQRAGMGEQLAAVFPVFAQIHREVL DLLDIPDL DIDQTGHAQPA
LFAFQVALAGLLDSWGV RPD AVIGHSIGELAAAYVAGLWSLQDACALVSARARLMQALPSGGAMVAVAVPEDEARAV
20 LIDGVEIAAVNGPSSVVLSGDETAVLQVAESLGGKSARLKTSHAFHSARMEPMLDQFRQVAEQLTYRSPVIEMTAGV
TPDYWVRQVRD TVRFGDQVRVHQGSVLVEIGPDRTLARLIDGIATSHGDDEVQAVMTALAE LHVRGVAVDWPGTTSA
RVLDLPTYAFQHDHYWAHPVDRTPEALLALVRDSA AVALGHAGAATVPATAAFQSLGMDSLI AVELRNNLARSTGLR
LPATLVFDYPTPAALATRL

25

SEQ ID NO: 127

EPLAIVGMACRLPGGVTS PEDLWRLVASGTDAITGLPTDRGWEEDDRFRGGFLAGVAGFDASFFGISP REAVAMDPQ
QRLVLEASWEAFERAGIEPGSVRGSDTG VFMGAYPGGYGFGADLGGFALTSGSGSVLSGRVSYFFGLEGPAMTVDTA
CSSLVALHQAGYALRQGECSLALVGGVTIMPTPQT FIEFERQRGLAADGRSKAFADSADGTGWSEGVGV LVVERLS
DAQANGHHILAVVRGSAINQDGASNGLTAPNGPSQQRVIRSALANAGLTTADIDVIEAHGTGTTLGDP IEAQAVIAT
30 YGQDRSQPVLLGSLKSNIGHTQAAAGVSGVIKMVMALQHDTV PATLHVDRPSRHVDWAAGAVELVTENR PWPENGRV
RRAGVSAFGVSGTNAHVILESPPDQPVKPSAPAAGPVPLPISAKTPAALAALENRLRAYLTPE TDLPAVASTLATR
AMFEHRAVLLGDDTITGTASTEPRVVFVFPQGWHWLGMG SALLASSAVFADRMAECNAALHEFVDWDLFTALDDPA
VFDRVDIVQPTCWAVMMSLAALWQHAGV RPD AVLGH SQGEIAAACFAGAI SLQDAARIVALRSQLIGRLAGRGAMAS
VSLPPDEIPLIDGVTVAVLNGPSAVIAGSPEAVDAVLADCEARGARVRKINVDYASHTPHVEQIRTE LLHITAAITA
35 ETPTVPWLSTVDGTWIDHPLDTEYWYRNLREPVGFGATI ELLQTQGDTIFIEVSASPVLLQAIDDSIAIPTLR RDDG
TPTRLLTALAEAHVNGVTIDWATVLGATGSPVDLPTYAFQHQRFWVG DRLHGRTSAEQHRIMLDLVLGHATSVLGHQ
TPDAVASDRAFKDLGMDSLTAVELRNHLVAETGLRLPATTA FHDHPTADDLARRL

40

SEQ ID NO: 128

EPIAIVSMACRAPGCVTSPEGLWRLVESGTD AIADEFPADRGWDLATLYSPDP IGYTSYCLQGGFLDAAADFDA AFFG
ISPREALGMDPQQRLLLETSWEAIERARIDPRSLRGRDVG VYVGATQGYGVGAVDQQRDNVITGSSISLLSGRLSY
ALGLEPGVTVDTACSSLVALHLASQALRQRECSMALVSGVSVIPTPDVFVEFSRQRGLASDGRCKSF SAAADGTI

PATENT
50869-016WO2

WAEGVGVLVLERLSEATRLGHEVLAVIRGSAVNSDGASNGLTAPNGASQQRVIRQALASAGLNAADVDTVEAHGTGT
KLGDPIDAEAILATYGQDRSSPVWLGLSKSNIGHSMASGVLGVKMEAMRHARLPRTLHVDEPSPHVDWASGDVA
LLTENQPWPDGARPRRAGVSSFGLSGTNAHVVLEQHRAPAVPVAAETVADDVPLPLLLSARHPKALRDQAARLHAAL
AEAPGWRPLDVGYSLATTRSFAHRAVAVGSGRELLRALAKLAEGAAWPALVTGTAKAGRVAF'LF'DGQGTQRLGMGR
5 VLHDRFPVFARAWDTV SARFDQHLDHSLTDVYLGRDTSAAALADDTLYAQAGIFTMEVALFELLAEWGVRPDLVSGH
SIGEVAAAYAAGLF'SLEDAATLIVARGRALRQMPPGAMLALRASEDQVRELLDRTGADLDVAAVNSPVSVVVSGBP
AVAAFRAEWEASERDARALNVHHA'FHSRRVDAVLDEFRAVLGTLTFRTPALPVVSTVTGRLAGPAEMSTPEYWLRQI
RRTVRFQDAVRELSGQGAGTFVEIGPSGALAAAGLECVDASFHAVQRPRSPEDACLLTAVAE'ELHAGGTAVDWAKVLA
GGRATDLPVYPFQHETYWIPPASPPADTRTMLEV'VEEAALVLGVTDPRVILDDSSFLDLGFDLSLSAMRLGNQLSAV
10 TGLDLPPSLLFEHPTVGELAAHLD

SEQ ID NO: 129

EPLAIVGMAARFPGGVASADDLWRLVVSGGDAIGGFPADRGWDLEELYDPDPAATGRSYVREGGFLNDATTFDASFF
RIGPREAKAMDPQQRLLETSWEAFEHAGIRPETLRGTATGVFAGISLQDYGVLGSDPELEGYAGTGNAPSVLSGR
15 LSYFYGLEGPAVTIDTACSSSLVALHLAGQSLRRDECTLAVVGGVTVMPSPNVFVEFSRQRGLAPDGRCKPFAAAD
GTGWSEGVGVLVVERLSDARRNKRRILAVVRGSAVNQDGASSGLTAPNGPSQQRVIRSALAAAGLTAGDVDVVEAHG
TGTTLGDPIDEAQGVLATYGDRSGAPVRLG'SVKSNLGHTQAAAGIAGVIKMQALRHGVMPRSLHIDEPSPHVDWTAG
RVELLTSNLPWPTSERPRRAAVSSFGISGTNAHVILEQAF'PATEPEPSFTPVVSGPALPLVFSARDSGALATRTHLS
DGPGVAYALATSRS'FMDHRSVRIGDMTVTGVATT'DPEVVVFVFGQGTQWAGMGRALMDASPVFAERMNECAALEPY
20 LDLWEAIDTPDQVETLQPASWAVMVSLAAVWQAAGVRPAAVIGHSQGEIAAACVAGSLSLADAAVVALRSKAIAAS
LGKGAMASIP'LVEEIELIDEVWVAALNGPSSTV'VAGAPDAVEQVRARYDGRRIAVDYASHTPHVEALRGQVVSVP
QAPDIPWFSTVDSEWVEGPLDDDYWFRNLRQPVQFGPAAARFDDAVFVEVSARPVLI'PALDASVTVP'SLRRDDGGPE
RMLASLAQAFVAGVAVDWTTIVPPAPFV'DLPTYPFQGERFWIDLDDVLAVVRDCAATVLGHTDPA'AIAPDRPFKDLG
FDSLAAVQLRNHLLTVTG'VRLSATAVFDFPTPAVLAGEV
25

SEQ ID NO: 130

EPIAVVGMACRLPGDVASPEDLWRLVAEGRDAVGPFPPADRGWELGEAAYARVGGFVTGATGFDAGFFGISPREALAM
DPQQRLLEVAWEAFERAGIAPDALRGSDTGVFVGTYGQGYGELAVDGD'AEGYVGICNSGSVVSGRVSYFFGLEGPA
VTVDTACSSSLVALHQAAQALRQGECSLALVGGVTVMSSPLIFQEFARQGG'LAADGRCKAFADGADGTGWGEGVGV
30 VVERLSEAQRRGHTVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRSALASAGLGFGDVDLVEAHGTGTALGDPID
QALLATYGSAGTPVWLGLSKSNIGHTQAAAGVAGVIKAVEAMRHGVLPQTLHADQ'PSSHVDWTAGAVELLTANRPWD
SAGRPRRAAVSSFGISGTNAHVILEEFSSAPVSPEPGAGAAPLLLSARSAAALAEFESRVAALRPSRDLAATLAGRV
F'F'DHRAVVLPGGEVVRGRVGDAPVVVFV'FAGQGSQRSDMASRLAGEFPLFAAAHERVWSLLDVDES'LDVDQTGFAQPA
LFAYEVALAE'LLGVRPDAVIGHSVGELAAAYVAGALSLEDACRLVSARARLMQALPPGGMVSVRVSEEAARAVLRD
35 GVELAAVNGPRAVVL'GDECAVLAAAAELGEFRRLRTSHAFHSALMEPMLEEFRAVASSVEFGEPEIALSFVPSADY
FVRQVRET'VRFGEQVA'AFEPGTLFVEVGPDGSLSRLTGGVNAAEPLTALAHLWAHGAVVDWTPYTS'DGRLDTAPTYP
FQPERYWPEQRRRRARRGDSLALVIATAAAVLGHPEGTDIPADTPFQSLGFDLS'AVDLRNQLAHATGVRLSPTAVF
DHPTPRALAERL

SEQ ID NO: 131

DP'IAIVGMACRYPPGGVATADDLWDLVAEGGDAVGPFPPADRGWDLAGLYDPDPEAAGKSYVREGGFLGGAADFDAFF
GISPREALAMDPQQRLLETAWEAFEHAGIDPLDLRRSDTGVFVG'TMAQEYGG'LVTD'SAHGLEGWIGTGNSQSVMSG

RLSYFFGLQGPAVTIDTACSSSLVALHQAAQALRSGECSLAVVGGVTVMSSPRTFQEF SRQ RGM A PDGRCKPF AAAAA
DGTGWSEGVGVLVVERLSEARRNGHAVLAVVRGTAVNQDGT SNGLTAPNGPAQQQVIRAALERAGLGVGDVDVVEAH
GTGTALGDPIEAQA ILDTYGSRTTGEPVRLG SVKSNLGHTQAAAGVAGVIK MVQAMRHATMPRSLHIDEPSPHVDWA
SGAVELLTAERGWPATDRPRRAAVSSFGISGTNAHVIVEGVTEPEPSREAAPSGPLPLMLSAPTAEALAEQETRLRR
5 FRADRPDADERDIAVTLAGRTGFAHRTVLIGELSVSGVAVADRRVVFVFPQGCTQWAGMGRDLMDASPVFAERMNEC
AAALEPYLDLWEAIDTPDRVETLQPASWAVMVSLAAVWQAAGVRPAAVIGHSQGEIAAACVAGSLSLADAAAVVALR
SKAIAASLGKGAMAS IPLPAEEIELIDEVWVAALNGPSSTVVAGAPDAVEQVRARYDGRRIA VDYASHTPHVEALRG
QVVSVP SQAPDIPWFSTVDSGWVEGPLDDDYWFRNL RQP VQFGPAAARFDDAVFIEVSARPVLI PVLEDAVTVP TLR
RDDGGIGRLHASVAQAWTAGADVDWAALLPAGGRRIALPPYAF THERFWPRRPAAAGQDLLTVVRTAAATVLGHRDA
10 ARVPADRAFKELGFDLSAVQLRNELLTATGVRLSATAVFDHPTAAALAEAL

SEQ ID NO: 132

EPIAIVGMACRLPGDVSSPDELWELVESGRDAIGPFPADRGWNLSTLFD PDPDAPGKSYVREGGFLT GAGLFDADFF
GISPREALAMDPQQRL LLEVAWEAFERAGIAPDALRGSDTGVYVGTYAQGYGELAAATAGEGFVGIGNSGSVVSGRV
15 SYFLGLEGP AVTVDTACSSSLVALHQAAQALRLGEC SLALVGGVTVMASPLMFQEF SRQ RGLSPDGRCKAFAEGADG
TGWGEGAGVLVVERLSEARRRGHTVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRAALAAAGLTFGDVDVVEGHGT
GTALGDPIEAQALLATYGAAGSPVRLGSLKSNIGHTQAAAGVAGVIK MVQAMRHGVMPRTLHVDQPSSHVDWSAGAV
ELLTANRTWEAPGRPRRAAVSSFGISGTNAHVILEGVPAPPEPAAGSAETAPLLLSARTVPALNDFEARVSARPSSPD
LAATLSRRVFFDHRAVVLPGGEVVRGRVGDAPVVFV FAGQGSQRADMASRLAGEFPVFAAAHERVWSLLDVDEGLAV
20 DQTGLAQPALFAYEVALAELLGVRPDAVIGH SVGELAAAYVAGALSLEDACRLVSARARLMQALPPGGVMVSVRVSE
EAARAVLRDGEIAAVNGPRAVVLSGDEDAVLAAAAELGEFRRLRTSHAFHSARMEPML EEFRAVASSVVFGEPEIA
MSFVPSADYFVRQVRET VRFGEQVASFDPGSLFVEVGPDGSLSRLTGGVSAAEPMKALAYLWVRGVGV DWAPYVGGG
RLDLGAPTYPFQREGFWPTREALAQLP PARRGRALLDLVQNRVAKTLGLVRPADPGRAFTDLGFTSLTALELRNSIA
EETGLPLPASLVFDHPNARALAA YLD

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SEQ ID NO: 133

EPLAIVGMACRLPGGISSAEELWRLVAEGGDAIGPFPGDRGWDIDALYD PDPDAAGRTYTRSGGFLPGAGDFDAAFF
GISPREAQAMDPQHRQLLETSWEALEHAGIDPAGLRGRDVGVFAGFSGQDYIAEMGVGP AEAGGYQVTGRAASVLSC
RLSYFYGFEGPAVTVDTACSSSLVALHLAGQSLRDGESSLALVGGVTVMSSPGLFVEFSRQ RGLAPDGRCKAFSVDA
30 DGTGWSEGVGVLVVERLS DARRNNHQILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALAQSGLSVGDVDVVEAH
GTGTALGDPIEAQAVLATYGSRTGGEPVRLGSLKSNIGHTQAAAGIASLIK MVQSIRYGVMPRTLHVSEPSPLVDWA
AGRVELLTSDVPWPEGVRRRAAVSAFGISGTNAHVILEEAPAPAEAVPSIRPVVSGPELPLVFSARDADALAAQSRLT
DGPVGAHALVTARTVFDHRSVRMGDVTVTGVATPDPEVVFVFPQGCTQWPGMGRDLMAASPVFADRMNECALALSPY
LDLWAAIDAPDRVETLQPASWAVMVSLAAVWQAAGVQPAAVIGH SQGEIAAACVAGSLSLADAAAVVALRSRAIASL
35 AGKGAMAS IPLPAEEIELVDEVWVAALNGPSSTVVAGTPDAVEQIRSR YDGRRIA VDYASHTPHVEALRGQVVSVP S
QSPAVPWFSTVDSAWVEGPLDEDYWFRNL RQP VQFGPAAAGFDNAVFEVSARPVLI PALDASVTVP SLRRDDGGPE
RMLASLAQAFVACVAVDWTTIVPPAPHVDLPTYPFRRQRHWIDMERLGQLPPGDRDRFLDLVRDAAA AVLGHGSRE
TVPASAAFKELGFDSLIAVQLRNAVAAATGVSLPATVTFDHPTPQALAVLL

40 SEQ ID NO: 134

EPLAIVGMACKFPGGVDS PERLWEMVEAGEDVIGPFPDDR GWDVDGGYDPDPEKAGSWYARAGGFLAGAADF DAAFF
GINPREALAMDPQQRL LLEVAWEAFERSGIAPDSL RGTDTGVFVGTFGQGYGRLVAAGAPGLEAYSGTGN TIGSVASG

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50869-016WO2

RLSYVFGLEGPAVTVDTACSSSSLVALHQAGRSLOSGECSLALVAGVTVMSTPDSFVEFSRQ RGLSPDGRCKAFAAAA
DGTGFSEGAGVLVVERLSDARRNNHQILALVRGSAVNQDGASNGLTAPNGPSQQRVITAALTDARLTTTDLVEAH
GTGTTLGDPIDAEQAILATYGNRTTGNPVHLGSKNLGHTQAAAGIAGVIKAIQAIRHTTMPKSLHIDQPSPHVDWT
SGRVELLTSNQFPWPATDRPRRAAVSSFGVSGTNAHVILEEQTPVEEPPPPASAGPVPLALSARTPEALTAQEKAVRGL
5 PDGDRRRAAPALALGRAALPHRAVLLGDSVIRGTASADDGRPVFLFPGQGAQWAGMGRELMAASPVFAERMRECAVA
LAGEVDWDLFAVLDDAEALRRTEIVQPASWAMMVSLAALWESWGVRPAAVVGHSQGETAAAVVAGAIGLRD GARLSA
TRSRVLALLAGHGALASIALPAGEVEVVDGVSVAAVNGPRATLISGDPAGVEAVTARYEASGVRVRRIPADVASHSP
HVERAEETLLAALAGIEARVPGVPWLSTATGDWITEPVDERYWYRNLRSPVLFHPAITT LRDRGHRLFLEISTHPQL
LPAMEDDLLTVGSLRRDDGDLDRMHAALAEAWAAGADV D WRAFLGSGPVRALDLPTYPFQRRRFWPEAGALPPAERE
10 RALVEIVRDQAAAVLGDPDAGALTPGTAFRDLGFDSLTA VQLRNHLATATGLTLPATVIFDHPTPRALATFLD

SEQ ID NO: 135

EPLAVVGMACRLPGGVSSPDQLWDLVVSGGDGIGPFP GDRGWATDEIYDPDPDASGKTYVREGGF LDSAGDFDAAFF
GISPREALAMDPQQRLLLETSWEAFEHAGIDPAGLRGGDTGVFVGGFTQAYGVGTADLEGYAATGT VGSVLSGRLSY
15 FYGFEGPAVTIDTACSSSSLVALHQAGQALRQGECTLAVVGGVTVMPTPVVFQEF SRQ RGLAADGRCKAFAD EADGTG
FAEGAGVLLVCRLSDARRDGRRILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRAALASARLGPGDV D LIEGHGTGT
TLGDPIEAQALLATHGSGASPVRLGSLKSNIGHTQAAAGVAGVIKVIQALRHGLMPRTLHVGT P SSQVDWSAGNVEL
LTSNLPWPATDRPRRAAVSSFGISGTNAHVILEEAPAPA AVPSITPVVSGPALPLVFSARDSGALAARTRLTDGPGV
AFALATSRSMFDHRAVRIGDLSVSGVAVADRRVVFVFP GGTQWAGMGRALMDASPVFAERMNECAAALSPYLDLWE
20 AIDAPDRVETLQPASWAVMVSLAAVWQAVGVEPAAVIGH S QGEIAAACVAGSISLPDAAAVVALRSKAIASLAGKGA
MASIPLPPDQIDLIDQVWIAALNGPSSTVVAGSPEAVEQVRARYDGRRIAVDYASHTPHVEALRGQVVSVP SQAPDI
PWFSTVDSAWVEKPLDGDYWFRNL RQP VQFGPAAARFDDAVFIEVSARPV LIPALDTSVTVP SLRRDDGGPERMLAS
LAQAFVAGVAVDWTTIVPPAPFVELPTYPFQRRRYWIDSSEEALRDLVREQAAAVLGYPDPSRITPGVAFRDLGFDS
LTAVQLRNALSAATGLRLSATVAFDHPTPAALAAAL

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SEQ ID NO: 136
EPIAIVGMACRLPGDVSSPDELWDLVESGRDAIGPFPADRGWNLD ELYDPDPDATGRSYVREGGF LAGAADFD A EFF
GINPREALAMDPQQR LVLEVAWEAFERAGIAPDSL RGTDTGVFLGAFAGGYLTLVNGAADLEGYAGTGNSVSVLSGR
LSYVLGLEGPAVTVDTACSSSSLVALHQAAQALRQGECSLAVAGGVTVMSTPDSHVEFSRQ RALSPDGR C RAFADGAD
30 GTGWSEGAGVLVVERLSEARRRGHTVLA VVRGSAVNQDGASNGLTAPNGPSQQRVIRSALASAGLGFGDV D LVEGHG
TG TALGDPIEAQALLATYGSAGTPVWLGSLKSNIGHTQAAAGVAGVIKAVEAMRRGVMPRTLHV D APSSHVEWSSGS
VELLTANRPWDGVGRPRRAAVSSFGISGTNAHVILEGVPAP EPAGTGQAPLLLSARSVSALAEFESRIAGLVPSRDL
AATLAGRAFFDHRAVILPDGDVVRGRAGGAPLVFVFAGQGSQRADMASRLAEFFPAFAAAHERVWSLLDVDEGLDVD
QTGLAQPALFAYEVALAELLGV RPD AVIGHSIGELAAAYVAGALSLEDACRLVSARARLMQDLPSGGAMVSVRVSEE
35 AARAVLRDGVEIAAVNGPQAIVLSGDEDAVLAAA AELGEFRRLRTSHAFHSGRMEPML EEFRLVASSVVFREPEIAM
SFVPSADYFVRQVRETVRFGEQVASFDAGAVFVEVGPDGSL SRLTGGSAAEPLTALAYLWVRGVGV DWAPYVGGGR
LDLGAPTYPFQ RERYWVRPRLAGRTTDERDALLISLVRDDVASVLGHPDRRRLATDRPLLELGFDSL TALRLRNRLA
AATDIALPATLIFDYPNIQAI AVHL

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SEQ ID NO: 137
EPLAVVGMACRYPPGGVASADDLWRLVTAGGDAIGPFPDDR GWELESLVDPDPEAVGRSTTGQGGFLADAAGFDAAFF
GISPREATAMDPQQRLLLEVSWAALEHAGLRADALRG SATGVFMGSNGQDYAGLLAGAPELEGWIGTGVSASV VSGR

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50869-016WO2

LSYFYGFEGPAVTVDTACSSSLVALHLAAQSLRTGESSLALVGGVTVMTSPTVFRSFSRQRCLAPDGRCKAFSAGAD
GTGWSEGVGVLVVERLSDARRNNHQILALVRGSAVNQDGASNGLTAPNGPSQQRVITAALTDARLTTTDLVEAHG
TGTTLGDPPIEAQAILATYGNRTTGNPVHLGSKNLGHTQAAAGIAGVIKAIQAIRHTTMPKSLHIDQPSPHVDWTS
GRVELLTSNQWPATDRPRRAAVSSFGVSGTNAHVILEEAPAPAEAVPPIRPVVSGPALPLVFSARDSGALATRTHL
5 SDGPGVAYALATSRSMDHRSVRIGDMTMTGTGATTDPEVVVFVPGQGTQWAGMGRALMDASPVFAERMNECAALEP
YLDLWAAIDAPDQVETLQPASWAVMVSLAAVWQAAGVRPAAVIGHSQGEIAAACVAGSITLQDAAAVVALRSKAIAA
SLGKGAMASIPLPVEEIELIDEVWVAALNGPSSTVVAGAPDAVEQVRARYDGRRIAVDYASHTPHVEALRGQVVSVP
SQTPAVPWFSTVDSEWVEGQLDDDYWFRNLQPVQFGPAAARFDDAVFIEVSARPVLPALDASVTVP SLRRDDGGP
ERMLASLAQAFVAGVAVDWTTIVPPAPFVDLPTYPFQHERFWIEGRVAAATGAERPRILLEVVLAETATV LGHGGA
10 AIGPDRAFQDLGFDSLTAVELRNRLAAATALTLPTTLVFNHPTPEALAAHL

SEQ ID NO: 138

ELVAIVGMACRLPGDVASPEDLWRLVAEGRDAVGPF PADRGWNLGTLDDPDAAGRSYVKEGGFLAGAAHFDPGFFGI
GPREALGMDPQQRILLEIAWESLERARIAPGSLRGSETGVYVGAAAQGYGVDAPLEGNNLTGGSTSAMSGRVAYS LG
15 LHGPAVTIDTACSSSLVALHLAAQALRNTECTLALAGGVAVMASPVLFTEFSRQRGLAPDGRCKAFAAAADGTGWSE
GAGLVVLERLSDAERHGHFVLAVIRGSAVNSDGASNGLTAPNGTAQRRVIRSALRAAGLGAGDVDVVEAHGTGTTLG
DPVEADALIATYGQRP GMPVVRIGSLKSNIGHTVAAAAGVAGVIK MVEAMRHDTMPRTLHVDRPTPHVDWSAGAAELL
TGEQPWPRGDRPRRAAVSAFGLSGTNAHLILEDVAPGAASGAEP PGAADETVPLLLSADDLPAVRDQAARLRAYLLA
RPELRMRDVAYALATTRTARPHRAAVAATEREFLRELALLAAGDQGP GTQLGEAVPHRRVAF LFDGQGTQRHGMGRA
20 LHQRHPVFAAAWDEVCAALDPLLGRGVADVYFAEAGRDLADDPLYTQAGLFALEVALYRLLTSWGVTPDAVAGHSVG
EVAAAHVAGVLSLPDAAALLAARGAALRRLPAGAMAAIRASEADTRAVLPDLDVAAVNGPEMTVVSGAPDAVDRFI
AEQAGAGRQVRRLRVGRAYHSRHVDAVLA EFGATLSALTFHEPVLPVVSTVTGRPAGAGDLTTPEYWLRHARRPVRF
GAALAALSELGMDSFVEVGPSGSLSSMAGETVAGTFHPMLDRRVPDEIAVAAGELFTAGMVL DWA AVLAGGRTIDL P
VYPFRRREFYWL GARRYDLMAAAEERRDALLDLVRVQVALLLGRADAIGVRDNTSFLDVGLDSL GASRLRNRLAAATGL
25 TLPGGVAFDHPTPARLADHL

SEQ ID NO: 139

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDATSGFPVDRGWADSSMRGGFLDAAADFDAFFGISPREALAMDPQQ
RLVLEASWEAFERAGIEPGSVRGSDTGVMGAFSGCYGAGADLGGFCVTAGAVSVLSGRVSYFFGLEGPAVTVDTAC
30 SSSLVALHQAGHALRQGECSLALVGGVTVMSTPDIFAEFSRQGGLASDGRCKAFADTADGTSWSEGVGVLVVERLSD
ARAKGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRV IQAAL THAGLTAEVDVVEAHGTGTTLGDPPIEAQAVIATY
CRDRERPVL LGS LKSNVGHTQAAAGVSGVIKVMALQHGVVPRTLHVDEPSRHVDWTACAVRLATESQPWPD TGRPR
RAAVSSFGVSGTNAHVILEGVAEEPAQSEESSELVPLVISAKTPAALTRLEERLRAYLTAESNLSAVASTLAETRSL
FEHRAVLLGDDTIKGT AQPNPRVVVFVSGQGSQRAGMGDELAAAFPVFAKIRQQVWDLLDVPDLEVNDTGHAQPALF
35 ALQVALFGLLESWGVRPQALIGHSIGELAAGYVSGIWSLED ACTLV SARARLMQSLPPGGAMVAVPVSEQQARAVLT
DCVEIAAVNGPSSVVLSGDEEAVLR AAAALDGRSKRLVTSHAFHSARMEPMLDEFRAVAEQ LTYRAPRIPMAVGEGP
EYWVRQVRET VRFGEQVA AHDGAVFVELGPEGTLARLIDGVAVLDREDEPRAALTALGKLHV RGVRVDWPLTSGRRV
DLPTYAFQ RERYWATALTPAEREQALLKLVRDSA AVVLGYTDAVPVSGSFKDLGIDSLTAVELRNSLATTTGLRLPA
TLVFDYPTPATLAARL

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SEQ ID NO: 140
EPLAIVGMACRLPGGVSSPEDLWRLVESGTD A IAPFP TDRGWDVEALFDPDPDAAGKSYCVRGGF LDGVADF DASFF

GISPREALAMDPQQRLILEASWEAFERAGIDPADARGSDTGVMGAFTSGYGADLEGFGGTAGALSVLSGRVSYFFG
LEGPAVTVDTACSSSLFALHQAGYALRQGECSMALVGGVTVMATPRTFVEFSRQRGLASDGRCKAFGDTADGTGWAE
GVGVLLVERLSDAQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAALHNARLTPADVVDVVEAHGTGTTLG
DPIEAQAVIAAYGQGRDEPLLLGSLKSNVGHTQAAAGVSGVIKVMMALQHGVVPRTLHVDEPSRHVDWTAGEVRLVT
5 ENQSWPDTGRPRRAGVSAFGVSGTNAHVILEGPPTQPPATAPQEPAPLVISAKTPAALADYEGRLRAYLAATPGTDA
RALAVTRSLFEHRAVLLGDDTISGAAVTDPRVVFVFPQGQWQWLGMGVALRDSSVVFAERMTECAAALSEFVDWDLF
AVLDDPAVVDRVDVVQPACWAVMVSLAAVWQAAGVHPDAVVGHSSQGEIAAACVAGAI SLRDAARVVALRSRLIGERL
GQGAMASVTLPADEISLVDGVWIAAYNGPASTVIAGSPDAVDQMVGDRVRRIAVDYASHSPQVEQIKDELLDITADV
GSRTPTVPWFSTVDGSWIEGPLDADYWYRNLRQPVGFFHFAVEALRALGETVFVEVSASPVLLPAMDDALTVATLRRD
10 DGTIARMHTALAEAHVHGVNVDWAAVLGVAARHVDLPTYAFQRQRFWADERELASLGPAEREQALRKLVSDTAAGVL
GYADPGAVPIKAAFRELGVDSLTAVELRNGLAKATGMRLPATMVFDYPTPHALAAARL

SEQ ID NO: 141

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDATSGFPVDRGWADSSMRGGFLDAAADFDAFFGISPREALAMDPQQ
15 GISPREALAMDPQQRLILEASWEAFERAGIEPGSVRGSDTGVMGAFSGGYGADVEGFGATAGAGSVLSGRVSYFFG
LEGPAITVDTACSSSLVALHQAGYSLRQGECSLALVGGATVMAKPQSFVEFSRQRGLAADGRCKAFADAADGTGWAE
GVGVLLVERLSDAERNNGHQLAVVRSSAVNQDGASNGLSAPNGPSQQRVIRQALANARLTAADVVDVVEAHGTGTTLG
DPIEAQALIAAYGQDREWPLLLGSLKSNVGHTQAAAGVSGVIKVMMALQHGVVPRTLHVDEPSRHVDWTAGAVRLVT
DNQWPETGRPRRAGVSSFGVSGTNAHVILESPPTQPSGTFKKPAHEPQPLIISAKTPAALADYEDRLGAYLTAAPG
20 VDVPAAVATLAVTRSLFEHRAVLLGDNTVTGTAITDPRVVFVFPQGQWQWLGMGAALRGSSVVFAERMTECAAALSE
FVDWDLFAVLDDPAVVDRVDVVQPACWAVMVSLAAVWQAAGVHPDAVVGHSSQGEIAAACVASAVSLRDAARVVALRS
RLISERLGQGAMASVALPADQIVLADGVWIAAHNGPTSTVVAGSPDAVEQMLGDRVRKIAVDYASHTPHVEQIKTEL
LGITAGIGSRTPTVPWFSTVDGSWIEGPLDADYWYRNLRQPVGFDAAVGRLRALGATVFVEVSASPVLLPAMDDAVT
IATLRRDEGSITRMHTALAEAHVLGVNVDWPTLLGDTDRRALDLPTYAFQRQRYWGDAAGLAPAEREQALLKLVDRS
25 AALVLGYAGGDAVPATDAFKDLGIDSLTAVELRNGLAKATGLRLPATLVFDYPTPQVLAARL

SEQ ID NO: 142

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDATSGFPVDRGWADSSMRGGFLDAAADFDAFFGISPREALAMDPQQ
RLVLEASWEAFERAGIEPGSVRGSDIGVFMGAYPGGYGIGADLAGFGATAGAGSVLSGRVSYFFGLEGPAVTVDTAC
30 SSSLVALHQAGHALRLGECSLALVGGVTVMATPDTFVEFARQGGGLASDGRSKAFADSADGAGFSEGVGVLLVERLS
AQRHGHHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAALAHAGLAPHEVDVVEAHGTGTTLGDPPIEAQAVIATY
GQDRDEPLLLCSVKSNVGHTQAAACVAGVIKVMMALRHGVVPQTLHVDEPSRHVDWTAGAVRLLTEKQPWPSTDRPR
RAGVSSFGISGTNAHVILEGVAAEPAQSEDSELVPLVISAKTPAALTQVEERLRAYLTAESNLSAVASTLAETRSL
FEHRAVLLDGHAVRGVAESNPRVVFVFSGQGSQRACMGDELAFAFPVFAKIRGQVWDLLDVPDLVDVNDTGHQAQPALF
35 ALQVALFGLLESWGVRPHALIGHSIGELAAGYVSGIWSLEDACALVSARARLMQALPPGGAMVAVPVSEQQARAVLT
DGVEVAAVNGPSSAVLSGDEEAVLRAAAALGGRWKRLATSHAFHSARMEPMLDEFRAVAEQLTYPRIIPMAVGEGP
EYWVRQVRETVRFGEQVAAHDGAVFVELGPDGSLARLIDGIATLDRDDEPRVALTALAELHVRGVDVDWPLTSCRRV
DLPTYAFQRQRYWIDRAGRTPAEREQALLKVVRDSAATVLGHADGGSGVAAAFAFKDLGVDSLTAVELRNSLAKATGL
RLPATLVFDYPTPAAVAVRL

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SEQ ID NO: 143

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDATSGFPTDRGWADSSMRGGFLVAAADFDAFFGISPREALAMDPQQ

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50869-016WO2

RLVLEASWEAFERAGIEPGTVRGSDTGVMGAYPGGYGIGADLAGFGATAGAGSVLSGRVSYFFGLEGPAVTVDTAC
SSSLVALHQAGHALRQGECSLALVGGVTVMATPDLFVEFARQGGLASDGRCKAFGDTADGTGWAEGVGVLLVERLSD
AQAKGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAALHNARLTPADVVDVEAHGTGTTLGDP IEAQAVIAAY
GQGRDEPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHGVVPRTLHVDEPSSHVDWTAGAVRLVTENQSWPDTGRPR
5 RAAVSAFGVSGTNAHVILESSAAPSPTIPQPPSAEPMPLVISAKTPAALADYEGRLRAYLTAPGVDVPAVAATLAVT
RSLFEHRAVLLGGNTVTGTAVADPRVVFVFPQGQGWQLGMGAALRGSSVVF AERMTECAAALSEFVDWDLFAVLDDP
AVVDRVDVVQPACWAVMVSLAAVWQAAGVHPDAVVGHSQGEIAAACVAGALS LRDAARVVALRSRLIGERLGRGAMA
SVSLPADQIVLADGVWIAAHNGPASTVIAGGAGAVDQMVGERVRRIAVDYASHTPDVEQIQTELLDITADVGSQAPV
VPWFSTVDGVWVDGPLDRDYWYRNLRQPVGFHPAVEALQALGETVFVEVSASPVLLPAMDDAVTVATLRRDEGSITR
10 MHTALAEAHVLGVNVDWPTVVGDTRRTLDLPTYAFQHHRYWISAAARLDGLTAAEKHSLLLDIVLANAATVLGHHT
VDTIAPDKPFKDLGIDSLTAVELRNGLAKATGLRLPATLVFDYPTPDMAAARL

SEQ ID NO: 144

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISDFPTDRGWADAAGAPYSPQGGFVDAAADFDAAFFGISPREALA
15 MDPQQRLVLEASWEAFERAGIEPGTVRGSDTGVMGAYPGGYGIGADQAGFGTTAGAGSVLSGRVSYFFGLEGPAVT
VDTACSSSLVALHQAGHALRQGECSLALVGGVTVMGTPDIFAEFSRQGGLASDGRCKAFGDDADGTGWGEGVGILLV
ERLSDAQRHSHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAALAHAGLAPHEVDVVEAHGTGTTLGDP IEAQQA
VIATYGQDRDEPLLLGSVKSNVGHTQAAAGVAGVIKMVMALRHGVVPRTLHADQPSRHVDWTAGAVRLATENQPWPA
IDRPRRAGVSSFGISGTNAHVILEGVAE EPAQSEESSPLMPLVISAKTPAALTRLEERLRAYLA AKPETS LGAVAST
20 LAETRSLFEHRAVLLNGDVVRGVAEPNPRVVFVFSGQGSQRAGMGDEVA AAFPVF AKIRRQVWDLLDVPDLVDNDTG
HAQPALFALQVALFGLLESWGVRPDALIGH SIGELAAGYVSGIWSLEDACALVSARARLMQALPAGGAMVAVPVSEQ
QARAVLTDGVEIAAVNGPSSVVLSGDEEAVLR AAAGLGSRWKRLATSHAFHSARMEPMLDEF RVVAEQLSYKTPRIP
VAVGEGPEYWVRQVRETVRFGEHVA AHDGAVFVELGPDGSLARLIDGIATLDRDDEPRAALTALAE LHVRGVDVDWP
LTSGRRVDLPTYAFQRQRYWTTAGLTRAEREQALLKLVRDTAAVVLGYGDGNAV PVTA AFKDLGVDSL TAVELRNGL
25 AEAIGLRLPATLVFDYPTPATLAVRL

SEQ ID NO: 145

EPLAIVGMACRLPGGVESPDDLWRLVESGTD AITGFPTDRGWPDVTGTSHSQHG GFLHTAADFDAAFFGISPREALA
MDPQQRLILEASWEAFERAGINPADAHGTDTGVFMGAFSAGYDADRDDSPATAGAVSVLSGRISYFFGLEGPAMTVD
30 TACSSSLVALHQAGYSLRQGECSMALVGGVTVMATPRTFVEFSRQGGLASDGRCKAFGDTADGTGWSEGVGVLVVER
LSDARAKGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALHNAHLTPADVVDVEAHGTGTTLGDP IEAQAVI
AAYGQDRDEPLLLGSIKSNVGHTQAAAGVSGVIKMVMALRHGVVPRTLHADQPSRHVDWNAGAVQLVTENQSWPETG
RPRRAAVSSFGISGTNAHVILEGVPEQPAQPEPPSERVPLMISAKSTSALSQLEDRLRAYLAARPEASLGAVASTLA
TRSLFEHRAVLLDGQVVKGVAEPNPRVVFVFSGQGSQRAGMGDELA AAFPVF AKIRGQVWDLLDVPDLVDNDTGHAQ
35 PALFALQVALFGLLESWGVRPDALIGH SIGELAAGYVSGIWSLEDACTLV SARARLMQALPAGGAMVAVPVSEQQAR
AVLTGGVEIAAVNGPSSVVLSGDEGAVLR AAAALGGRWKRLATSHAFHSARMEPMLDEFRAAAEQ LTYQTPRIPMVV
GDGPDYWVRQVRETVRFGEQVA AHDGAVFVELGPDRLARLIDGIATLDRDDEPRAALTALAE LHVRGVDVDWPHDG
QLVDLPTYAFQRERYWATALAALPLAEREQALLAVVSDNAAVVLGYAEGRDVTQTAAFKDLGVDSL TAVELRN TLAK
ATGLRLPATIVFDYPTPDTLAARL

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SEQ ID NO: 146

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISRFPDDR GWDVEGLFDPDPDAPGKSY SVEGGFLDAVADFDAAFF

GISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTGVMGAYSGGYGIGADLPGLGVTAGAVSVVSGRVSYF
FGLEGPAVTVDTACSSSLVALHQAGHALRRRECSLALVGGVTVMATPFGFVEFSRQRGLAADGRCKAFADTADGTSW
SEGVGVLVVERLSDARANGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIQAALAHADLAPHEVDVVEAHGTGTR
LGDPIEAQA VIATY GQGRDEPLLLGSIKSNVGHTQAAAGVSGVIKMVMALRHGVVPQTLHVDEPTQHVDWTAGAVRL
5 ATENQPWPD TGRPRRAGVSSFGVSGTNAHVILEGVAEEPAQSEESSELVPLVISAKTPAALTRLEERLRAYLSAESN
LSAVASTLAETRSLF'EHRVLLGDDTIKGTAQPNPRVVF'V'FSGQGSQRAGMGDELA AAF'PVFARIRRQVWDLLDVPD
VSVDDTGFAQPALFALQVALFGLLESWGV RPDALIGH SIGELAAGYVSGIWSLED ACTLV SARARLMQALPAGGAMV
AVPVSEQQARAVLTGGVEIAAVNGPSSVVLSGDEEAVLRAAAAALGGRSKRLVTSHAFHSARMEPMLDEFQAVAEQLT
YQAPRIPMAVG DGPDYWVRQVRET VRF GDQVAAQDGA VFVELGPDRSLARLIDGIATLDRDDEPRAALTALAE LHVR
10 GVDVDWPLTSGRRVDLPTYAFQRQRYWIDSALT PAEREQALLKVVRDSA AVVLGYTDAVPVSGSFKDLGIDSLTAVE
LRNSLAKVTGLRLPATLVFDYPTPATLAARL

SEQ ID NO: 147

EPLAIVGMACRLPGGVESPD DLWRLVESGTDAITGFPTDRGWP DVTGTSHSQHG GFLHTAADFDAAFFGISPREALA
15 MDPQQRLILEASWEAFERAGINPADAHGTDTGVFMGAYSGGYGIGADLAGFGATSGATSVLSGRVSYFFGLEGPAIT
VDTACSSSLVALHQAGHALRQGE CAMALVGGVTVMATPDIFVEFSRQRGLAADGRCKAFADAADGTGWAEGVGVLLV
ERLSDAERNGHRVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALHNARLTPADV DVVEAHGTGTTLGDPIEAQA
VIAAYGQGRDEPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHGVVPRTLHVDEPSSHVDWTAGAVRLATENQSWPD
TGRPRRAAVSAFGVSGTNAHVILESSAAPSPTIPQPPSAEPMPLVISAKTPAALADYEDRLRAYLTNPGVDVPAVAA
20 TLAMTRSLFEHRVLLGGNTVTGTAVADPRVVFVFPQGQWQLGMGAALRGSSVVF AERMTECAAALSEFVDWDLFA
VLDDPAVVDRVDVVPACWAVMVSLAAVWQAAGVHPDAVLGHSQGEIAAACVAGAI SLQDAARVVALRSQAI SGLSG
KGAMASIALPADQIALPDGAWIAAHNGPASTVVAGSPDAVEQMLGDRVRKIAVDYASHTPHVEQIQTELLDITAGIG
SRTPTIPWFSTVDGMWVDGPLDRDYWYRNLRQPVG FHPAVEALQALGETVFVEVSASPVLLPAMDDAVTVATLRRDE
GSITRMHTALAEAHVLGVNV DWPTLLGDTGRRTL DLPTYAFQH HRYWINGSRLIGRTTAEQHRLMLAFVLGNVASVL
25 GHGSADAIAADKPFKDLGMDSLTSVELRNSLAKATELRLPATIVFDHPTADALAAHL

SEQ ID NO: 148

EPIAIVSMACRVPGCVTSPEGLWRLVESGTD AISAFPGDRGWDIANLYSPDPDAPGKSYSVQGGFLDGAAAFDASFF
GISPREALGMDPQQRVLLETAWEAVERARIDPRSLRGRDVG VYVGGA AQGYGLGAAEAHRDNLITGGSISLLSGRLS
30 YALGLEGPGLTVDTACSSSLVALHLAAQALRQGECSLALVSGVSVMPTPDVFVEFSRQRGLASDGRCKSF AASADGT
SWSEGVGVLVLERLSEARRLGHQVLAVVRGTAVNSDGASNGLTAPNGAAQQRVIRQALANAGLSTADVDAVEAHGTG
TTLGDPIEAEA I L ATY GKDRSTPVWLGSLKSNIGHTMAASGV LGVIKMVEAMRHGVLPRTLHVDEPSPHVDWAAGEV
ALLTENQTWPGDVRRRAGVSSF'GLSGTNAHV VLEQDEAPAAPVTTKESG PLPWVLSAQSPKALRQRAGQLATALAE
DSTWHPLDVAYS LATTRSDFAHRVVVGADRELLRTL GKVADGAGWPGLTTGTAKARRVAF LFDCQCTQRLTMGQGL
35 YGSFPFAFARAWDTVSAEFGKHL DHPLADVFDGSGGAATADLVDDPLYAQAGIFAVEVALVELLAEWGV RPDVVTGH
SIGEAAAAYTAGMLSLSDVTTLIVARGAALRSAPPGAMLALRAGEQEVRNFLDGTGAALDLAAVNGPAAVVVS GAPD
AVTDFASAWTASGREARRLKVRRAFHSRHVEGVLD DFRTALESLSFRTPLLPVVSTVTGRLIDPAEMGTPEYWLDQV
RQPVRFQEAVQELAGQG VGTFVEVGPSGTLASAGMECLDGDASFHALLRPRSAEDVG VLTALAE LHAGGTAIDWPTV
LAGGRPMDLPVYPFQHQS YWL VSTDEPRTTLELVHLEVARVLGITDPD TVLDDASFLELGFDSLGGVRLRNRLAQVT
40 GLTLPPTLLFDHVTPAALAAELD

SEQ ID NO: 149

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPADRGWDVENLYDPDPEAAGKSYCVQGGFLDSAGGFDASFF
GISPREALAMDPQQRLVLEASWEAFERAGIEPGSLRGSDTGVMGAYPGGYGVGADLGGFGA TAGAVSVLSGRVSYF
FGLEGPAVTVD TACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQSFVEFSRQRGLASDGRCKAFAD AADGTGW
5 AEGAGVLLVERLSDAQAKGHQVLAVVRGSAVNQDGASNGLSAPNGPSQQRVIRAALS NAGLSTAEVDVVEAHGTGTT
LGDPIEAQALLATY GQDREQPLLLG SVKSNLGHTQAAAGVSGVIKMVMALQHGLVPRTLHVDEPSRHVDWTDGAVAL
VTENQPWPDMGRPRRAGVSSFGISGTNAHVILESAPPTQAVDDVPPAEAPVVASELVPLVISARTLPALVEYEDRLR
AYLAASPGVDVRCVASTLAVTRSVFEHRAVLLGDDTVTGTTVSDPRVVVFVFPQGQSQRAGMGEELAAAFPVFARIHQ
QVWGLLDVPDLEVNETGYAQPALFALQVALFGLLESWGVRPDAVVGH SVGELAAGYVSGLWSLED ACTLV SARARLM
10 QALPPGGVMVAVPVSEDEARAVLGEGVEIAAVNGPSSVVLSGDETAVLQAAAALGKSTRLATSHAFHSARMEPML EE
FRTVAERLTYQTPRLAMAAGDRVTTA EYWVRQVRD TVRFGEQVASYEDAVFIELGADRSLARLVDGVAMLHTDHEAQ
AAISALAHLYVNGVTVDWTALLGDAPATRVDLPTYAFQH QRYWLEGWLAALAPEERAKALLKVVRDTAATVLGHADA
RTIPVTGAFRDLGIDSLTAVELRNGLAKVTGLRLPATLVFDYPTPAVLAARL

15 SEQ ID NO: 150

EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFPADRGWDAESLFDPDPAVGKSYCVEGGFLDSAASF DAGFFG
ISPREALAMDPQQRLIMEVSWEAFERAGIEPGSVRGSDTGVMGAYAGGYGAGADLGGFAATASATSVLSGRVSYFF
GLEGPAITVD TACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQSFVEFSRQRGLASDGRCKAFADSADGTGWA
EGVGVLLVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLSAPNGPSQQGVIQAALS NAGLAAHEVDVVEAHGTGTTL
20 GDPIEAQAVIATY GQDRERPLLLGSLKSNIGHAQ AASGVSGVIKMVMALQHNTVPRTLHVDEPSRHVDWAAGAVELV
RENQPWPGTDRPRRAGVSSFGVSGTNAHVILESAPPAQPAEEAQPVETPVVASDVLPLVISAKTQPALTEHEDRLRA
YLAASPGVDTRAVASTLAVTRSVFEHRAVLLGDDTVTGTA VSDPRVVVFVFPQGQWQWLGMG SALRDSSIVFAERMAE
CAAALREFVDWDLFTVLDDPAVVDRVDVVQPASWAMMVSLAAVWQAAGVRPDAVIGH SQGEIAAACVAGAVSMRDAA
RIVTLRSQAIAGLAGRCAMASVALPAQDVELVDGAWIAAHNGPASTVIAGTPEAVDHVLT AHEARGVRVRRITVDYA
25 SHTPHVELIRDEL LDITS DSSSQAPVVPWLSTVDG SWVDSPLDVEYWYRNLREPVG FHPAVGQLQAQGD TVFVEVSA
SPVLLQAMDDD VVTVATLRRDDGDATRMLTALAQA YVHGVTVDWPA ILGTTTTTRVDLPTYAFQH QRYWVEWLAALAP
AEREKALLKVVCD SAAVVLGHADARTIPVTGA FKDLGVDSL TAVELRNSLVKATGLRLPATMVFDYPTPTAL AARLD

SEQ ID NO: 151

30 EPLAIVGMACRLPGGVSSPEDLWRLVESGTD AVSGFPTDRGWDVEGLFDPDPDAAGKSYRAEGGFLDTAAGFDAGFF
GISPREALAMDPQQRL LLEVSWEA FERAGIEPGSVRGSDTG VF IGAFPVGYGAGAAREGYGATAAPNVLSGRLSYFF
GLEGPAITMD TACSSSLVALHLAAQALRN GECSMALAGGVTVMATPEVFTEFARQRGLASDGRCKAFADSADGAGFS
EGAGLLLVERLS DARRNGHQVLAVVRGSAVNQDGASNGFTAPNGPAQQRVIRQALANAGLT TAEVDVVEAHGTGTTL
GDPIEAQAVIATY GQDREQPLLLGTLKSNVGHTQAAAGVSGVIKMVMALQHSTVPRTLHVNEPSRHVDWSAGAVELV
35 TENQSWPVTGRPRRAGVSAFGVSGTNAHV VLESAPPAQSVNNAQPVATPVVASELVPLVISAKTLPALTEHEDRLRA
YLAASPGADMRAVGSTLALTRSVFEHRAVLLGHDTVTVTGTGTAVSNPRVVVFVFPQGQWQWLGMG SALRGSSVVFAE
RMAECAALSEFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGH SQGEIAAACVAGAVSL
RDAARIVTLRSQAIAGLAGRGAMASVALPAHEIELVDGAWIAAHNGPASTVVAGAPEAVDRVLAVHEARGVRVRRIA
VDYASHTPHVELIRDEL LDITAGIGSQAPVVPWLSTVDGTWVEGPLDVEYWYRNLREPVG FDSAVGQLRAEGD TVFV
40 EVSASPVLLQAMDDD VVTVATLRRDDGDATRMLTALAQA FVEGVTVDWPA ILGTATTRVDLPTYAFQH QRFWAEGWL
ARLAPVEREKALLKLVCDGAATVLGHADASTIPATAAFKDLGIDSLTAVELRNSLT KATGLRLPATLVFDYPTPTAL
AARL

SEQ ID NO: 152

EPLAIVGMACRLPGGVSSPEDLWRLLESGETDAVSGFPTDRGWDVENLFGPAAGDSYRLQGGFLDAAAGFDASFFGIS
PREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGTDGTGVFMGAYPGGYGIGADLGGFGATASAVSVLSGRVSYFFGL
5 EGPAITVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQTFVEFARQGGLAGDGRSKAFADSADGAGFSEG
VGVLLVERLSDAQAKGHQVLAMLRSSAVNQDGASNGLTAPNGPSQQRVIIQAALSNAGLAAHEVDVVEAHGTGTTLGD
PIEAQALLATYQGDRQPLLLGSVKSNLGHTQAAAGVSGVIKVMALQRGFVPRTLHVDEPSRHVDWSAGAVALTVE
NQPWPDMMGRARRAGVSSFGISGTNAHVILEAPPTQPADNAVIERAPEWLPVISARTQSALTEHEGRLRAYLAASP
GVDMAVASTLAMTRSVFEHRAVLLGDDTVTGTAATDPRVVFVFPQGGSQRAGMGEELAAAFPVFARIHQQVWDLDD
10 VPDLEVNETGYAQPALFALQVALFGLLESWGVRPDAVVGHVSVGELAAGYVSGLWSLEDACTLV SARARLMQALPAGG
VMVAVPVSEDEARAVLGEGVEIAAVNGPSSVVLSGDEAAVLQAAEGLGKWTRLATSHAFHSARMEPML EEFRTVAEG
LTYRTPQVSMAAGDQVTTTEYWVRQVRD TVRFGEQVASYEDAVFVELGADRSLARLVDGVAMLHGDHEAQAAVSALA
HLYVNGVTVDWPALLGDAPATRVLDLPTIYAFQHQRWLEGRWLAALAPEERAKALVKVVCDSAATVLGHADVDSIPVT
AAFRDLGVDSLTAVELRNSLT KATGLRLPATLVFDYPTPGALAAARL

15

SEQ ID NO: 153

EPLAIVGMACRLPGGVSSPEDLWRLVESGETDAISGFPTDRGWDVENLSDPDAAGKSYCVEGGFLATAANFDASFFGI
SPREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGSDTGVMGAFPGGYGIGADLEGYGATAGLNVLSGRLSYFFGL
EGPAVTVDTACSSSLVALHQAGYALRQGECSLALIGGVTVMATPHTFVEFSRQRGLASDGRCKAFADSADGTGWSEG
20 VGVLLVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLSAPNGPSQQRVIRQALANAGLT TAEVDVVEAHGTGTTLGD
PIEAQAVIATYQGDRDQPVLLGSVKSNVGHTQAAAGVSGVIKVMALQHGLVPRTLHVDEPSRHVDWTDGAVELVTE
NQSWPEAGRPRRAGVSSFGVSGTNAHVILEAPPTQAVDDVRPADAPVVASVMASELVPLVISAKTQSALAEYEGRL
RAYLAASPGVDMAVASTLAMTRSVFEHRAVIVGDDTVSGTAATDPRVVFVFPQGGSQRAGMGAELAAAFPVFARIH
QQVWDLDDVPDLEVNETGYAQPALFALQVALFGLLESWGVRPDAVIGHVSVGELAAAYVSGLWSLEDACTLV SARARL
25 MQALPAGGVMVAVPVSEDEARAVLGEGVEIAAVNGPSSVVLSGDEAAVLQAAEGLGKWTRLATSHAFHSARMEPML E
EFRAVAQCLTYHAPGVVMAAGDRVMTAEYWVRQVRD TVRFGEQVASYEDAVFVELGADRSLARLVDGVAMLHGDHET
QAAIGALAHLYVNGVTVDWTALLGDVPVTRVDLPTIYAFQQQRYWAERWLAALAPAEREKALLKLVSDGAATVLGHAD
TSTIPATTAFKDLGIDSLTAVELRNSLAKATELRLPATLVFDYPTPTALAAARLD

30 SEQ ID NO: 154

EPLAIVGMACRLPGGVSSPEDLWRLVESGETDAISGFPTDRGWDVENLYDPDPDAPGKSYSVQGGFLDAAAGFDASFF
GISPREALAMDPQQRLMLEVSWEAFERAGIEPGSVRGSDTGVF IGAYPGGYGIGADLGGFGTTAGAASVLSGRVSYF
FGLEGPAFTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQTFVEFSRQRGLSADGRCKAFADAADGTGW
AEGVGVLLVERLSDAQANGHQILAVVRSSAVNQDGASNGLSAPNGPSQQRVIRAALSNAGLAPHEVDVVEAHGTGTT
35 LGDPIEAQAVIATYQGGRGEPLLLGSLKSNVGHTQAAAGVSGVIKVMALQHSMVPRTLHVDEPSRHVDWSAGAVEL
VAENQWPETGRPRRAGVSSFGISGTNAHVILESAPAQSVGDTAGSTPVLVSELVPLVISAKTQPALTEHEDRLRAY
LAASPGVDIRAVASTLAVTRSVFEHRAVLLGDET VTGTAVSDPRIVFVFPQGQWQWLGMGSALRDSVVF AERMAEC
AAALSEFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGHVSVGELAAAYVSGLWSLEDACTLV SARARL
IVTLRSQAIAGLAGRGAMASVALPAQDVELVDGAWIAAHNGPASTVIAGTPEAVDHVLTAEHAQGVRRRITVDYAS
40 HTPHVELIRDELDDITS DSSSQTPLPVWLSTVDGTWVDSPLDGEYWYRNLREPVGFHPAVSQLQAQGD TVFVEVSAS
PVLLQAMDDDDVVTVATLRRDDGDATRMLTALAQAAYVHGVTVDWRAVLGDVPATRVLDLPTIYAFQHQRWAEAWLVGLA
PEERAKALLKVVRDSAATVLGHADARSIPATGAFKDLGVDSLTAVELRNSLT KATGLRLPATMVFDYPTPADLAARL

SEQ ID NO: 155

EPLAIVGMACRLPGGVSSPEDLWRLLESGTDAVSGFPTDRGWDVENLYDMAGKSHRAEGGF'LDAAAGF'DAGFF'GISP
REALAMDPQQRLVLEVSWEAFERAGIEPGSVRGSDTGVMGAYPGGYGAGADLGGFAATASATSVLSGRVSYFFGLE
5 GPAF'TVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPELFT'EF'SRQRGLASDGRCKAFADSADGTGWAEV
GVLLVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALSNAGLAAHEVDVVEAHGTGTTLGDP
IEAQAVIATYGQDRERPLLLGSLKSNIGHAQAASGVSGVIKMVMALQHNTVPRTLHVDEPSRHVDWAAGAVELVREN
QPWPGTDRPRRAGVSSFGVSGTNAHVILESAPPAQPAEEAQPVETPVVASDVLPLVISAKTQPALTEHEDRLRAYLA
ASPGVDTRAVASTLAVTRSVFEHRAVLLGDDTVTGTAVSDPRVVFVFPQGQWQWLGMGSALRDSSVVF'AERMAECA
10 ALSEFVDWDLFTVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGHSQGEIAAACVAGAVSLRDAARIV
TLRSQAIAGLAGRGAMASVALPAQDVELVDGAWIAAHNGPASTVIAGTPEAVDHVLTAEHARGVRVRRITVDYASHT
PHVELIRDELIDITSDDSSSQAPLVPWLSTVDGSWVDSPLDGEYWYRNLREPVGFHFAVGQLQAEGDTVFEVVSASPV
LLQAMDDDVVTVATLRRDDGDATRMLTALAQAAYVHGVTVDWPAILGTATTTRVDLPTYAFQHORYWLRSWLAALAPAE
REKALLKLVCD SAAMVLGHADARSIPAAGAFKDLGVDSLMAVELRNGLVKATGLRLPATLVFDYPTPTVLAARLD

15

SEQ ID NO: 156

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDVSGFPTDRGWDVENLYDSDPEAAGKSYCVQGGFLDTAAGFDAGFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSVRGSDTGVF'IGAF'PVGYGAGFDREGYGATSGPSVLSGRVSYVF
GLEGPAITMDTACSSSLVALHLAAQALRNGECSMALAGGVTVMATPEVFTEFARQRGLASDGRCKAFADSADGAGFS
20 EGAGLLLVERLSDARRNGHQVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRAALSNAGLSTADVVDVVEAHGTGTTL
GDPIEAQALLATYGQDREQPLLLGSLKSNIGHTQAASGVSGVIKMVMALRHGFVPRTLHVDEPSRHVDWAAGAVELV
RENQPWPGTDRPRRAGVSSFGVSGTNAHVVLESAPPAQPAEEEEQPVETPVVASDVLPLVISAKTQPALTEHEDRLRA
YLAASPGADTRAVASTLAVTRSVFEHRAVLLGDDAVTGTAVTDPRVVFVFPQGQWQWLGMGSALRDSSVVF'AERMAE
CAAALSEFVDWDLFAVLDDPAVVDRVDVVQPASWAVMVSLAAVWQAAGVRPDAVIGHSQGEIAAACVAGAVSLRDAA
25 RIVTLRSQAIAGLAGRGAMASVALPAHEIELVDGAWIAAHNGPASTVIAGTPEAVDHVLTAEHARGVRVRRITVDYA
SHTPHVELIRDELLGITAGIGSQPPVVPWLSTVDGSWVDSPLDGEYWYRNLREPVGFHFAVSQQLQAQGDVAVFEVSA
SPVLLQAMDDDVVTVATLRRDDGDATRMLTALAQAAYVHGVTVDWPAILGTTTARVLDLPTYAFQHORYWVKS
WLAAL APEERAKALLRVVCD SAATVLGHADIDSIPVTAAFKDLGVDSLTAVELRNSLAKATGLRLPATLVFDYPTPTALAAR
LD

30

SEQ ID NO: 157

EPLAIVGMACRLPGGVSSPEDLWRLVESGTDALSDFPADRGWDVENLYDPDPDASGKSYCVQGGFLDSAGGFDAFF
GISPREALAMDPQQRLVLEVSWEAFERAGIEPGSLRGSDTGVF'IGAY'PGGYGAGAGADLEGYGTTSGPSVLSGRVSY
FFGLEGPAITVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPDVFTEFARQRGLATDGRSKAFADSADGAG
35 FSEGIGVLLVERLSDAEAKGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQTALSNAGLTAEVDVVEGHGTGT
TLGDPIEAQAVIATYGQDREQPLLLGSLKSNIGHTQAAAGVSGVIKMVMALRHALVPRTLHVDEPSRHVDWTAGAVE
LVTENQPWPEIGRPRRAGVSSFGVSGTNAHVILESAPPTQAEDAAQPVEAPVMGSEPVPLVISAKTLPALNAHEDRL
RAYLAASPGVDMRAVASTLAMTRSMFEHRGVLLGDGTVSGTAVSDPRVVFVFPQGQSQRAGMGEELAAAFPVFARIH
QQVWDLLDVPDLVDNETGYAQPALFALQVALFGLLESWGVRPDAVIGHSVGELAAAYVSGVWSLEDACTLV SARARL
40 MQALPAGGVMVAVPVSEDEARAVLGEGVEIAAVNGPSSVVLSGDEAAVLQAAEGLCKWTRLATSHAFHSARMEP
MLE EFRVAEGLTYRTPQVAMAAGDQVMTAEYWVRQVRDTRVRFGEQVASFEDAVFVELGADRSLARLVDGVAM
LHGDHEA

QAAVGALAHLYVNGVSVEWSAVLGDVPVTRVDLPTYAFQHQRYWLEGRWLAALAPAEREKALLKLVSDGAATVLGHA
DTSTIPATTAFKDLGINSLTAVELRNSLAKATELRRLPATLVFDYPTPAALAARLD

SEQ ID NO: 158

5 EPLAIVGMACRLPGGVSSPEDLWRLLLESGTDAVSGFPTDRGWDVENLYDMAGKSHRAEGGF'LDAAAGF'DAGFF'GISP
REALAMDPQQRLVLEVSWEAFERAGIEPGSVRGS DTGVFMGAYPGGYGIGADLGGFGATASSVSVLSGRVSYFFGLE
GPAFTVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQTFVEFSRQGGLASDGRCKAFADAADGTGWAEGV
GVLLVERLS DARRNGHQVLAVVRGSAVNQDCASNGLTAPNGPSQQRVIRAALSNAGLSTA EVDVVEAHGTGTTLGDP
IEAQALIATY GQDRDQPVLLGSVKSNLGHTQAAAGVSGVIKMVMALQHGLVPRTLHVDEPSRHVDWSAGAVQLVTEN
10 QPWPDMGRARRAGVSSF'GISGTNAHVILESAPPTQPADNAVIERAPEWVPLVISARTQSALTEHEGRLRAYLAASPG
VDMRAVASTLAMTRSVFEHRAVLLGDDTVTGTAVSDPRAVFVFPQGCSQRAGMGEELAAAFPVFARIHQQVWDL LDV
PDLEVNETGYAQPALFAMQVALFGLLESWGVRPDAVIGHSVGELAAAYVSGVWSLEDACTLV SARARLMQALPAGGV
MVAVPVSEDEARAVLGEGVEIAAVNGPSSVVL SGDEAAVLQAAEGLGKWTRLATSHAFHSARMEPML EEFRAVAEGL
TYRTPQVSM AVGDQVTTAEYWVRQVRD TVRFGEQVASYEDAVFVELGADRSLARLVDGVAMLHGDHEIQAAIGALAH
15 LYVNGVTVDWPALLGDAPATRVDLPTYAFQHQRYWLEGRWLAALAPAEREDALLKLVRDS AALVLGHADASTIPAAA
AFKDLGIDSLTAVELRNSLAKATGLRLPNTTVFDYPTPAILATRL

SEQ ID NO: 159

20 EPLAVVGMACRLPGGVSSPEDLWRLVESGTDALISGFPADRGWDAESLFDPDPAVGKSYCVEGGFLDSAASF DAGFFG
ISPREALAMDPQQR LIMEVSWEAFERAGIEPGSVRGS DTGVFMGAYAGGYGAGADLGGFAATASATSVLSGRVSYFF
GLEGPAITVDTACSSSLVALHQAGYALRQGECSLALVGGVTVMATPQSFVEFSRQRGLASDGRCKAFADSADGTGWA
EGVGVL LVERLSDAQAKGHQVLAVVRSSAVNQDGASNGLTAPNGPSQQRVIQAALSNAGLAAHEVDVVEAHGTGTTL
GDPIEAQALIATYGGDRERPLLLGSLKSNIGHAQAASGVSGVIKMVMALQHNTVPRTLHVDEPSRHVDWAAGAVELV
RENQPWPGTDRPRRAGVSSFVSGTNAHVILESAPPAQPAEEAQPVETPVVASDVLPLVISAKTQPALTEHEDRLRA
25 YLAASPGADIRAVASTLAVTRSVFEHRAVLLGDDTVTGTAVTDPRI VFVFPQGQWQLGMGSALRDSSVVF AERMAE
CAAALREFVDWDLFTVLDDPAVVDRVDVVQPASWAMMVSLAAVWQAAGVRPDAVIGH SQGEIAAACVAGAVSLRDAA
RIVTLRSQAIAGLAGRGAMASVALPAQDVELVDGAWIAAHNGPASTVIAGTPEAVDHVLT AHEAQGVRVRRTITVDYA
SHTPHVELIRDEL LDITSDSSSQITPLVPWLSTVDGTWVDSPLDGEYWYRNLREPVG FHPAVSQLQAQGD TVFVEVSA
SPVLLQAMDDDVVTVATLRRDDGDATRMLTALAQA YVHGVTVDWPAILGTTTTRVDLPTYAFQH QRYWLKSRLTGRT
30 SVEQHRIMLELVLGEAASVLGHSSADAIATDTSFKDLGMDSLTAIELRNRLVAETGLQLPATMVF DYPTANALAAHL

SEQ ID NO: 160

35 EPIAIVAMACRLPGGVSSPEGLWHLVESCTDAISGFPTDRGWDVEGLFDPDPDAAGKSYCVQGGFLDTAADFDAPFF
GISPREALGMDPQQRLLETTWEAIERAQIDPKSLRGRDVGYYVGGAAQGYGVGVDDQHDNGITGSSVSLLSGRVSY
ALGLEPGVTVDTACSSSLVALHLASQALRQRECSLALVSGVSVMS SPAMFVEFSRQRGLSSDGRCKSFAASADGTI
WSEGVGVLVVERLSDARRLGHRVLATVRGSAVNSDGASNGLTAPNGTSQQRVIRQALANAGLTASDVDVVEAHGTGT
KLGDPIDAEAILATYQERSAPAWLGSLKSNIGHAMAASGVLSVIKMVEAMGHGSLPRTLHVDAPSPHVDWTSGSVA
LLTEHQPWPD DTKLRRAGVSSFGLSGTNAHVVLEQYQAPAPPVTPVTPAPPTPVTPVTPNEPGPLPWVLSAQSPKAL
40 REQAGRLYASLAGDSEWNSLDIGYSLATTRSDFAHRAVAVGSGREFLRALSKLADGAPWPGLTTATATAKARRVAFL
FDGQGTQRLCMGKELYDSYPAFARAWDTVSA GFDKHL D HSLTDVCFGE GGGSTTAGLVDDTLYAQAGIFAMEAALFGL
LEDWGV RPDFVAGHSIGEATAAYASGMLSLENTTLIVARGRALRTTPPGAMVALRAGEEEVREFLSRTGAALDLAA
VNSPEAVVVS GEPEPVADFEAAWTASGREARKLKVRHAFHSRHVEAVLDEFRTALES LKFRAPALPVVSTVTGRLID

QDEMGTP EYWLRQVRRPVRFQDAVRELAEQGVGTFVEVGP SGALASAGVECLGGDASFHAVLRPRSPEDVCLMTAIA
ELHAGGTAIDWAKVLSGGRAVDLPVYPFQHQS YWLAPAEPSYADEPRTMLELVHMEVASLLGMADPGVILDDSSFLE
LGFDSL SAVRLRNRLSKATGLDLPSTLLFEHPTSAE
LAAHLD

5

SEQ ID NO: 161

MSRAELVRPIYDLLRANAERLGDKMAYVDSRLALTHAELAARTGRIAGHLVDMGVDRGDRVAILLGNRVENIESYLA
IARASAVAVPLNPDATEAEVAHFLSDSGAVVVITDSAHLDDVRRRTAPAVTIVLVGEERIPPGVRSFAELATAEPQQS
ARDDLGLDEAAWMLYTS GTTGT PKGVLSTQGSGLWSAAYCDIPAWELTENDVLLWPAPLFHSLALHLCVLATTAVGA
TARIMNGFVASEVLEELTEHPCTVLVGVP T MFRYLLGAADTFEPRTSSLKMGLVAGSVAPASLIEGFEDVFGVPLLD
TYGCTETSGSLTVNWL SGERVPGSCGLPVPGLSLRFVDPI SGADVADGEEGELWASGPSIMIGYHEQPEATAEVLSD
GWYRTGDLARRSETGHVTITGRIKELIIRSGENIHPHEIEAVALDVPGVKDAAAAGKRHPVLGEVPVLYVVPETGGV
DADMVLAVCRERLSYFKVPEEIYRVDAIPRTASGKVKRSSLTEEPAELLAGASGGETLHRLEWIPLELPEQAAPDGH
VVVRVDSLASDDSDLADADLADAVRDLARSWLADKRRADSTLVFVTRRAVHTGPSDIPSPEHAAVWDAIRREQTENP
GVFVVIDVDDDDDDDDDDVNDREDDDTLLPALAGLGEPQVALRDGNPLVPRLAHANTPDSGSLTIPEDRAWLLEHSRS
GTLRDLALVPADAAERPLHPGEVRI SVRAAGLNFRDVLIALGTYPGEGLMGGEAAGVVLEV GSEVSD LAPGDRVFGL
VGSAGFTVAIADRRLGAIPDTWSFATAASIPIVFATAYYGLVDLAGLSAGESVLIHAAAGGVGMAATQIARHLGAR
IFATASVGKQHILSEAGLEDTRIAGSRTLAFREAF LNTTDGQGV DVVLNSLSGDFVDASLDLLPRGGRFLEMGKTDI
RDADRITADRP GTTYQAFDLLDAGPDRLREIIAELLPLFAQGVLRLPLLLTWDIRKARDAFSWMSRARHTGKITFTI
PRQLDPGGTVLIADGSGVLTGTVARHLVAEQGVRHLLLLSRSTPDEALINELIESGARVDTAVRDVSDRAGLEQALA
GISPEHPLTAVIHTGGPAVAHESHQLHGLTKRDLAA FVVSQDAPASVDALARRRRAEGLPTTTIAWGIPEAEAVV
VQGPLLGRAMASADSAHIVTRLNTVGLRALAAADTL PPLLRLNLVGAQTDNTQQQAWSRQLLAEEAAREQALRDLVRS
CVM DILGLS AADRYAPDKTFREM GIDSLTAVELRNSLAKATDLRLPATMVFDYPTPAMLVVRLGE

25

SEQ ID NO: 162

MSREEFIQPIHDLRLVNAERLGDKIAYADSRRELTHAELRTRTGRIAGHLVDLAVERGDRVAILLGNRVETIESYLA
IARAGAI AVPLNP DATGA EVAHFLADSGAVLVITDSAHLDDVRRRAAAAVTVVLVDEGPLPAGTRSFAELATAEPPTP
ARDDLGLDEAAWMLYTS GTTGT PKGVVSTQGSGLWSAANC DVPAWELTENDVLLWPAPLFHSLAHHLC LLATTAVGA
TARIMSGFVAGEVLHELEEHACTVLVGVP T MYHYLLGAVGEAGPRLPSLKMGLVAGAVSPPALIEGF'ERVFGVPLLD
TYGCTETTGS LTVNRLSGPRMPGSCGQAVPGISLRFVDPHTGAEVAEGEEGELWASGPSLMIGYHGRPDATREVLSD
GWYRTGDLARRSETGHVTITGRVKELIIRGGENIHPRDIEA VALELPGVRDAAAAGKQHPVLGEIPALYLVPDADGV
DAEAVLAACREKLSYFKVPEEIYRVDAIPRTL SGKVKRAALTEAPAELL SAASGN GSLYRLEWVPAETPPAGTGGPV
AVHVTRRAVATGPADLPDQEQAATWDALRGEQTGPGGPVLIDLDGADID DARLSALASLGEPQIVVRDDTPLVARLA
REKSPALTIPGERAWVLEPDHSGVLQELALVAADTDVRPLRPGEVRIEVRAAGLNFRDVLVALGTDLDGDGVFGAEGA
GVVLETGSDVRDLRPGDRVFG LLEGGHGSIAIADRRMLAVIPEGWSFATAASVPEVFVIAYYGLVDLAGLRAGESVL
IHAAATGGVGMAATQIARHLGAQVYATAGVGKQHILRDAGLGDDRIADSRTTDFREAFRDSTQGRGVDVVLNSLKGDF
VDASLDLLADGGRFLELGQTDIRDAGEIAAERP GTTYHSFTRMNAGPDRLREIIAELLALFEQGVLRPSPVHTWDIR
HAREAFSWMSGGRHTGKMVLTMPQRIDPGGTVLIAGDSEALARIAARHLGVRHLLLLDRGVADAAPDAVVCDVSDHDA
LERVLADLSPEHPLTAVIHTGGA AVTDEIRRLHDLTESLDLTDFVVSQDAPAAVEAFARSRRAHGLPVRTIAWGIP
EADPVVADEHLLGRALASAEQAQIVARVNTAGLRALTAANALPTLLRNLIRAEPEETGQSAWPHRFEAAGADREEAL
LDLIRANVVDILSLPTADRYAPDRTFREM GIDSLTAVGLRNSLAKATGLPLPTTMVFDYPTP

40

SEQ ID NO: 163

MSHAKLIQPIYDLLRVNAERLGDKIAYADSRHALTYTELEARTGRLAGHLADLGVERGDRVAILLDNRVETIESYLA
IARASAIIVPLNPAAAGDELAHF'LSDSGSLVITDSAHLDDVRLVAPAVTVVRVDEDPVPPGVRSF'AE'LVAVEPRTQ
ARDDLGLDEAAWMLYTS GTTGT PKGVVSTQGSGLWSA'AFCDVPAWELTEEDVLLWPAPLFHSLAHHLCLLATITAGA
5 TARIMNGFVASEVLNELEKHACTVLVCVPTMYHYLLGAVGEGESRTFSLKLGVVAGSVSPPALIEGF'EKA'FGAPLLD
TYGCTETTGS'LT'VNWLNGPRVPGSCGTAVPGVTLRFVDPSTGADVADGEEGELWASAPSVMTGYHGQPEATREVLTD
GWYHTGDLARRSETGHVTITCRIKELIIRGGENIHPQEIEAAVLGLPGVRDAAAACRPH'PVLGDVPALYIVPDADGV
DADAVLAACRERLSYFKVPEEIYRVDAIPRTMSGKVKRTSLTEAPAELLAGASGSDALYRLKWVPAETPGPAATGGH
VIVRVASLRADGTELAGAARDLARSWLS'DERRAGATLVFVTGRAVSAGPSDVPVPEHAAVWDAIRDEQTENPGAFVL
10 IDLEEAETE'EPESA'APEAGDPQADTPGADDTRLSTLVALGEPQIALRDSTPLVPRLAPESSTALTTPAARAWVLEPA
RSGTLRELSLVAADTDARPLRPGEVRVDVRAAGLNFRDVLIALGTYPGDGVMGGEAAGVVLEVGP'EVNDLSVGDRVF
GLVTDGFGPVTITDRLLAAMPQDWSFTTAASAAMAFATAHYGLVELAGLKAGESVLIHAATGGVGMAATQIAHHLG
AHIYATASSGKQHLLRAAGIDDDRIANSRTTGFRDAFLDSTGGRGVDVVLNSLSGEFVDSSLDLLAHGGRFIEMSTD
IRDAGRIAAERPGTTYQAFHLVDADPDRLREILTELLALFDQGILDPLPVQAWDIRQAREAFSWSR'ARHTGKLVLT
15 IPQHIDPDGTVLITGGSGGLAGVVARHLVADKGARRLLLLSCDTLDATLAAELTESGARVDTAVCDVSDRAALAQVL
AGVSPEHPLTAIVHAGGA'AVADESRQLHHLTKNRDLAAFVVF'SQDAPAATEAFAGIRQAEGLPVTTIAWGIPEAEPV
VVGQHLLDRAMASADRAHVAARVNTAGLRALAAANALPPVLKNLVGAETDGTGHQDWSRRFMVAE'AAARQQE'LLDLIR
TTVMEILSLPTTARYFPDRTFRENGIDSLTAVELVNSLAKTTGLRLSATMVFDYPTPTALAGRMREL

20 SEQ ID NO: 164

MSRLDLIRPLSESLCASAASF'GDKVAYTDSRRSVTYAELQ'IRTGRLAGHLAEHGVARGDRVAILLGNRVEIIIESYLA
VARASAVAVPLNPDAMDAELA'HF'LRDSGAVVVITDLAHLEQTRGVAPAMTVVLIGDGRTVPGTSSFAELADTEPAS
ARDDLRLDEPAWMLYTS GTTGT PKGVVSAQRSGLWSA'ASCDVPAWDLSD'EDLLLWPAPLFHSLGHHLCLLAVVAVGA
SARIMSGFAADEVLDALREHPCTVLVGVPTMYRYLLA'AVGESGADAPALKMALIAGSVTPASLVEAFERSFGVPLID
25 TYGCTETTGSVTANRLHGERVPGSCGVPVPGVEIRLVDPVTGADVPLGAEGELWAKTPSVMIGYHGQPEATGEVLVD
GWYRSGDLARRQESGHITITGRVKELIIRSGENIHPREIETVALEVPGVEDAAAAGKPHRVLGEVPVLYVVP'AEAGV
DVTAVFAACREQLSYFKVPEEIYQVESIPRTPSGKVKRGLLTEQPAELLAAADGGGSLYRVEWRPAVPPGAGDTGGD
SPVVVRVDSLPADEQELLGAVRDLIHDRIADPRRTTAPLVFVTRHAVLSRNP'AHAAVWDLVSRAQADNPGLF'VLV
DADGDDAPLPSAVGLGEPRVAWRDGGLLVPRLAHPGTEALIAPESGSWLLAETGGGTLRDLALVGTD'TADRVLLPGE
30 VRIAVRAAGLNFRDVTVALGVVSDDRLMGGEAAGVVLDVAPDVT'DLEPGDRVFG'LV'EGAFASVAVTD'RRL'LGRI'PAG
WSFATAASVPVVFSTAYHALTDLVDLRPGEAILIHAAAGGVGMAATQLARHIGAKIYATASPAKQHALLGVDQVANS
RTTEFRGT'FLEATGGRGVDVVLNSLAGEHIDASLELLPRGGRF'LELGKTDLRDPRHLPAGVSYQVLNRLDSSPDRVR
EILAE'LLVMFERGVLRPLPVRTWDIREAPEAFSWSRGRHLGKIVLTIPRDLDPDGTVLVTGASADHMARYLSAERG
HAHVLVSDDPA'AVPATHPLTAVVHTGGDEVVSESTRLHQLTRELDLAAFAVFSQSAPASVEALVRHRRTEGLPATAV
35 SWGLPEAE'PAPVQGALLDRTIASVEPAHVVTRVNSAGLRALANS'GELPSVLRDVT'PALS'AKWPRPGT'PRPGT'PRPGT
PHPAALDQAALLDLVRESLTTVLGLPGVESCAPDRPFRETGLDSLTTIGLANTLSARLGRKLPATMIFDHPTPRTLA
TRLAEEL

SEQ ID NO: 165

40 MTPAYDVRPLPELLIANAERLGDKPAYTGLHRTVGHAELADRTRRAAGHLAGFAARGDRIALLGNRVEMVEGYLAV
ARAAVAVAVPLNPQASDAELA'HF'LT'DSEAVAVLADA'EHTEQVRRVAPGLRLVPIGEWETLATTEPDRPARDDLGLDEV
AWMLYTS GTT GAPKGVLS'TQGSGLWSAYHCDVPALGLTDADVLLWPAPLFHSLAHHLAVLAATVSGATVRLLSGFAA

DEVLRELREEGCTLLAGVPTMYHYLLGAAGPDDEV RAPALRGAVVAGAVTPAALITAFGERFGAPLLDTYGCTETTG
SLTINRLDGPRVPGSCGVAVPGVRLRLVDPRTGDDAPEGGEGEIWASGPSLMRGYHRRPDATAEVLADGWYRTGD
LA VRAATGHITITGRVKELIIRGGENIHPREIEAVLAIEVPGVADVAVAGRSHAVLGDLVPAYLVTEAGLDPAALFAACR
ERLSSFKVPPEEVYRVAAVPRTPSGKIKRREL VAGPAELLATAGGAETLLRTRWTAVDVLDPASLDGWRVVHADQ
EVD
5 LGGRLDDDGP AIVVTTRAVRTSADERPSASAAA WDLVTAAQARRPGRYLLVDTDGVPGGLGAALATGEPQVAV
RED
VVLVPRLEAAGETGAPVRLDGTVLVTGEHTE RVARHLRARGVTVTDDPAARPLHAVVHVGGTSGLAELAE
LTGCPER
AAFVVCTEDSRATADALVRAIPGGVAVGVGLPGIEPAALLPELLDRLTADGPYVVARPGSTGLRALATAGRL
PAGLG
ALVDTGAAPDPDAAVRRDLVRRLLIALPRRARDQALVELVWD AVRATLGAGATPGGPGQAFSEVGFDSLTSV
QLRNRL
VAATGVRLSATAVFDFPTPRALADELGRVLI

10 In another aspect, the disclosure provides a chimeric polyketide synthase, wherein at least one module of the chimeric polyketide synthase has been modified as compared to a polyketide synthase having the sequence of SEQ ID NO: 166-167.

15 SEQ ID NO: 166
MSREEFIQPI HDLLRVNAERLGDKIAYADSRRELTHAELRTRTGRIAGHLVDLAVERGDRVAILLGNRVETIESYLA
IARAGAI AVPLNP DATGA EVAHFLADSGAVLVITDSAHLDDVRRAAA VTVVLVDEGPLPAGTRSFAELATAEPPTP
ARDDLGLDEAAWMLYTS GTTGT PKGVVSTQGSGLWSAANC DVPAWELTENDVLLWPAPLFHSLAHHLCLLATTA
VGA
TARIMSGFVAGEVLHELEEHACTVLVGVPTMYHYLLGAVGEAGPRLPSLKMGLVAGAVSPPALIEGFERVFGVPLLD
20 TYGCTETTGSLTVNRLSGPRMPGSCGQAVPGISLRFVDPHTGA EVAEGEGELWASGPSLMIGYHGRPDATREVLSD
GWYRTGDLARRSETGHVTITGRVKELIIRGGENIHPRDIEA VALELPGVRDAAAAGKQHPVLGEIPALYLVPDADGV
DAEAVLAACREKLSYFKVP EEEIYRVDAIPRTLSGKVKRAALTEAPAELLSAASGNGSLYRLEWVPAETPPAGTGGPV
AVHVTRRAVATGPADLPDQEQAATWDALRGEQTGPGGPV LIDLGDADIDDARLSALASLGEPQIVVRDDTPLVARLA
REKSPALTIPGERAWVLEPDHSGVLQELALVAADTDVRPLRPGEVRIEVRAAGLNFRDVLVALGTDLDGDGVFGAEGA
25 GVVLETGSDVRDLRPGDRVFGLLLEGGHGSI AIAADRMLAVIPEGWSFATAASVPEVFVIAYYGLVDLAGLRAGESVL
IHAATGGVGMAATQIARHLGAQVYATAGVGKQHILRDAGLGDDRIADSRTTDFREAFRDSTQGRGVDVVLNSLKGDF
VDASLDLLADGGRFLELGQTDIRDAGEIAAERP GTTYHSFTRMNAGPDRLREIIAELLALFEQGVLRPSPVHTWDIR
HAREAFSWMSGGRHTGKMVLTMPQRIDPGGTVLIAGDSEALARIAARHLGVRHLLLD RGVADAAPDAVVC DVSDHDA
LERVLADLSPEHPLTAVIHTGGA AVTDEIRRLHDLTESLDLTDFV VFSQDAPAAVEAFARSRRAHGLPVRTIAWGIP
30 EADPVVADEHLLGRALASAEQAQIVARVNTAGLRALTAANALPTLLRN LIRAEPEETGQSAWPHRFEAAGADREEAL
LDLIRANVVDILSLPTADRYAPDRTFREMGIDSLTAVGLRNSLAKATGLPLPTTMVFDYPTPAVL TARMRELLAGES
PAPARTAARAVAQDEPLAIVGMACRLPGGVSSPDDLWRLVAAGTDAISEFPADRGWDVDNLYDPDPDAPGKTYTVLG
GFLDGVAGFDASFFGISPREALAMPQQRLMLEVSWEAFEHAGIPPRSVRGSDAGVFMGAFFPSGYDAGLEEFGMTGD
AVSVLSGRVSYFFGLEGPAITVDTACSSSLVALHQASSALRQGECSLALVGGVTVLATPQTFVEFSRQRGLALDGRS
35 KAFADAADGAGWAEGVGVLVVERLS DARAKGHQIWGVIRGS AVNQDGASNGLSAPNGPSQQRVIRQALANAGLAPHE
VDVVEAHGTGTTLGDP IEAQAVIATYGQDREQPLLLGSLKSNVGHTQAAAGVSGVIKMVMALQHDTV PATLHV DAPS
RHVDWTAGAVELVTENRPWPETGRVRRAGVSSFGISGTNAHVILESAPEQPVPSPPEAVAPVVASDRVPLVISAKTPA
ALAEMENRLRAYLAAAPGADPRAVASTLATARSVF EHRVLLGENTITGTVAGADPRVVFVFPQGQWQQLGMGRALR
ESSPVFAARMAECAAA LSEFVDWDLFTMLDDPAVIDRIDVLQPACWAVMMSLA AVWQAAGVRPDAVIGHSQGEIAAA
40 CVAGALSLRDAARIVALRSQLLAREMVGHGVMAAVALPADDIPLVDGVWIGACNGPSSTVISGTPEAVEVVAACEE
RGARVRRITA AVASHSPLGEKIRTELLGISASIPSRTPVVPWLSTADGIWIEAPLDPAYWWRNLREPVGFGPAVDLL
QARGENVFLEMSASPVLLPAMNDAVTVATLRRDDGTPDRMLTALAEAHAGVIVDWPRVFGSTTRVLDLPTYAFEHQ

RYWAVSADRPDAGHPMVETVVPLPASGCVALTGRVSLATHAWLADHAVRGTALLPGTAFVELVTRAATEVDCPVID
ELVIEAPLPLTQTGAVQLSTTVGEADESGRRPVTVFSQADGTDWTRHVTATIGRAASLPDPVAWPPAQAEPVDTV
FYDELAAAGYEYGPAPFQGLRAAWSGDITVYAEVVLAEQAEVDRIYAVHPALLDAALQAGMVNTAGTGQGVRLPFSW
NGIQVHSTGATTLRVAATPLADGWSVRAAADNGRPVATIGSLVTRPVTTDMLGSTTDDLFAVVWTEITAPEPGDPSD
5 VGVFTALPEAGGDPLTQTRALTAQVLQTVQQWLAGEDRPLVVRTGTDLASAAVSGLVRSQAQSEHPGRLILVESDDEL
TPEQLAGTAGLDEPRIRIDGGHYEVPRLAREDAASLTVPEDRAWLLELPGSGTILRDLRVIPTDTAERPLRWGEVVRGV
RAGGLNFRDVVVALGMVTDPRPAGGEAAGVVLETGPGVEDLSPGDRVFGILDGGFGSVIAIDRRLLAVIPDGWSFTT
AASIPVVFATAYYGLVDLAGLRAGESVLIHAATGGVGMAATQIARHLGAEIYGTAGIAKQHVLRDAGLGDDRIADSR
TTGFRETFRDSTQGRGVDVVLNSLSGDFVDASLDVLAEGGRFIEMGKTDIRDIAEQITHATYRAFDLMDAGPDRVREI
10 IAELLGLFEQGVLRPLPVQAWDIRQARDAFTWMSRARHIGKEVLTIPQQLDPDGTVLISGGSGVLAGILARHLVAER
GVRHLLLVSRSAPEALISELTALGAQVETVACDVSDRVALEQVLDGVPLTAVFHTAAALDDGVVESLTPQRVDTV
RPKADAAWYLHELTRDADLAAFVVMYSSVAGIMGAAGQGNIAAANAFLDALAAHRRREGLPALSLAWGLWEDASGLSA
GLTETDHDRIIRGGLEAIAAEHGMRLFDTATRQGEVLLASPLNLTRQGEVPALLRTLHRPVARRAATANGRPADLT
PEALLKLVCGRAAAVLGHVDADAVPVAVAFRDLGVDSLTAVELRNSLAKATGLRLPATLVFDYPTPTVLAGRLGELL
15 AGGTAPVRAAVVRRAAASDEPLAIVGMACRLPGGVLSPEDLWRLVESGGDAISGFPVDRGWDVENLFDPDPAAGRT
YAVRGGFLDGAAGFDASFFGISPREAQAMDPQQRLVLEVSWEAFERAGIEPGSVRGS DTGVFMGAYPGGYGVGTDLG
GFGMTSVAVSVLAGRVSYFFGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVMPTPQTFVEFSRQRG
LAADGRCKAFADAADGTGFSEGVGVLLVERLSDAQARGHNILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALAN
AGLAGAEVDVVEAHGTGTTLGDPPIEAQAVIATYGQDRDQPVLLGSLKSNLGHTQAAAGVSGVIKVMALRHDTV PAT
20 LHIDEPSRHIDWTAGAVELVTENQSWPETGRARRAAVSSFGISGTNAHVILESAPAQPVPVLVDTPVSAVTAGVVPLP
ISARTVPALADLEDRLRAYLTTPETDLPVASTLAVTRSVFEHRAVLLGEETVTGIAVSDPRVVFVFSGQGSQRVG
MGEELAAAFPLFARLHRQVWDL LDVPDLEVDDTGYVQPALFALQVAFGLLESWGVRPEAVIGHSVGEVAAGYVAGV
WSLEDACTLV SARARLMQALPAGGAMVAVPVSEERARAVLVDGVEIAAVNGPASVVL SGDESAVLRVAEGLGRWTRL
SASHAFHSVRMEPMLEEF RQVASELT YREPRIVMAAGEQVTTP EYWVRQVRD TVRF GDQVAAF GDAVFLEIGPDRTL
25 SRLIDGIPTLHGDDEQHAVVAALAEHLVQGVPI DWSSILGANPARVLDLPTYAFQH ERYWMVSTGRVGGEGHPLLGW
GVPVAEAGGRLYTGRVARQDGPVLSVAAFVEMAF AAAGGRP IRELSVDALLYIPDDGTAE LQTWVSEHRLTIHARYR
DTEPWTRLATAALDTTAPATTHTPHPGLITTALT LTGDEAPAIWHDLT LHTSNATELHTHITPGDDGTLTITATDTT
GQPVLT AHTATPTTIPVHTPTTPADDLLTLTWTQIPTPGPGDPTDIAVCTALPD PDGDPLAQTRTLTAQVLQSIQTT
LTGEDRPLVVHTGTGLASAAVSGLVRSQAQSEHPDRFILVESDDSLPQAQLAAVAGLDEPWLRITGSCYEVPRLTKTT
30 TATATAVSEP VWNPDGTVLITGGSGALAGILARHLVTERGVRHLLLSRSTPSTTLTDELRELGAHV DVAACDVSDR
DALARVLDGVDLTAVFHTAGALDDGVVESLTPQRLDTVLT PKADGAWHLHELTRDRDLTAFVMYSSAAGVMGAAGQG
NYAAANAFLDALAEHRHADGLPALSLAWGMWDDTDGMTASLSGTDHRRIRRSQRAITA EHGMRLLDKASGRSEPV
VATAMNPIPDTDLPALRLSLYPKTARKSQPIQELSPEALLKIVRDSAALMLGHPNTDAIAATTA FRDLGVDSLIAVE
LRNSLAKATGLRLPATLVFDYPTPTVLAGRLGELLAGVTPQRHATVRTGTASDEPLAIVGMACRLPGGVSSPEDLWR
35 LVESGTDAITDFPTDRGWD TDDLFDPDPD TAGKTYTVHGGFLDDVAGFDASFFGISPREAQAMDPQQRLVLEAAWEA
FERAGIEPGSVRGS DTGVFMGAYPGGYGIGADLGGFGATAGAGSVLSGRLSYFFGLEGPAMTVDTACSSSLVALHQA
GSALRQGECSLALVGGVTVIANPQIFVEFSRQRGLAADGRCKAFADSADGTGWSEGVGVLLVERLSDAQARGHNILA
VVRGSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLAGAEVDVVEAHGTGTTLGDPPIEAQAVIATYGQDRDQSVLL
GSLKSNLGHTQAAAGVSGVIKVMALQNGVVPRTLHADQPSRHIDWTAGAVELVTENQPWPELDRPRRAAVSAFGVS
40 GTNAHVILESAPDQVPVLVDTPVSAVTAGVVPLPISARTVPALADLEDQLRAYLT TAPETDLPVASTLATRSVFE
HRAVLLGEDTVTGTAIPDPRIVFVFSGQGSQRAGMGEELAAAFPLFARLHRQVWDL LDVPDLDVDDTGYVQPALFAL
QVALFGLLESWGVRPRAVIGHSVGEVAAGYVAGVWSLEDACALVSARARLMQALPAGGAMVAVPVSEERARAVLVDG

VEIAAVNGPASVVLSGDEAAVLRVAEGLGRWTRLSASHAFHSVRMEPMLLEEFQVVSRLTYREPRIVMAACEQVTTPEYWVRQVRET
TVRFGDQVAAFGDAVFLEIGPDRTLSRLIDGIAMLDGDDEVRAAVAALAMMHVQGVGVDWPAILGTTTGRVLDLPTYAFQH
ERYWMANADEGHPLLKGVEHPLLGSVMALPNSDGVVLTGRISLATHAWLADHVVRGTVLLPGTG
F'VEMVARAAAEVGCVIDELLIEAPLLLPEHGGVHLSVSVGEADGAGRRPVTVFAQADDAEVWVRQVTATISPAGPA
5 VSLPELEVWPPVQAEPVDVSTFYERLARADWQWGPAFQGLRAAWRDGDTIYAEIVLADEEAREADQFLVHPALLDAA
LQTSVLKTPDDLRLPFSWNQIEFHATGAAILRVAVTPVADRWIVHAADSTGRPVATIGALVSRPVTAETLGSNTDDL
FALTWTEIPTPGPGDPADVAVCTALPEPDS DPLTQTRTLTAQVLQSIQTSLTGEDRPLVVHTGTGLASA AVSGLVRS
AQSEHPDRFILVECDDETLPDQLAATAGLDEPWLRITGGHYEVPRLTKTTTAAATTVSEP VWDPDGTVLITGGSGA
LAGILARHLVTERSVRHLLLSRSTPSTTLINELRELGAHIETAACDVSDRDALARVLDGVDLTAVFHTAGALDDGV
10 VESLTPQRLDTVLMPKADA AWHLHELTRDRDLAA FVMYSSAAGVMGAAGQGN YAAANAFDLALAEHRRADGLPALS
LAWGMWDDADGMTASLSGTDHRRIRRSQRAITAEHGMRLLDKASGRSEPV LVATAMNPAGEGEVPALLRTLHRPVAR
RAATTNGRPADLTPEALLKVVRDSAAVVLGHASADTVPAATAFQELGLDSLIAVELRNSLAKATGLRLPATMVFDYP
TPAALAGRLGELLAGETTPATAAVVRRATASDEPLAIVGMACRLPGGVSSPEDLWRLVESGFDAITGFPTDRGWDVD
NLYDPDPDAPGKSTTLHGGFLDDVAGFDASFFGISPREAVAMDPQQRLAMEVSWEAFERAGIEPGSVRGSDTG VFMG
15 AYPGGYGIGAEELGGFMLTGRAGSVLAGRVSYFFGLEGPAMTVDTACSSSLVALHQAAAYALRQGECSLALVGGVTVM
TPVMFVEFSQQQNLADDGRCKAFADSADGTGWSEGVGVLLVERLSDAQARGHNILAVVRGSAVNQDGASNGLTAPNG
PSQQRVIRSALTSAGLTTADVDVVEAHGTGTTLGDP IEAQAVLATYQQDRDQPVLLGSLKSNLGH TQAAAGVSGVIK
MVMALQNGVVPRTLHVEEPSRHVDWTAGAVELVTENQSWPETGRARRAAVSSFGFSGTNAHVILESAPAQPVP PMDT
PAPAVTTGVVPLPISAKSLPALADLEDQLRAYLTATPETDLPAVASTLAMTRSVFEHRAVLLGEETVTGT AIPDPRI
20 VFVFSGQGSQRVGMGEELAAAFPLFARLHRQVWDLLDVPDLVDVDDTGYVQPALFALQVALFGLLESWGVRPRAVIGH
SVGEVAAGYVAGVWSLEDACALVSARARLMQALPAGGAMVAVPVSEERARVALVDCVEIAAVNGPASVVLSGDEAAV
LQIAEGLGRWTRLSASHAFHSVRMEPMLLEEFQQVASELTYQEPRIVMAACEQVTTPEYWVRQVRDTVRFCDQVAAFC
DAVFLEIGPDRTLSRLIDGIAMLDGDDEVRAAVAALAEHLVQGVPI DWPAVLGTTTGRVLDLPTYAFQH QRYWAAST
DRPAGDGHPLLDTVVALPGADGVVLTGRISLATHAWLADHAVRGTVLLPGTG FVEMVARAAAEVGC AVVDELVIEAP
25 LLLPASGGVQLSVSVGEADDAGHRPVTVHSQADETEAWVRHVTATISP SGPIVSPPEFEVWPPAQAEPVEVARFYDE
LAAAGYEYGAAFQGLRAAWRAGETIYAEVVLAEDQTL EAA RFTVHPALLDAALQANILNASGDLRLPFSWGQVQFHT
TGAATLRVAVTPVADGWTIQATDDAGRPVATVGSVVARPVAGLGATAEDL FALTWNEIPAPGQGGRTVGRFEDLADD
GPVPELVVFTALPDVDADPLVRTRALTARVLEAIQRWLGEPRFADSTLVVRTGTDLASA AVSGLVRS AQSEHPDRFI
LVEGDSSPVEIGLDEPWLRVDGGRYEVPRLIRLSAEPVQEA AAWNPDGMVLITCGTGALAGILARHLVAENKARRLLL
30 VSRVPPDALISELTELGAEVGTAVCDVSDRAALARVLAGVPSLTAVIHTAGVLD DGVMESLTPQRLDTVLRAKADG
AWHLHELTRDRDLAA FVMYSSAAGLMGSPGQGN YAAANAFDLALAVERRAEGLPALS LAWGFW EETTGLTANLTGAD
RDRIIRRGGLQTITAERGMRMFD TATQHGE PVLLAAPI SPVRDGEVPALLRSLHRRGTRRGTTADASAQWLAGLAPEE
REGALIKVVRDTAAVVLGHADAGTIPVTA AFKDLGLDSL TAVELRNSLAKSTGLRLPATMVFDYPTPASLAARLDDL
MNPRVSSTALLAE LDRIEGMFDSVTFDEKQASLVKDRLS AALGKWQQISR SADVATVALANADAGEILDFIDREFGN
35 PTI

SEQ ID NO: 167

MPDHDKLVEYLRWATAELHTTRAKLQAATEAGTQPLAIVGMACRLPGGVSSPEDLWRLVESGTD AISGFVDRGWDV
DGLYDPDPDVP GKSYTVEGGFLDAVTGFDAPFFGISPREALAMDPQQRLVLEASWEAFERAGIEPGSVRGSDTG VFM
40 GAFPGGYGTGADLGGFGMTGGAASVLSGRVSYFFGLEGPAMTVDTVCS SSSLVALHQAGYALRHGECSLALVGGVTVM
STPQTFVEFSRQRGLAADGRCKAFADNADGTGWSEGVGVLLVERLSDAQARGHNILAVVRGSAVNQDGASNGLTAPN
GPSQQRVIRQALANAGLTGADV DVVEAHGTGTTLGDP IEAQAVIATYGRDRDQPVLLGSLKSNLGH TQAAAGVSGVI

KMVMALQNGVVPRTLHIEEPSRHVDWTAGAVQLVTENRPWPPELGRARRAAVSSFGLSGTNAHVILESAPDQPPAPT
DTPVSAVTAGVVPLPISAKTVPALADLEDRLRTYLTTPDSDLPAVASTLATRSLFEHRAVLLGEDTVTGTAIPDP
RVVFVFPQGQWQWQGMGSALLTSSTVFAERMAECAALSEFVDWDLTLVLDDPSVVDRVDVVQPACWAVMISLAAVW
QAAGIHPDIVLGHSQGEIAAACLAGAISLPDAARIVAQRSQQLIAHQLTGHGAMASISLPADDIPTTDKVVWIAAHNGT
5 STVIAGDPQAVEAVLATCETR GARVRKINVDYASHTPHVEQIRTELDDITTGIEAHTPAVPWLSTTDNTWIDQPLDP
TYWYRNLREPVRFGPAIDLLQTQDNNLFIEISASPVLLQTMDNAATVATLRRDEDTTQRLLTAFAEAHVHGATIDWP
TVLDTTTTTPVLDLPTYPFQRQRYWATSNGRSTGQGHPLLETVVALPGTDGVALTGRI SLATHPWLTDHTVTRGTVLLP
GTAFVELVTRAATEVNQCIIIDELIIEAPLPLPQTDGVQLSVTVGEADEAGHRPVTVYSQTDESDDWIQHVTATIGPG
ASLPETAAWPPAHAEPVNV TGLYDNLAAAGYEYGP AFQGLQAAWRAGDTVYAEVTLAEEQAQETARFTMHPALLDAA
10 LHTIALHDTGDLHLPFSWTRVQFHGTGAATLRVAVTPAADGWNIRATDDTGRAVATIGSLVTRPMAAETTDDLLALT
WTEIPAPEPVDPD TDVVFTALPD TVEDVPAQTRALTTRVLHTIQEWLADDDRTLIVRTGTDLASAAVSGLVRS AQSE
HPGRFILVESADEALTQEQLAATAGLDEPRLRITGGRYEVPRLTREDTALAVPTDRAWLLEQPRSGSLEDLALLPTD
AERPLQAGEVRIGVRAAGMNF RDVVVALGMVTDTRLAGGEAAGVVLEVGT DVNDFRPGDRVFGILEGGFGSVAICD
HRTLAVIPDGWSFTTAASVP IAFATAYYGLVDLAGLRAGESVLIHAATGGVGIAATQIARHLGAEIYG TASVGKQHV
15 LRDAGLADDRIADSRTTDFRD TFRDGTQGRGVDVVLNSLRGEFIDASLDLLVDGGRFIEMGKTDIRDAAQIPDATYH
AFDLMDAGHDLRLREIMTELLALFEQGV LHMPVHAFDIRQAREAFSWMSRARHIGKLVLTIPQPIDPDGTVLITGGS
GVLGIVARYLV TENRARHLLLLSR SAPSASLIDELTALGAHV DVAACDVADRAALAEILDGVDLTAVIHTAGALDD
GVVESLTPQRLD TVLTPKADGAWHLHELTRDRDLAAFIVYSSAAGVLGAAGQGN YAAANAFLDALAVHRRLEGLPGL
SLAWGLWEDASGLTADLT DADRDRIRRSQRAIT AAYGMRMLDAATRQSEAILLAAPISPIQDGDVPAILRSLHRRV
20 GRRASVAHGHPADLTPEALLKVVRDS AAMVLGHTNADTVPTATAFQELGLDSL TAVELRNSLT KATGLRLPATMAFD
YPTPDALAARLGELLAGEAAPKAAA A VRRATASDEPLAIVGMACRLPGGVSSPEDLWRLVESGTDAITDFPTDRGWD
TDTLFDPDPTPGKTYTVHGGFLNDVAGFDAPFFGISPREAVAMPQQRLVLESSWEAFERAGIQPDSIRGSDTG VF
MGAYPDGYGIGADLAGFGVTAGAGSVLSGRVSYFFGLEGPAMTVDTACSSSLVALHQAAYALRQGECSLALVGCVTV
MPSPRTFIEFSRQRGLAADGRSKAFADAADGTGFSEGVGVLLVERLSDAQAKGHNILALVRSSAVNQDGASNGLTAP
25 NGPSQQRVIQSALAGAGLTSADVDVVEAHGTGTTLGDP IEAQAVLATYQQDRDQPVLLGSLKSNLGHTQAAAGVSGV
IKMVMALQHNTVPATLHVDAPS RHVDWTAGAVRLATENQPWPETNRPRRAGVSSF GVS G TNAHVILEQAPAASPVEP
VDTTDVVIPLVVSARSSGSLSDQADRLAALVGSPDAPALTSLADALLTRRTVFSQRAVVVAGSHEQAAAGLRALASG
DSHPALVTGAAGPARGVVLVFPQGGSQWAGMGAELLDTS PVFAARIAECAEALRPWVDWSLDEVLRGDASADVLGRV
DVVQPASFVVMVGLAAVWESAGVRPDAVLGHSQGEIAAAYVAGALS LTDAAKIVAVRSRLIAARLAGRGGMASVALA
30 PDEAAAKLGRTELA AVNGPASVVIAGDAEALDETLAMLEGEAVRVRRAVDYASHTPHVEELEQSMAEALADVRSRQ
PRVGFLSTVTGDWVTEAGALDGGYWYRNL RQPVRFGPAVASLAEAGYTVFVEAS AHPVLVQPVAETLDRTDAVVTGT
LRRQDGGLPRLLT SMAELFVGGVPVNWPVLLPAGAVRGWVDLPTYAFDHQRYWLENRVATDAAALGLAGADHPLLGA
IVAVPQSGGVAMTSRLSPRNHPWLA EHTLGGVPTVPTSVLVELAVRAGDEVGCGVVEELTVDAPLLLPERGGVRVQV
IVGATDANGQRGLDIFSAPEDTGQEA WTRHATGTLAPGGDIAADV DLSAWPPANAQPVDVTDGYDLLERAGYGYGPA
35 FQGVRAIWRRGEELFAEVALEPELTDTAARFGLHPALLDAAWHPELRDEVAETSPDGRRWSQPSRWAGLRRLHTAGA
TVLRVRLAPVDADSMSLQAADETGDPVLTVDLSLSLCAVSADQLTTAESSDDALFRLEWTPLSKAPTAA RSWPVETG
ADVAALDGQAVVDAVMLEAAGTGDALELTCRVLEV VQAWLTLPGWDESRLVVVTRGAVGAVGDPAGSAVWGLVRAAQ
AENPDRIALLDL DGGRPVEPLLAESE PQLAIRGAEALVPRLIRAAAATDAPALFDESQTVLITGGTGSLGGLLARHL
VGRYGLRRLV LVSRGPDAPGAYELAAELAAHGAEALVACDLTD RDAVARLLTEHHPTAVVHAAGVSDDGVIGTLT
40 SDRLAYVFGPKATAARHLDEL TRELLPDLA AFVTYSSISAVFLGAGSGGYAAANAYLDGLMARRHAEGLPGLSLAWG
LWDQEADGGGMAAGLQDITRNMRRRGVLSFTPAEGMALFDAAMATDEALVVPVRLDLPALRAEAVAEGRSAPVLL
RGLVRPGRR LARTVSGGTGVLADLTPEALLKLVRGAAAVLGHVDADAVPVAAAFKDLGVDSL TAVELRNSLAKATG

LRLPATLVFDYPTPTVLAGRLGELLAGGTAPVRAAVVRRAAASDEPLAIVGMACRLPGGVLSPEDLWRLVESGGDAI
SGFPVDRGWDVENLFDPDPAAGRTYAVRGGFLDGAAGFDASFFGISPREAQAMDPQQRLVLEVSWEAFERAGIEPG
SVRGSDTGVMGAYPGGYGMGTDLGGFGMTSVAVSVLAGRVSYFFGLEGPAMTVDTACSSSLVALHQAGSALRQGEC
SLALVGGVTVMPTPQTFVEFSRQRGLAADGRCKAFADAADGTGFSEGVGVLLVERLSDAQARGHNILAVVRGSAVNQ
5 DGASNGLTAPNGPAQQRVIQSALAGAGLASADVDVVEAHGTGTTLGDPIDIEAQAVIATYQQDRDQPVLLGSLKSNLGH
TQAAAGVSGVIKMMALQNGVVPRTLHIDEPSRHIDWTAGAVELVTENQSWPETGRARRAAVSSFGISGTNAHVILE
SAPAQPVPVLDTPVSDVTAGVVPLPISARTVPALADLEDQLRAYLTTPETDLPVASTLAMTRSVFEHRAVLLGEE
TVTGIAVSDPRVVFVFSGQGSQVRVGMGEELAAAFPLFARLHRQVWDLLDVPDLEVDDTGYVQPALFALQVALFGLLE
SWGVRPRAVIGHSVGEVAAGYVAGVWSLEDACTLV SARARLMQALPAGGAMVAVPVSEERARAVLVDGVEIAAVNGP
10 ASVVLSGDESAVLRVAEGLGRWTRLSASHAFHSVRMEPMLLEEFRQVASELTYREPRIVMAAGEQVTTPEYWVRQVRD
TVRFGDQVAAFQDAVFLEIGPDRTLSRLIDGIAMLDGDDEVRAAVAALAMMHVQGVGVDPVAVLGTGTTTGRVLDLPTY
AFQHERYWMVSTGRPGGEGHPLLGWGVPVAEADGRLYTGRVARQDGPVLPVAAFVEMAFVAAAGGRPIRELSVDALLY
IPDDGTAEELQTVWSEHRLTIHARYRDTEPWTRLATATLDTTEPATHTHTPHPLITLTLTGDEAPAIWHDLTLLHTS
NATELHTHITPGDDGTLTITATDATGQPVLTAAHAATPTTIPVHTPTTPADDLLTLTWTQIPTPGPGDGADIAVCTAL
15 PDPDSPLAQTRTLTAQVLHSIQASLTGEDRPLVVHTGTGLASAAVSGLVRSAQSEHPDRFILVESDETLPDQLAA
VAGLDEPWLRITDGRYEVPRLTKTITTTATATAVSEPVDPDGTVLITGGSGALAGILARHLVTERGVRHLLLVSRST
PSTTLIDELRELGAHVDAACDVSDRAALARVLDGVDLTAVFHTAGALDDGVVESLTPQRVDAVLRPKADGAWHLHE
LTRDRDLTAFVMYSSAAGVMGAAGQGNIAAANAFLDALAEHRRADGLPALSLAWGMWDDADGMTASLSGTDHRRIRR
SGQRAITAEGMRLLDKASGRSEPVLVATAMNPIPDITDLPALLRSLYPKTARKSQPIQELSPEALLKIVRDSAAMVL
20 GHANADTVPTATATLQELGLDSLTAVELRNSLTATGLRLPATMAFDYPTPAALAGRLGELLAGDTPATAAVVRRAT
ASDEPLAIVGMACRLPGGVSTPEDLWRLVESGTDAITDFPTDRGWDTDLFDPDPDTPGKTYTVHGGFLDDVAGFDA
SFFGISPREALAMDSQQRLVLEAAWEAFERAGIEPGSVRGSDTGVMGAYPDGYGIGADLGGFGATAGAGSVLSGRL
SYFFGLEGPAMTVDTACSSSLVALHQAGSALRQGECSLALVGGVTVIANPQIFVEFSRQRGLAADGRCKAFADNADG
TGFSEGVGVLLVERLSDAQAKGHNILALVRSSAVNQDGASNGLTAPNGPSQQRVIRQALANAGLTGAEVDVVEAHGT
25 GTTLGDPIDIEAQAVLATYQQDRDQPVLLGSLKSNLGHGTQAAAGVSGVIKMMALRHDTVPATLHIDEPSRHIDWTAGA
VELVTENQPWPVLGRPRRAAVSAFGVSGTNAHVILESAPDQPPAPATDTPAPAATAGVVPLPISAKTVPALADLEDR
LRTYLTTPETDLPVASTLATRSLFEHRAVLLGEDTVTGTTIPDPRIVFVFPQGQWQWQGMGSALLTSSTVFAER
MAECAALSEFVDWDLTLVLDDPSIVDRVDVVQPACWAVMISLAAVWQAAGIHPDIVLGHSQGEIAAACLAGAISLP
DAARIVAQRSQLIAHQLTGHGAMASISLPADDIPTTDKVIWIAAHNGTSTVIAGDPQALDVLATCETHGARVRKINV
30 DYASHTPHVEQIRTELDDITDIEAHTPTVPWLSTTDNTWIDQPLDPTYWYRNLREPVRFGPAIDLLQTQDNNLFIE
ISASPVLLQTM DNATTVATLRRDEDTTQRLLTAFAEAHVHGATIDWPTVLDTTTTPVLDLPTYPFQRQRYWATSNGR
PTSQGHPLLETVVALPGTHGVALTGRISLATHPWLT DHTVRGTVLLPGTAFVELVTHAATEVNCQVIDELIIEAPLP
LPQNGGVQLSVTVGEADEAGHRPVTIVYSQTDDESDDWVQHVTATIAPGVSSSESAAWPPAQAEPVNVTGLYDNLAAG
YEYGP AFQGLQTAWRDGSTVYAEVTLAE EQAQETARFTMHPAL LDAALHTIALHDTADLQLPFSWRQVQFHGSGAAT
35 LRVAVTPAADGWNIRATDDTGQTVATIGSLVTRPMAAETTNDLLALTWTEIPAPEPVDPADVVF TALPEPGSDPLA
QTRALTTRVLHTIQEWLADDDRTLIVRTGTDLASAAVSGLVRSAQSEHPGRFILVESDDETLTHEQLAATAGLDEPR
LRITDGRYEVPRLTREDTALAVPEGGAWMLDQPSRSGTLQDLRLVPTDAAERPLRPGEVRVGVRAAGLNFRDVAVAL
GMVTDTRLIGGEGAGVVLEAGPGVEDLRPGDRVFGLLEGFGPVAVADRRALALIPDGWSFTTAASVP IAFATAYYG
LLDLAGLRAGESVLIHAATGGVGMAATQIARHLGADVYATASTGKQHVLRDAGLSDDRIADSRTTGFRETF RDSTDG
40 RGVDVVLNSLKGDFVDASLDLLVDGGRFIEMGKTDIRDAAQIPDATYRAFDLMDAGERLREIITELLALFEQGVLR
PLPVHAFDIRQARDAFGWMSRARHIGKLVLTIPQPIDPDGTVLITGGSGVLAGIVARHLVIAEGLRNLLLLSRAPS
EALIGELTALGAQVETAACDIADRAALARVLDGVPLTAVIHTAGALDDGVVESLDPQRLDVLTLPKADGAWHLHELT

RDRDLAAFIMYSSAAGVLGAAGQGNIAAANAFVDALAVHRRFMGLPALSLAWGLWDDTSALTAGLTDSHDRIIRSG
ARTITAHEGMRMFDAATRQSEAVLLAAPMGPIRGEDVPALLRGLATVRQPRTRAKRDMGPERLRDRLNGRTSVEQHR
IMVELVLAHATSVLGHESPDAIAPDRAFKDLGMDSLTAIELRNHLVAETGVRLPATTAFDHPTADDLAKRLLAEVGL
TPAPQRTEADIREEVVVREPAGDDSWTSEPIAIVSMSCRAPGGVDSPESLWRLVESGTDAITDFPGDRGWDVAGLYS
5 PDPDTGYKTYCVQGGFLDAAADFDAFFGISPREALGMDPQQRLLLETSWEAIERARIDPRSLRGRNVGVYVCGAAQ
GYGVGAIDQQRDNVITGSSISLLSGRLSYALGLEPGVTVDTACSSSLVALHLACQALRQRECSMALVSGVSVIPTP
DVFEVFSRQRGLAADGRCKSFSASADGTIWAEGVGVLVLERLSEATRLGHRVLAVVRGSAVNSDGASNGLTAPNGVS
QQRVIRQALTGAGLTAADVVDVVEAHGTGTKLGDPIEAAILATYGQDRSTPVCLGSLKSNIGHAMAASGVLAVIKMV
EAMRHGLIPRTLHVEEPSPHVDWASGDVALLTENQWPDDAKLRRAGVSSFGLSGTNAHVVLEQYRAPAAPDITTE
10 HEPLAWTLSARDPKALREQAGRLHAALTESPQWRPLDIGYSLATTRSNFAHRAVAVGSDREDLLRALSKLADGSAWP
ALVTATAKDRRVAYLFDGQGSQRPDMGSGLYERFPFAFARAWDRISAIEFGKHLHDHSLTDVYLGRGDAATADLVDDTLY
AQAGLFTMEIALFELLAEWGVRPDFVSGHSIGETAAAYAAGVLSLEDVTTLIVARGRALRQVPPGAMVALRAGEDEA
REFLGRTGAALDLAAVNSPTSVVVSGASEAVAGFRARWTESGREARTLNVRHAFHSRHVEAVLGEFREVLESLTFRT
PALPVVSTVTGRLIEPTTELSTSEYWLQRQVRQTVRFHDAVRELSGQGVGTVEIGPSGALASAGLECLGDEASFHAVQ
15 RPGSPGDVCLMTAVAEHLHAGGTTVDWATVLAGGRATDLPVYPFQHGSYWLAPVTRAADGAPSAGVPAPGEYARPSAP
EEPRTMLELVRLEAAIALSITDPGLIADDSSFLDLGFDSISALRLSNRLAAVTGLDLPPSLFLDHPTPAELAARLDE
LSAADLDGAGVYALLEEIDELDDEDLDMTEEEQTAISELLTKLSAKWSR

In some embodiments, the disclosure provides a chimeric polyketide synthase where at least one
20 module includes a portion having at least 90% identity to any one of SEQ ID NO: 1-165.

In another aspect, the disclosure provides a nucleic acid encoding any one of the above
described polyketide synthases.

In some embodiments of any of the above described aspects, the nucleic acid encoding any one
of the above described polyketide synthases further encodes an LAL in which the sequence encoding the
25 LAL is operatively linked to the sequence encoding the polyketide synthase.

In some embodiments, the LAL may be a heterologous LAL.

In some embodiments, the LAL may include a portion having at least 80% (e.g., at least 80%, at
least 85%, at least 90%, at least 95%, at least 99%) sequence identity to SEQ ID NO: 168. In some
embodiments, the LAL may include a portion having the sequence of SEQ ID NO: 168. In some
30 embodiments, the disclosure provides a nucleic in which the LAL has the sequence of SEQ ID NO: 168.
In some embodiments, the LAL lacks a TTA inhibitory codon in an open reading frame.

SEQ ID NO 168:

MPAVESYELDARDDELRRLEEAVGQAGNGRGVVVTITGPIACGKTELLDAAAAKSDAITLRVCSEEERALPYALIG
QLIDNPAVASQLPDPVSMALPGEHLSPEAENRLRGDLTRILLALAAERPVLIGIDDMHHADTASLNCLLHLARRVGP
35 ARIAMVLTELRRRLTPAHSQFHAELLSLGHHRERIALRPLGPKHIAELARAGLGPVDDEDVLTGLYRATGGNINLGHGL
IKDVREAWATGGTGINAGRAYRLAYLGSLYRCGPVPLRVARVAAVLGQSANTTLVRWISGLNADAVGEATEILTEGG
LLHDLRFPHPAARSVVLNDLSARERRRLHRSALVLDVPEVVAHHQAGAGFIHGPKAAEIFAKAGQELHVRGELD
AASDYLQLAHHASDDAVTRAALRVEAVAIERRRNPLASSRHLDELTVAAARAGLLSLEHAALMIRWLALGGRSGEAAE
VLAAQRPRAVTDQDRAHLRAAEVSLALVSPGASGVSPGASGPDRRPRPLPPDELANLPKAARLCAIADNAVISALHG
40 RPELASAEAEENVLKQADSADGATALSALTALLYAENTDTAQLWADKLVSETGASNEEEGAGYAGPRAETALRRGDL
AAAVEAGSAILDHRRGSLLGITAALPLSSAVAAAIRLGETERAEEKWLAEPLPEAIRDSLFGLHLLSARGQYCLATGR
HESAYTAFRTCGERMRNWGVDVPGLSLWRVDAAEALLHGRDRDEGRRLIDEQLTHAMGPRSRALTLRVQAAYSPPQAQ

RVDLLEEAAADLLLSCNDQYERARVLADLSEAFSALRHHSRARGLLRQARHLAAQCGATPLLRRRLGAKPGGPGWLEES
GLPQRIKSLTDAERRVASLAAGGQTNRVIADQLFVTASTVEQHLTNVFRKLGVKGRQHLPaelanae

In some embodiments of any of the foregoing nucleic acids, the nucleic acid includes an LAL binding site, in which the sequence encoding the LAL binding site is operatively linked to the sequence encoding the polyketide synthase.

In some embodiments, the LAL binding site includes a portion having at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 99%) sequence identity to the sequence of SEQ ID NO: 169 (CTAGGGGGTTGC). In some embodiments, the LAL binding site includes a portion having the sequence of SEQ ID NO: 169 (CTAGGGGGTTGC). In some embodiments, the LAL binding site has of the sequence of SEQ ID NO: 169 (CTAGGGGGTTGC). In some embodiments of the above described aspect, the LAL binding site has the sequence of SEQ ID NO: 170 (GGGGGT).

In some embodiments of any of the foregoing nucleic acids, the binding of an LAL to the LAL binding site promotes expression of the polyketide synthase.

In some embodiments of any of the foregoing nucleic acids, the nucleic acid encoding any one of the above described polyketide synthases, further encodes a nonribosomal peptide synthase.

In some embodiments of any of the foregoing nucleic acids, the nucleic acid encoding any one of the above described polyketide synthases further encodes a P450 enzyme.

In some embodiments of any of the foregoing nucleic acids, the nucleic acid encoding any one of the above described polyketides and a first P450 enzyme, further encodes a second P450 enzyme.

In another aspect, the disclosure provides an expression vector including any of the foregoing nucleic acids. In some embodiments, the expression vector may be an artificial chromosome, e.g., a bacterial artificial chromosome.

In another aspect, the disclosure provides a host cell including any of the above described expression vectors.

In another aspect, the disclosure provides a host cell including any of the foregoing polyketide synthases, in which the polyketide synthase is heterologous to the host cell.

In some embodiments of any of the foregoing host cells, the host cell naturally lacks an LAL and/or an LAL binding site.

In some embodiments of any of the foregoing host cells, the host cell includes an LAL capable of binding to an LAL binding site and regulating expression of a polyketide synthase. In some embodiments, the LAL and/or LAL binding site may be heterologous to the cell. In some embodiments, the host cell includes an LAL with a portion having at least 80% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 99%) sequence identity to the sequence of SEQ ID NO: 168.

In some embodiments of any of the foregoing host cells, the host cell is a bacterium, e.g., an actinobacterium, such as an actinobacterium selected from the group consisting of *Streptomyces ambofaciens*, *Streptomyces hygroscopicus*, or *Streptomyces malayensis*. In some embodiments in which the host cells is an actinobacterium, the actinobacterium is S1391, S1496, or S2441.

In some embodiments of any of the foregoing host cells, the host cell has been modified to enhance expression of a polyketide synthase. For example, the host cell has been modified to enhance expression of a compound-producing protein by (i) deletion of an endogenous gene cluster which expresses a compound-producing protein; (ii) insertion of a heterologous gene cluster which expresses a

compound-producing protein; (iii) exposure of the host cell to an antibiotic challenge; and/or (iv) introduction of a heterologous promoter that results in an at least 2-fold increase in expression of a compound compared to the homologous promoter.

5 In another aspect, the disclosure provides a method of producing a polyketide by culturing any of the foregoing host cells under suitable conditions.

In another aspect, the disclosure provides a method of producing a polyketide by culturing a host cell engineered to express any of the foregoing polyketide synthases under conditions suitable for the polyketide synthase to produce a polyketide.

10 In another aspect, the disclosure provides a method of producing a compound, the method including: (a) providing a parent polyketide synthase sequence capable of producing a compound; (b) determining the compatibility of at least one module of a second polyketide synthase with at least two modules of the parent polyketide synthase; (c) producing a nucleic acid encoding a modified polyketide synthase, wherein the modified polyketide synthase includes at least one module of a second polyketide synthase which has been determined to be compatible with the at least two modules of the parent
15 polyketide synthase.

In another aspect, the disclosure provides a method of producing a compound, the method including: (a) providing a parent nucleic acid encoding a parent polyketide synthase; (b) modifying the parent nucleic acid to create a modified nucleic acid encoding a modified polyketide synthase capable of producing a compound, wherein the modification produces a modified polyketide synthase including at
20 least one heterologous module.

In another aspect, the disclosure provides a method of producing a compound, the method including: (a) providing a parent polynucleotide sequence capable of producing a compound; (b) identifying one or more heterologous modules suitable for replacement of one or more modules in the parent polynucleotide sequence; (c) producing a nucleic acid encoding a modified polyketide synthase,
25 wherein the modified polyketide synthase includes at least one heterologous module identified in step (b).

In another aspect, the disclosure provides a method of producing a plurality of engineered polyketide synthases, wherein each of the plurality of polynucleotides corresponds to an engineered polyketide synthase, and wherein each of the plurality of polynucleotides includes one or more heterologous modules with altered enzymatic activity relative to a reference polyketide. The method
30 includes the steps of: (a) providing a parent polynucleotide sequence encoding a polyketide synthase; (b) identifying one or more modules for replacement in the parent polynucleotide sequence; (c) identifying two or more heterologous modules suitable for replacement for each of the modules identified in step (b); (d) generating a plurality of polynucleotides, wherein each of the plurality of polynucleotides corresponds to an engineered polyketide synthase, and wherein each of the plurality of polynucleotides includes a
35 heterologous module selected from the two or more heterologous modules identified in step (c) in replacement of each of the one or more modules to be replaced identified in step (b)..

Definitions

40 A "polyketide synthase" refers to an enzyme belonging to the family of multi-domain enzymes capable of producing a polyketide. A polyketide synthase may be expressed naturally in bacteria, fungi, plants, or animals.

As used herein, the term "engineered polyketide synthase" is used to describe a non-natural polyketide synthase whose design and/or production involves action of the hand of man. For example, in some embodiments, an "engineered" polyketide synthase is prepared by production of a non-natural polynucleotide which encodes the polyketide synthase.

5 A cell that is "engineered to contain" and/or "engineered to express" refers to a cell that has been modified to contain and/or express a protein that does not naturally occur in the cell. A cell may be engineered to contain a protein, e.g., by introducing a nucleic acid encoding the protein by introduction of a vector including the nucleic acid.

10 The term "gene cluster that produces a small molecule" or "gene cluster that produces a compound," as used herein, refers to a cluster of genes which encodes one or more compound-producing proteins.

The term "heterologous," as used herein, refers to a relationship between two or more proteins, nucleic acids, compounds, and/or cell that is not present in nature. For example, the LAL having the sequence of SEQ ID NO: 168 is naturally occurring in the S18 *Streptomyces* strain and is thus
15 homologous to that strain and would thus be heterologous to the S12 *Streptomyces* strain.

The terms "homologous" or "native," as used interchangeably herein, refer to a relationship between two or more proteins, nucleic acids, compounds, and/or cells that is present naturally. For example, the LAL having the sequence of SEQ ID NO: 168 is naturally occurring in the S18 *Streptomyces* strain and is thus homologous to that strain.

20 The term "recombinant," as used herein, refers to a protein that is produced using synthetic methods.

As used herein, the term "reference polyketide synthase" refers to a polyketide synthase that has a sequence having at least 80% identity (e.g., at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 99% identity, or 100% identity) to the sequence of an engineered
25 polyketide synthase except to the sequence of the one or more modules which are modified.

As used here, the term "compatibility" refers to a measure of the likelihood of two adjacent modules to form a competent module-module junction, in which polyketide translocation is not substantially inhibited. A heterologous module may be considered compatible if it meets at least one of the following criteria: 1) the module is present in the same module clade as one or more adjacent
30 modules of the reference PKS, as determined by the module-level phylogeny classification described in the detailed description of the invention; 2) the module is assigned a score of greater than or equal to 0.90 in the inter-module covariation analysis algorithm described in the detailed description of the invention; or 3) the module belongs to the same functional clade or sub-clade as one or more adjacent modules of the reference PKS, as determined by the evolutionary trace methodology outlined in the
35 detailed description of the invention.

As used here, the term "linking sequence" refers to a sequence directly upstream or downstream of an inter-modular junction. For example, in a single module swap, the ACP for the upstream homologous module, the ACP and KS-AT didomain of the inserted heterologous module, and the KS of the downstream homologous module may all be considered linking sequences.

40 As used herein, the term "module" refers to a region of a polyketide synthase that includes multiple domains. Modules present in a polyketide synthase may include i) a loading module; ii)

extending modules; and iii) releasing and/or cyclization modules, depending on whether the final polyketide is linear or cyclic. The domains which may be included in a given module include, but are not limited to, acyltransferase (AT), acyl carrier protein (ACP), keto-synthase (KS), ketoreductase (KR), dehydratase (DH), enoylreductase (ER), methyltransferase (MT), sulfhydrolase (SH), and thioesterase (TE).

As used here, the term "acceptor module" refers to a homologous module within a PKS cluster subject to engineering by module swapping. In the resulting engineered PKS cluster, the acceptor module is absent.

As used here, the term "donor module" refers to a heterologous module that is introduced into an engineered PKS cluster.

As used here, the term "module swapping" refers to the exchange of one or more heterologous donor modules for one or more homologous acceptor modules.

As used here, the term "does not substantially inhibit polyketide translocation" refers to the ability of a heterologous PKS module to function in a biosynthetic assembly line. For example, a heterologous loading module does not substantially inhibit polyketide translocation if the loading module is able to load a starter unit onto its ACP domain and pass the starter unit to the KS domain of the adjacent (n+1) extender module. A heterologous extender module does not substantially inhibit polyketide translocation if the extender module is able to receive a starter unit or polyketide chain from the previous (n-1) module, catalyze the addition of an extender unit, and pass the elongated polyketide chain to the adjacent (n+1) module. In some embodiments, a heterologous module does not substantially inhibit polyketide translocation if the engineered PKS that includes the heterologous module produces a compound in levels that are detectable by a highly sensitive detection method, e.g., LC-TOF mass spectrometry.

An extender unit, e.g., a malonyl-CoA, is loaded onto the acyl carrier protein domain of the current module catalyzed by another acyltransferase domain. The polyketide chain is then elongated by subsequent extender modules after being passed from the acyl carrier protein domain of module n to the ketosynthase domain of the n+1 module. The acyl carrier protein bound extender unit reacts with the polyketide chain bound to the ketosynthase domain with expulsion of CO₂ to produce an extended polyketide chain bound to the acyl carrier protein. Each added extender unit may then be modified by β -ketoprocessing domains, i.e., ketoreductase (which reduces the carbonyl of the elongation group to a hydroxy), dehydratase (which expels H₂O to produce an alkene), and enoylreductase (which reduces alkenes to produce saturated hydrocarbons).

Brief Description of the Figures

FIGS. 1A and 1B are schematics illustrating the mechanisms by which PKS biosynthesis proceed. FIG. 1A depicts polyketide chain elongation and β -carbonyl processing within a module. FIG. 1B depicts translation between modules.

FIG. 2A is a diagram depicting complementary bioinformatics approaches to the prediction of functional protein-protein interactions at the module-module junction.

FIG. 2B is a phylogenetic tree resulting from multiple sequence alignments of complete FK-family modules.

FIGS. 2C-2E depict how inter-module residue covariation is used to generate an algorithm that ranks module-module junction compatibility. FIG. 2C is a diagram that illustrates the upstream and downstream module-module junctions used to determine the compatibility of a given heterologous module. FIG. 2D is a correlation map that depicts the alignment of the ACP domain of a given module and the KS-AT didomain of a second module. FIG. 2E depicts the compatibility score resulting from inter-domain residue covariation analysis for a series of heterologous modules. Scores are normalized to the homologous module for the polyketide synthase in question, which is given a score of 1.00.

FIGS. 2F and 2G depict how evolutionary trace analysis is used to predict module-module junction compatibility. FIG. 2F is a phylogenetic tree generated by multiple sequence alignments of FK-family KS and ACP domains, in which group-specific residues have been concatenated into functional clades or sub-clades. The distance between modules can be used to predict module-module junction compatibility. FIG. 2G is a schematic depicting the compatibility relationships predicted by evolutionary trace analysis between KS and ACP domains for the FK-family.

FIG. 3A is a schematic depicting a single module swap in which a donor module replaces either module 3 or module 4 of the PKS gene cluster that produces Compound 1.

FIG. 3B is an image of the engineered PKS that includes the heterologous module 3 from the S17 *Streptomyces* strain in place of the homologous module 3 in the PKS that produces Compound 1. The engineered PKS module 3 now includes an ER domain, and thus, the resulting compound produced by the engineered PKS, Compound 2, is reduced relative to Compound 1.

FIG. 3C is an image depicting compounds, e.g., Compound 2, Compound 3, Compound 4, and Compound 5, produced by single module swaps of either module 3 or module 4 in the PKS that produces Compound 1 with compatible heterologous modules.

FIG. 4A is a schematic depicting combinatorial swapping of a dimodule unit.

FIG. 4B is a schematic depicting the synthesis of dimodule units from exogenous donor modules by a first round of Gibson assembly. The dimodule product is shown as analyzed by DNA gel electrophoresis.

FIG. 4C is a schematic depicting dimodule capture, amplification, and enrichment in a shuttle vector. Dimodule units resulting from a first round of Gibson assembly are captured in a shuttle vector by a second round of Gibson assembly. This allows for the dimodule assembly to be amplified, enriched, and ligated into the intended PKS.

FIG. 4D is a schematic depicting the construction of dimodule libraries by combinatorial synthesis.

FIG. 4E is an image depicting the possible resulting compounds that may be generated by an exemplary dimodule library swapped into module 3 and module 4 of the PKS that produces Compound 1.

FIG. 4F depicts oversampling required for sufficient coverage of a large combinatorial dimodule library. FIG. 4F is a graphical representation of the oversampling required to achieve 90% or greater coverage of a 225 member dimodule combinatorial library. 18% of the 650 sampled clones were found to have produced polyketide compounds resulting from the engineered PKS cluster, as determined by LC-TOF mass spectrometry analysis.

FIG. 4G is a schematic depicting a method of preparing combinatorial dimodule libraries and characterizing the resulting libraries using NanoPore sequencing.

FIG. 4H is a schematic depicting the core informatics workflow for deconvoluting the sequences of combinatorial dimodule libraries by NanoPore sequencing.

FIGS. 5A and 5B depict the construction of trimodule libraries by combinatorial synthesis. **FIG. 5A** is a schematic illustrating a trimodule swap of modules 4, 5, and 6 of the PKS cluster that produces Compound 7, to produce a theoretical library size of 2,197 engineered polyketide synthases. **FIG. 5b** is an image of high efficiency trimodule assembly by Gibson assembly as analyzed by DNA gel electrophoresis.

FIG. 6A is a schematic illustrating a module swap that results in ring expansion by exchanging a single module acceptor for a dimodule donor. The resulting expanded ring compound produced by the engineered PKS, Compound 8, is also depicted.

FIG. 6B is a spectrogram that shows the production of an expanded ring compound, Compound 8, as analyzed by LC-TOF mass spectrometry.

FIG. 7A is schematic depicting the enzymatic domains of five PKS loading modules, including Rapamycin and novel PKS cluster, X23. Also shown is the starter unit associated with each loading module.

FIG. 7B depicts the compounds produced by engineered PKS clusters resulting from single module swaps in the X23 PKS cluster. The products include Compound 11 and 12, which are produced by an engineered PKS that contains a heterologous loading module.

Detailed Description of the Invention

The present invention describes compositions and methods for the production of polyketide compounds by an engineered polyketide synthase that includes one or more heterologous modules. The present invention also describes methods for predicting the compatibility of linking sequences of heterologous module-module junctions to produce an engineered polyketide synthase that does not substantially inhibit translocation during polyketide biosynthesis.

Compounds

Compounds that may be produced with the methods of the invention include, but are not limited to, polyketides and polyketide macrolide antibiotics such as erythromycin; hybrid polyketides/non-ribosomal peptides such as rapamycin and FK506; carbohydrates including aminoglycoside antibiotics such as gentamicin, kanamycin, neomycin, tobramycin; benzofuranoids; benzopyranoids; flavonoids; glycopeptides including vancomycin; lipopeptides including daptomycin; tannins; lignans; polycyclic aromatic natural products, terpenoids, steroids, sterols, oxazolidinones including linezolid; amino acids, peptides and peptide antibiotics including polymyxins, non-ribosomal peptides, β -lactams antibiotics including carbapenems, cephalosporins, and penicillin; purines, pteridines, polypyrroles, tetracyclines, quinolones and fluoroquinolones; and sulfonamides.

Proteins

Polyketide Synthases

Polyketide synthases (PKSs) are a family of multi-domain enzymes that produce polyketides. Type I polyketide synthases are large, modular proteins which include several domains organized into

modules. The modules generally present in a polyketide synthase include i) a loading module; ii) extending modules; and iii) releasing and/or cyclization modules depending on whether the final polyketide is linear or cyclic. The domains which generally are found in the modules are acyltransferase (AT), acyl carrier protein (ACP), keto-synthase (KS), ketoreductase (KR), dehydratase (DH),
5 enoylreductase (ER), methyltransferase (MT), sulfhydrylase (SH), and thioesterase (TE).

A polyketide chain and the starter groups are generally bound to the thiol groups of the active site cysteines in the ketosynthase domain (the polyketide chain) and acyltransferase domain (the loading group and malonyl extender units) through a thioester linkage. Binding to acyl carrier protein (ACP) is mediated by the thiol of the phosphopantetheinyl group, which is bound to a serine hydroxyl of ACP, to
10 form a thioester linkage to the growing polyketide chain. The growing polyketide chain is handed over from one thiol group to another by trans-acylations and is released after synthesis by hydrolysis or cyclization.

The synthesis of a polyketide begins by a starter unit, being loaded onto the acyl carrier protein domain of the PKS catalyzed by the acyltransferase in the loading module. An extender unit, e.g., a
15 malonyl-CoA, is loaded onto the acyl carrier protein domain of the current module catalyzed by another acyltransferase domain. The polyketide chain is then elongated by subsequent extender modules after being passed from the acyl carrier protein domain of module n to the ketosynthase domain of the n+1 module. The acyl carrier protein bound extender unit reacts with the polyketide chain bound to the ketosynthase domain with expulsion of CO₂ to produce an extended polyketide chain bound to the acyl
20 carrier protein. Each added extender unit may then be modified by β -ketoprocessing domains, i.e., ketoreductase (which reduces the carbonyl of the elongation group to a hydroxy), dehydratase (which expels H₂O to produce an alkene), and enoylreductase (which reduces alkenes to produce saturated hydrocarbons). Once the synthesis of the polyketide is complete, a thioesterase domain in the releasing
modules hydrolyzes the completed polyketide chain from the acyl carrier protein of the last extending
25 module. The compound released from the PKS may then be further modified by other proteins, e.g., nonribosomal peptide synthase. In some cases, the biosynthetic cluster harbors polyketide megasynthases and a non-ribosomal peptide synthase (NRPS). This hybrid architecture is referred to as hybrid PKS/NRPS.

30 *Polyketide synthase extender modules*

PKS biosynthesis proceeds by two key mechanisms: polyketide chain *elongation* within a module and *translocation* between modules (FIGS. 1A and 1B). The basic functional unit of polyketide synthase clusters is the extender module, which encodes a 2-carbon extender unit derived from malonyl-CoA. Within the extender module, the minimal domain architecture required for polyketide chain elongation
35 includes the ketosynthase (KS), acyl-transferase (AT) and the ACP (acyl-carrier protein) domains, and the specific chemistry of each module is encoded by the AT domain and by the presence of the beta-carbonyl processing domains: ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) domains. Productive chain elongation depends on the concerted function of numerous domains

β-ketone processing domains

β-ketone processing domains are the domains in a PKS which result in modification of the elongation groups added during the synthesis of a polyketide. Each β-ketone processing domain is capable of changing the oxidation state of an elongation group. The β-ketone processing domains include ketoreductase (which reduces the carbonyl of the elongation group to a hydroxy), dehydratase (which expels H₂O to produce an alkene), and enoylreductase (which reduces alkenes to produce saturated hydrocarbons).

Module swapping to produce engineered polyketide synthases

The present disclosure provides methods and compositions related to engineered polyketide synthases produced by swapping modules between related PKS clusters. Polyketide translocation is controlled by protein-protein interactions at the inter-modular junctions. In some embodiments, module swapping is guided by bioinformatic predictions to determine which modules have the highest probability of functioning in assembly-line polyketide biosynthesis. Multiple bioinformatics methods are used to determine the structural information in PKS sequence alignments to predict protein-protein interactions that mediate polyketide translocation at the inter-modular junction. The present disclosure includes a DNA assembly strategy to swap one or more heterologous donor modules for one or more acceptor modules to generate hybrid PKS clusters.

In some embodiments, module swapping is achieved by single, di- or tri-, or multi-module capture. In some embodiments, module swapping may be performed by exchange of the loading module. In some embodiments, module swapping may be performed by exchange of one or more extender modules. In some embodiments, module swapping may be performed by exchange of one or more releasing or cyclization modules. In some embodiments, two or more heterologous donor modules may replace a single acceptor module which may result in the production of a ring-expanded compound. In some embodiments, a single heterologous donor module may replace two or more acceptor modules which may result in a contracted ring compound. In some embodiments, the engineered polyketide synthases may produce novel compounds.

Combinatorial libraries of engineered polyketide synthases

In some embodiments, the pooled capture and transfer of single, di- or tri-, or multi-module units enables the production of combinatorial libraries of engineered polyketide synthases. A dimodule unit, for example, consists of two heterologous modules, each of which may be independently selected from a pool of heterologous modules. A trimodule unit, example, consists of three heterologous modules, each of which may be independently selected from a pool of heterologous modules. One or more modules of a polyketide synthase may be replaced with a single, di-, tri-, or multi-module unit, where the single, di-, tri- or multi-module unit is selected from a pool of single- di-, tri- or multi-module units produced by combinatorial synthesis. Exemplary methods for the production of combinatorial libraries of engineered polyketide synthases (e.g., dimodule and trimodule combinatorial libraries) are provided in Examples 2 and 4.

Characterization of engineered PKS libraries by single-molecule long-read sequencing

In some embodiments of the invention, single-molecule long-read sequencing technology (e.g., Nanopore sequencing or SMRT sequencing) may be used to characterize libraries of engineered polyketide synthases which are produced by any of the methods described herein. In particular, single-molecule long-read sequencing (e.g., Nanopore sequencing or SMRT sequencing) may be used to characterize (e.g., deconvolute) combinatorial libraries of engineered polyketide synthases (e.g., combinatorial libraries of engineered polyketides synthases which are produced by pooled capture and transfer of single, di- or tri-, or multi-module units). Single-molecule long-read sequencing enables the identification of the module or modules which are incorporated into the combinatorial library. This further enables the prediction of the chemistry of the resulting plurality of engineered polyketide synthases. The predicted enzymatic chemistry can therefore be connected to the compounds produced by the engineered polyketide synthases. The resulting compounds may be identified by chemical methods of analysis known to one of skill in the art (e.g., mass spectrometry or high performance liquid chromatography). Furthermore, the predicted enzymatic chemistry can be connected to the function of the resulting compounds (e.g., binding to a target protein or inducing a phenotype, such as a cell based phenotype). Accordingly, long-read sequencing of a genetically encoded molecule may allow for genotypic-phenotypic linkage.

Single-molecule long-read sequencing technologies may be considered to include any sequencing technology which enables the sequencing of a single molecule of a biopolymer (e.g., a polynucleotide such as DNA or RNA), and which enables read lengths of greater than 2 kilobases (e.g., greater than 5 kilobases, greater than 10 kilobases, greater than 20 kilobases, greater than greater than 50 kilobases, or greater 100 kilobases). Single-molecule long-read sequencing technologies may enable the sequencing of multiple single molecules of DNA or RNA in parallel. Single-molecule long-read sequencing technologies may include sequencing technologies that rely on individual compartmentalization of each molecule of DNA or RNA being sequenced.

Nanopore sequencing is an exemplary single-molecule long-read sequencing technology that may be used to characterize libraries of engineered polyketide synthases that are prepared by any of the methods described herein. Nanopore sequencing enables the long-read sequencing of single molecules of biopolymers (e.g., polynucleotides such as DNA or RNA). Nanopore sequencing relies on protein nanopores set in an electrically resistant polymer membrane. An ionic current is passed through the nanopores by setting a voltage across this membrane. If an analyte (e.g., a biopolymer such as DNA or RNA) passes through the pore or near its aperture, this event creates a characteristic disruption in current. The magnitude of the electric current density across a nanopore surface depends on the composition of DNA or RNA (e.g., the specific base) that is occupying the nanopore. Therefore, measurement of the current makes it possible to identify the sequence of the molecule in question. Exemplary methods for the use of Nanopore sequencing to characterize combinatorial libraries of engineered polyketide synthases are provided in Example 3.

Single molecule real-time (SMRT) sequencing (PacBio) is an exemplary single-molecule long-read sequencing technology that may be used to characterize libraries of engineered polyketide synthases that are prepared by any of the methods described herein. SMRT is a parallelized single molecule DNA sequencing method. SMRT utilizes a zero-mode waveguide (ZMW). A single DNA

polymerase enzyme is affixed at the bottom of a ZMW with a single molecule of DNA as a template. The ZMW is a structure that creates an illuminated observation volume that is small enough to observe only a single nucleotide of DNA being incorporated by DNA polymerase. Each of the four DNA bases is attached to one of four different fluorescent dyes. When a nucleotide is incorporated by the DNA
5 polymerase, the fluorescent tag is cleaved off and diffuses out of the observation area of the ZMW where its fluorescence is no longer observable. A detector detects the fluorescent signal of the nucleotide incorporation, and the base call is made according to the corresponding fluorescence of the dye.

Computational approaches for the prediction of functional inter-modular junctions

10 The present disclosure provides complementary bioinformatic approaches for the prediction of functional protein-protein interactions at the module-module junction (FIG. 2A). In some embodiments, these bioinformatic approaches serve as the predictive basis for the design of chimeric PKS proteins by module swapping.

Module-level phylogeny

15 Sequence divergence between polyketide modules and inter-module linkers suggests importance in module-module compatibility. In some embodiments, a module-level phylogenetic map may be constructed by multiple sequence alignment of PKS modules. For example, a module-level phylogenetic map was generated by multiple sequence alignments of complete FK-family modules (FIG. 2B). This
20 enabled the identification of 10 module clades including 8 elongation, 1 loading, and 1 off-loading. In some embodiments, a heterologous module is compatible if it is present in the same module clade as the adjacent modules.

Inter-module residue covariation

25 Inter-module residue covariation across the intermodular junction was computed to generate an algorithm to rank order intermodule compatibility (FIGS. 2C-2E). Type I polyketide synthase protein sequences were extracted from Genbank and an internal database using Hidden Markov Models trained on the ketosynthase (KS) and acyl carrier protein (ACP) domains. Shorter peptide sequences, starting with the ACP of a module and extending through the KS and acyl transferase (AT) of the following
30 module, were extracted to generate a multiple alignment. Positions not aligning to an amino acid from PDB entry 2JU1 (for the ACP) or 2HG4 (for KS and AT and associated linkers) were removed to compress the multiple alignment. Evolutionary couplings were then calculated using the package FreeContact. These couplings take the form of a score matrix with two indices: the first amino acid position in the multiple alignment (I) and the second amino acid position in the multiple alignment (J,
35 which is always greater than I) and the amino acid at position J. I,J pairs with a score above a specified cutoff and in which I is within the ACP and J within the KS-AT didomain are saved.

To generate a score for a potential single module substitution, the following alignments are retrieved from the original multiple alignment: the ACP for the upstream domain, the ACP and KS-AT didomain for the inserted module, and the KS for the downstream module. These are used to synthesize
40 two rows compatible with the original multiple alignment: one with the ACP of the upstream module and KS-AT of the inserted module and a second with the ACP of the inserted module and KS-AT of the

downstream module. For each I,J pair in the saved coupling matrix, the amino acids at position I and J in the synthesized alignment are retrieved (aal, aaJ). The mutual information for this amino acid pair within the alignment is multiplied by the coupling score to generate a raw score. The raw scores are computed for each I,J pair in the saved coupling matrix and for each of the two synthesized alignments. The sum of the raw scores for the heterologous donor domain is divided by the sum of the raw scores for the homologous native domain to generate a normalized percentage score. Candidate swaps with the same chemistry are ranked by this score. In the case of multiple module swaps, the process is expanded, e.g., if N donor domains are to be swapped in, then one synthetic alignment is generated for the preceding module's ACP domain and the first donor module's KS-AT didomain, another for the first donor modules' ACP domain and the second donor module's KS-AT didomain and so forth, concluding with the final donor domain's ACP and the first module of the recipient synthase downstream of the breakpoint. Scores are computed and normalized in the same manner: the scores for the swapped modules are normalized for the score computed for the native modules. In some embodiments, a heterologous module is compatible if the module is assigned a score of greater than or equal to 0.90 in the inter-module covariation analysis algorithm described herein.

Evolutionary trace analysis to identify modules within functional clades or sub-clades

As an additional test of module compatibility, evolutionary trace analysis may be used to identify modules that belong to the same functional clade or sub-clade (FIGS. 2F-2G). For example, phylogenetic trees with uniform branch lengths were constructed based on multiple sequence alignments of FK-family KSs and ACPs. For every non-terminal node in a tree, a vertical cutoff was applied by which terminal nodes were partitioned into groups based on shared parental nodes at the cutoff. Residues globally conserved across all groups and residues locally conserved within groups, but specific to a given group, were identified as functional residues. Globally conserved residues suggest rules that likely must be observed for all members of the FK-family. Group-specific residues suggest guidelines that may provide predictive power for engineering within the FK class. For each tree, the earliest cutoff at which the number of group-specific residues exceeded the number of globally conserved residues was selected for further analysis. Group-specific residues were concatenated into functional clades and unrooted phylogenetic trees of the clades were constructed. Distances between terminal nodes in the phylogenetic tree were used to create an evolutionary distance score (EDS). The KS and ACP EDSs between a homologous acceptor module and a proposed heterologous donor module were calculated and used to predict engineering compatibility. KS and ACP clade classifications were then used to create network maps of neighboring KSs and ACPs weighted by the frequency a given KS-ACP or ACP-KS pair was observed in FK-family polyketides. Superimposing a proposed module swap onto the network map was used to predict engineering compatibility with upstream ACPs and downstream KSs. In some embodiments, a heterologous module is compatible if the module belongs to the same functional evolutionary clade or sub-clade as one or more adjacent modules in the reference PKS.

Regulation of polyketide synthase expression

The Large ATP-binding regulators of the LuxR family of transcriptional activators (LALs) are known transcriptional regulators of polyketides such as FK506 or rapamycin. The LAL family has been

found to have an active role in the induction of expression of some types of natural product gene clusters, for example PikD for pikromycin production and RapH for rapamycin production. Binding of the LAL or multiple LALs in a complex to specific sites in the promoters of genes within a gene cluster that produces a small molecule (e.g., a polyketide synthase gene cluster) potentiates expression of the gene cluster and hence promotes production of the compound (e.g., a polyketide). In some embodiments, LALs may be used for the regulation of the expression of engineered PKS clusters.

LALs

LALs include three domains, a nucleotide-binding domain, an inducer-binding domain, and a DNA-binding domain. A defining characteristic of the structural class of regulatory proteins that include the LALs is the presence of the AAA+ ATPase domain. Nucleotide hydrolysis is coupled to large conformational changes in the proteins and/or multimerization, and nucleotide binding and hydrolysis represents a "molecular timer" that controls the activity of the LAL (e.g., the duration of the activity of the LAL). The LAL is activated by binding of a small-molecule ligand to the inducer binding site. In most cases the allosteric inducer of the LAL is unknown. In the case of the related protein MalT, the allosteric inducer is maltotriose. Possible inducers for LAL proteins include small molecules found in the environment that trigger compound (e.g., polyketide) biosynthesis. The regulation of the LAL controls production of compound-producing proteins (e.g., polyketide synthases) resulting in activation of compound (e.g., polyketide) production in the presence of external environmental stimuli. Therefore, there are gene clusters that produce small molecules (e.g., PKS gene clusters) which, while present in a strain, do not produce compound either because (i) the LAL has not been activated, (ii) the strain has LAL binding sites that differ from consensus, (iii) the strain lacks an LAL regulator, or (iv) the LAL regulator may be poorly expressed or not expressed under laboratory conditions. Since the DNA binding region of the LALs of the known PKS LALs are highly conserved, the known LALs may be used interchangeably to activate PKS gene clusters other than those which they naturally regulate. In some embodiments, the LAL is a fusion protein.

In some embodiments, an LAL may be modified to include a non-LAL DNA-binding domain, thereby forming a fusion protein including an LAL nucleotide-binding domain and a non-LAL DNA-binding domain. In certain embodiments, the non-LAL DNA-binding domain is capable of binding to a promoter including a protein-binding site positioned such that binding of the DNA-binding domain to the protein-binding site of the promoter promotes expression of a gene of interest (e.g., a gene encoding a compound-producing protein, as described herein). The non-LAL DNA binding domain may include any DNA binding domain known in the art. In some instances, the non-LAL DNA binding domain is a transcription factor DNA binding domain. Examples of non-LAL DNA binding domains include, without limitation, a basic helix-loop-helix (bHLH) domain, leucine zipper domain (e.g., a basic leucine zipper domain), GCC box domain, helix-turn-helix domain, homeodomain, srf-like domain, paired box domain, winged helix domain, zinc finger domain, HMG-box domain, Wor3 domain, OB-fold domain, immunoglobulin domain, B3 domain, TAL effector domain, Cas9 DNA binding domain, GAL4 DNA binding domain, and any other DNA binding domain known in the art. In some instances, the promoter is positioned upstream to the gene of interest, such that the fusion protein may bind to the promoter and induce or inhibit expression of the gene of interest. In certain instances, the promoter is a heterologous

promoter introduced to the nucleic acid (e.g., a chromosome, plasmid, fosmid, or any other nucleic acid construct known in the art) containing the gene of interest. In other instances, the promoter is a pre-existing promoter positioned upstream to the gene of interest. The protein-binding site within the promoter may, for example, be a non-LAL protein-binding site. In certain embodiments, the protein-binding site binds to the non-LAL DNA binding domain, thereby forming a cognate DNA binding domain/protein-binding site pair.

In some embodiments, the LAL is encoded by a nucleic acid having at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%) sequence identity to any one of SEQ ID Nos: 171-203 or has a sequences with at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%) sequence identity to any one of SEQ ID Nos: 171-203.

SEQ ID NO: 171

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SEQ ID NO: 172

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CCGCAACCCGCTGGCCTCGAGCCGGCACCTCGACGAGCTGACCGTCGTCGCCCGTGCCGGGCTGCTCTTCCCCGAGC
25 ACACGGCGCTGATGATCCGCTGGCTGGGCGTCCGGCGGGCGGTCCGGCGAGGCAGCCGGGCTGCTGGCCTCGCAGCGC
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GTCCGGCCCCGACCGGCGGGCCGCGTCCGCTCACGCCGATGAGCTCGCGAACCTGCCGAAGGCGGGCCCGGCTCTGCG
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CAGCACGCCGACTCGGCGGGCGGCCGGCACACCAGCCCTCGCCGCGCTGACCGCCTTGCTGTACGCGGAGAACACCGA
30 CACCGCTCAGCTCTGGGCCGACAAGCTGGTCTCCGAGACCGGGGCGTCAACGAGGAGGAGGCGGGCTACGCGGGGC
CGCGCGCCGAAGCCGCGTTGCGTCGCGGGCGACCTGGCCGCGGCGGTTCGAGGCAGGCAGCACCGTTCTGGACCACCGG
CGGCTCTCGACGCTCGGCATCACCGCCGCGCTACCGCTGAGCAGCGCGGTGGCCGCCGCCATCCGGCTGGGCGAGAC
CGAGCGGGCGGAGAACTGGCTCGCCCAGCCGCTGCCGCAGGCCATCCAGGACGGCCTGTTCCGGCCTGCACCTGCTCT
CGGCGCGCGGCCAGTACAGCCTCGCCACGGGCCAGCACGAGTCGGCGTACACGGCGTTTCGCGACCTGCGGGGAACGT
35 ATGCGGAACTGGGGCGTTGACGTGCCGGGTCTGTCCCTGTGGCGCGTCGACGCCGCCGAGGCGCTGCTGCACGGCCG
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TGCGGGTGCAGGCGGCGTACAGCCCGCCGGCGAAGCGGGTTCGACCTGCTCGATGAAGCGGCCGACCTGCTGCTCTCC
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40 CCAAGCCCCGAGGCCCCGGCTGGCTGGAGGAATCCGGCCTGCCGCAGCGGATCAAGTCGCTGACCGACGCGGAGCGG
CGGGTGGCGTCGCTGGCCGCCGGCGGACAGACCAACCGCGTGATCGCCGACCAGCTCTTCGTCACGGCCAGCACGGT
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GTGGTTCCTGAAGTGCGAGCAGCCCCGACGAACTGATCGCCCGCGATGACGAGCTGAGCCGCCTCCAACGGGCACT
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5 ACGCCGGAGCGGCCAAGTCCGGCTTCGTGCGCACTCCGTGCGGTGTGCTCCTGGGAAGAGCGCACTCTGCCGTACGGG
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GAGCCCTCAGGCCGGTACCGACAACCGCCTGCGGGCCGAGTTACCCCGCACCCCTGCTGGCGCTCGCCGCGGACTGGC
CCGTCTGATCGGCATCGACGACGTGCACCACGCCGACGCGGAATCACTGCGCTGTCTGCTCCACCTCGCCCGCCGC
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10 ACTGCTGAGCCTGCGCTCCTACCAGGAGATCGCGCTCAGACCGCTCACCAGGGCGCAGACCGGGCGAACTCGTACGTC
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CGCGTACCTCAGCTCGCTCTACCGCTGCGGCCCGAGCGCGCTGCGTGTCGCCCGGGCGTCCGCCGTGCTCGGCGCGA
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15 GAGGGACGGCTGCTGCAGGGCGAGCGGTTTCCGCACCCGGCGGGCCCGCTCCATCGTCTTGACGACCTGTGGGCCCT
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20 CCGCGTCGCGCGCGGGACTGCTCTCCAGCGAGCACGCCGTGTCGCTCGCCGACTGGCTGGCGATGGGCGGGCGCCCG
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25 GTTGCTGGCCCTGCTCTACGCGGAGAACACCGATGCTGTCCAGTTCTGGGTGACAAACTGGCCGGTGACGAGGGCA
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35 CCCAGTGCGGCGCCGTGCCGCTCCTGCGGCGGCTCGGCGCGGAACCCTCGGACATCGGCGGAGCCTGGGACGCGACG
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GGAGATCGCCGAGCAGCTGTTGCTACGGCCAGCACGGTGGAACAGCACCTCACGAACGTGTTCCGCAAACCTGGCGG
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ATGGTTCCTGAAGTGCGAGCAGCCCCGACGAACTGATCGCCCGCGATGACGAGCTGAGCCGCCTCCAACGGGCACT
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ATGCTGGGCCAGCTCTTCGACCATCCCGAACTGGCCGCCAGGCGCCGGACCTTGCCCACTTCACGGCTTCGTGCGA
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5 ATCGGCCCCGGCCCGCATCGCGGTCTGACTGACCGAGCTGCGCAGACCGACGCCCGCCGACTCCCGCTTCCAGGCGGA
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10 GCGCCGAAGCCGTGCTCGTCCAGCGGATGACCGGACTGAACAAGGACGCGGTCTGAACAGGTCTATGAGCAGCTGAAC
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15 ACTACGCGTCGGCGCCCGCCGCGATCGAGCGCCTCTGCAATCCGGTACGGGCAGGCCGGCATCTGCCCGAGCTGCTCA
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20 GACCGGGCGGACGCCAACGCGGAGAGCGTTCTCCAGCACACCGACGCCACGGCGGACCGGACCACGGCCATCATGGC
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25 AGACGCCGGAGAGCCTCTTCGGGCTGCACCTGCTCTGGGCCCCGCGGGCAGCACCACTCGCGACCGGGCGGCACGGG
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30 CTTGGCAGAGGCCTCCAGCATGGTCCGGCAGCACAGCAGGGCGCGGGGTCTGCTCCGCCGGGCACGGCACCTCGCCA
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GGAGATCGCCGAGCAGCTGTTTCGTACAGGCCAGCACGGTGAACAGCACCTCACGAACGTGTTCCGCAAACCTGGCGG
TGAAGGGCCGCCAGCAGCTTCCGAAGGAACTGGCCGACGTGCGGCGAGCCGGCGGACCGCGACCGCCGGTGCGGGTAG
35

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GTGATAGCGCGCTTATCTCCCCAGACCTGATCGCCCGCGATGACGAGTTCGGTTCCCTCCACCGGGCGCTCACCCG
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40 GGCCAGCTCCTCGACCAAGCCGAGCTGGCCGCCCGGACACCGGAGCTGGTCCGGCTGACGGCATCGTGCGAAAACCT
GCCGGCCGACGTCGACAACCGCCTGGGGACCGAACTCACCCGCACGGTGTGACGCTCGCCGCGGAGCGGGCCCGTAC
TGATCGGCATCGACGACGTGCACCACGCCGACGCGCCGTGCTGCGCTGCCTGCTCCACCTCGCGCGCCGCATCAGC

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5 CGCCTACCTCGGGTCGCTCTATCGTTGCGGCCCCGGCCGCGCTGAGCGTCGCCCGAGCTTCCGCCGTGCTCGGGCAGA
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10 CGCGGCGAGCTCGACGAGGCCGTCACCTACCTGGAGTTCGCCTACCGGGCCCTCCGACGACCCCGCCGTCCACGCCGC
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15 TCGCCTCGTTTTCCGGAGCCGTCCGGCACCGCGCCGTTCGCCGACAAGGCCCTGAGCAACGCGCTGCGCGGCTGGTCC
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25 ATCGAACTGCTCGACGAGGCCGCCGATCTGCTCATCATGTGCCGCGACCAGTACGAGCTGGCCCGCGTCTCTCGCCGA
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30 TGAAGGGCCGTAGCAACTGCCCAAGGAACTGTCCGACGCCGGCTGA

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35 CCGCGGCCAAGGCCGGCTTTCGTACCCCTTCGCGCGGTGTGCTCCATGGAGGAGCGGGCCCTGCCGTACGGCATGCTC
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40 GAGTCTGCGCCACTACCAGGAGATCGCGCTGCGCCCGCTCACCAGGGCGCAGACCACCGAACTCGTGCGCCGGCACC
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CGCCTACCTCGGGTCGCTCTATCGTTGCGGGCCCGGCCGCGCTGAGCGTCGCCCCGAGCTTCCGCCGTGCTCGGCGAGA
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5 ACCAGATGGGTACCGGCCGGGTGCACGGCGCCGAGGTGCGCCGGGCTGTTACCGACGCCGCGCGGAGCACCACCTG
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10 GGACCTGTCCCTCGCGCTGATCTATCCCGGCGCGGCCGATCCGCCGCGTCCGGCCGATCCGCCGGCCGAGGACGAGG
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25 GGAGATCGCCAGCCAGCTGTTCTGTCACCTCCAGCACGGTGAACAGCACCTACCAACGTGTTCCGCAAGCTGGGGG
TGAAGGGCCGTCAGCAACTGCCCAAGGAACTGTCCGACGCGCGCTGA

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40 TGCGCCGGATCAGCGGGCTCGACGCCGAGACGGTGGACGAGGCGACCGCGATCCTACCGAGGGCGGCCTGCTCCGG
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5 CTGCAGCGGGCGCTGGCCGTCACCGACCACGACCGGGCCCCGCCCTGCGGGCGGCGGAGGTGTGCTCGCGCTGTTCCA
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15 TGACCGGGCGGAGGGCCGGCGGCTGATCGACGAGCAGCTCACCCGGCCGATGGGGCCCCGGTCACGAGCCCTGACCC
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40 GAGTACCTGCAACTGGCCTACCGGGCCTCCGACGACGCCGGCGCCCCGGGCGCCCTGCAGGTGGAGACCGTGGCCGG
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GTGTGACCGCCGACAACGCGGTGCTGGCGGGCGCTGCGCGGCCGTCCCGAGTCGGCCGCGCCGAGGCGGAGAACGTG
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5 CGACGCCGCCAGCTCTGGGCGGACAAGCTGGCCCGGGGCATCGGGGCGGGGGAGGGGGAGGCCGGCTACCGGGGGC
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10 ATGCGCCGGTGGGACGTCGACGTGCCCGGGCTGGCCCTGTGGCGGGTGGACGCGGCCGAGGCGCTGCTGCCCGGGCGA
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15 TCAAGGCCGGCCGGTCCGGTCGGCTCGGCCGGCCGCCGCAGGGAATCCGCTCCCTGACCGAGGCCGAGCGCCGGGTG
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25 TCACGCCGACACCGCCTCTTTGAACTGTCTGCTGCATTTGGCGCGCCGGGTCCGTCCGGCCCCGGATATCCATGATCT
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10 CGGCCGGATCGACGACGCCGGCCTGCCGCAGCGGAGCACATCGTTGACCGATGCGGAGCGGCGGGTGGCGGCGCTGG
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5 CGCTGCTGCGCAGGCTCGGGGGCGAGCCCCGGCCGGATCGACGACGCCGGCCTGCCCGAGCGGAGCACATCGTTGACC
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5 AAGACGTGATCCAAC TCGTGC GG TCTGCTCGGCGGAGGAGCAGGAGCTGCCGTACGCGATGGTTCGGACA ACTACTC
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35 CCGCGATGGCCGCCCGCCGGGCAGACCAACCGGGAGATCGCCGGTGGCTCTTCGTACAGGCCAGCACGGTGGAGCAG
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10 CTGCTGCGTGACCAGCAGTTCCCGCACCCGGCGGGCCCGCTCGGTGCTGCTCGACGACATGTCCGCGCAGGAACGCCA
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25 CGCCCGGACGAGGGCCGCAAGCTCATCGACGACCAGCTCACCCGTGAGATGGGGGCCCGCTCCCGGGCGCTGACGCT
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CGAACCCGTACGCATCGGCACCCGGCGTGGTGAACCCGGCCTGCCGCAGCGGATCAGGCTGCTGACCGATGCCGAGC
30 GCGGGGTTGCCGCGATGCCCGCCCGCGGGCAGACCAACCGGGAGATCGCCCGTCCGCTCTTCGTACGGCCAGCACG
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40 TCACCGAGTTGCGCAGCCTCACCCCTACTCAGTCACGGTTCAAGGCGGAGCTGCTCAGCCTGCCATACCACCACGAG
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5 CTGGAAGTGTGACGAGGCGCCGGTTGAAGTGCTCGCGCACCACCAGGTCGGCGCCGGTCTCATACACGGGCCCAA
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25 CCGCGGCCGGACAGACCAACCGGGAGATCGCCGAACAGCTGTTTCGTACGGCCAGCACAGTGGAACAGCACCTCACA
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40 GCGTTTCGCACCTGCGGAGAACGTATGCGCAGCTGGGATGTTGACGTGCCTGGTCTGGCCCTGTGGCGTGTGACGC
CGCCGAGGCGCTGCTCAGCCTCGACCGGAACGAGGGCCAGCGGCTCATCGACGAACAACCTACCCGTCCGATGGGAC
CTCGTTCCCGCGCGCTGACGCTGCGGATCAAGGCGGCATACCTCCCGCGGACGAAGCGGATCCCCCTGCTCCATGAG

GCGGCCGAGCTGCTGCTCCCCTGCCCCGACCCGTACGAGCAAGCGCGGGTGCTCGCCGATCTGGGCGACACCGCTCAG
CGCGCTCAGACGCTATAGCCGGGCGCGGGGAGTTCTCCGGCAGGCTCGTCACCTGGCCACCCAGTGCGGTGCTGTCC
CGCTGCTGCGCCGACTCGGGGGCGAGCCCGGCCGGATCGACGACGCCGGCCTGCCGCAGCGGAGCACATCGTTGACC
GATGCGGAGCGGCGGGTGCGGCGCTGGCCGCGGCCGGACAGACCAACCGGGAGATCGCCGAACAGCTGTTTCGTACAC
5 GGCCAGCACAGTGGAACAGCACCTCACAAAGCGTCTTCCGCAAGCTGGGCGTCAAGGGCCGCAAGCAGCTGCCGACCG
CGCTGGCCGACGTGGAACAGACCTGA

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GTGCGAGCTATTAATGCGTCCGACACCGGTCCTGAACTGGTCGCCCCGGAAGACGAACTGGGACGTGTACGAAGTGC
10 CCTGAACCGAGCGAACGGCGGCCAAGGTGTCCTGATCTCCATTACCGGTCCGATCGCCTGCGGCAAGACCGAACTGC
TTGAGGCTGCCGCCTCGGAAGTTGACGCCATCACTCTGCGCGCGGTCTGTGCCGCCGAGGAACGGGCGATACCTTAT
GCCCTGATCGGGCAGCTTATCGACAACCCCGCGCTCGGCATTCCGGTTCCGGATCCGGCCGGCCTGACCGCCCAGGG
CGGACGACTGTCATCGAGCGCCGAGAACCGACTGCGTCGCGACCTCACCCGTGCCCTGCTGACGCTCGCCACCGACC
GGCTGGTGCTGATCTGTGTCGATGACGTGCAGCACGCCGACAACGCCTCGTTGAGCTGCCTTCTGTATCTGGCCCGA
15 CGGCTTGTCGCCGGCTCGAATCGCTCTGGTATTCACCGAGTTGCGAGTCCTCACCTCGTCTCAGTTACGGTTCAACGC
GGAGCTGCTCAGCTTGCGGAACCACTGCGAGATCGCGCTGCGCCCACTCGGCCCCGGGGCATGCGGCCGAGCTGGCCC
GCGCCACCCTCGGCCCCGGCCTCTCCGACGAAACACTCACGGAGCTGTACCGGGTGACCGGAGGCAACCTGAGTCTC
AGCCGCGGGCTGATCGACGATGTGCGGGACGCCTGGGCACGAGGGGAAACGGGCGTCCAGGTGGGCCGGGCGTTCCG
GCTGGCCTACCTCGGTTCCTCCACCGCTGTGGTCCGCTGGCGTTGCGGGTCGCCCCGCGTAGCCGCCGTACTGGGCC
20 CGAGCGCCACCAGCGTCCTGGTGCGCCGGATCAGTGGGCTCAGCGCGGAGGCCATGGCCCAGGCGACCGATATCCTC
GCTGACGGCGGCCTCCTGCGCGACCAGCGGTTACACATCCAGCGGCCCGCTCGGTGGTGCTCGACGACATGTCCGC
CGAGGAACGACGCAGCGTGACAGCCTCGCCCTGGAACCTGCTGGACGAGGCACCGGCCGAGATGCTCGCGCACCAAC
GGGTGCGCGCCGGTCTCGTGACGGGCCGAAGGCCGCGGAGACATTACCGGGGCCGGCCGGGCACTGGCCGTTTCGC
GGCATGCTGGGCGAGGCAGCCGACTACCTGCAACTGGCGTACCGGGCCTCCGGCGACGCCGCTACCAAGGCCGCGAT
25 ACGCGTCGAGTCCGTGGCGGTCGAGCGCCGACGCAATCCGCTGGTCGTCAGTCGCCATTGGGACGAGCTGAGCGTCG
CGGCCCCGCGCCGGTCTGCTCTCCTGCGAGCACGTGTCCAGGACGGCCCCGCTGGCTGACCGTCCGTGGGCGGCCCGGC
GAGGCGGCCAGGGTGCTGGCGTCGCAACACCGACGGGTGCTACCGATCAGGACCGGGCCACCTGCGGGTCGCCGA
GTTCTCGCTCGCGCTGCTGTACCCCGGTACGTCCGGCTCGGACCGGCGCCCGCACCCGCTCACGTTCGGACGAACTCG
CGGCCCTACCGACTGCGACCAGACACTGCGCGATCGCCGATAACGCTGTTCATGGCTGCCTTGCGTGGTTCATCCGGAG
30 CTTGCCACCGCCGAGGCAGAAGCCGTTCTGCGAGCAAGCCGACGCGGGCGGACGGCGCTGCTCTACCGCGCTGATGGC
CCTGCTGTACGCGGAGAGCATCGAGGTCGCTGAAGTCTGGGCGGACAAGCTGGCGGCAGAGGCCGGAGCATCGAACG
GGCAGGACGCGGAGTACGCCGGTATACGCGCCGAAATCGCCCTGCGGCGCGGCGATCTGACCGCGGCCGTTCGAGACC
GCCGGCATGGTCCTGGACGGCCGGCCGCTGCCGTGCTCGACATCACCGCCACGTTGCTGTTGGCCGGCAGGGCGTC
CGTCGCCGTCCGGCTGGGCGAACTCGACCACGCGGAGGAGCTGTTTCGCCGCGCCGCCGGAGGACGCCTTCCAGGACA
35 GCCTCTTCGGTCTGCATCTGCTCTCGGCGCACGGCCAGTACAGCCTCGCGACAGGCCGGCCCCGAGTCGGCATACCGG
GCCCTTTCGTGCCTGCGGCGAACGTATGCGCGATTGGGGCTTCGACGCGCCCGGTGTGGCCCTGTGGCGCGTCGGCGC
CGCCGAGGCGCTGCTCGGCCTCGACCGGAACGAGGGCCGACGGCTCATCGACGAACAGCTGAGCCGGACGATGGCCC
CCCGGTCCCACCGGTTGACGCTGCGGATAAAAGCGGCGTACATGCCGGAGCCGAAGCGGGTCGACCTCCTCTACGAA
GCGGCTGAGCTGCTGCTCTCCTGCCGGGACCAGTATGAGCGAGCGCGGGTGCTCGCCGATCTGGGCGAGGCGCTCAG
40 CGCGCTCGGGAACCTACCGGCAGGCGCGAGGTGTGCTCCGGCAGGCTCGGCATCTGGCCATGCGAACCAGGCGCGGACC
CGCTGCTGCGCCGGCTCGGAATCAGGCCCGGCCGGCAGGACGACCCCGACCCGCGAGCCGCGGAGCAGATCGCTGACC
AACGCTGAGCGGCGTGCGGCGTCGCTGGCCGCGACCGGACTGACCAACCGGGAGATCGCCGACCGGCTCTTCGTAC

CGCCAGCACCGTGGAGCAGCACCTCACCAACGTCTTCCGCAAGCTGGGCGTCAAGGGCCGCAAGCAGCTGCCGGCCG
AGTTGGACGACATGGAATAG

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5 ATGCGAGCTATTAATGCGTCCGACACCGGTCCTGAACTGGTCGCCCCGGAAGACGAACTGGGACGTGTACGAAGTGC
CCTGAACCGAGCGAACGGCGGCCAAGGTGTCCTGATCTCCATTACCGGTCCGATCGCCTGCGGCAAGACCGAACTGC
TTGAGGCTGCCGCCTCGGAAGTTGACGCCATCACTCTGCGCGCGGTCTGTGCCGCCGAGGAACGGGCGATACCTTAT
GCCCTGATCGGGCAGCTTATCGACAACCCCGCGCTCGGCATTCCGGTTCCGGATCCGGCCGGCCTGACCGCCCAGGG
CGGACGACTGTCATCGAGCGCCGAGAACCGACTGCGTCGCGACCTCACCCGTGCCCTGCTGACGCTCGCCACCGACC
10 GGCTGGTGCTGATCTGTGTGATGACGTGCAGCAGCGCCGACAACGCCTCGTTGAGCTGCCTTCTGTATCTGGCCCGA
CGGCTTGTCCCGGCTCGAATCGCTCTGGTATTCACCGAGTTGCGAGTCCTCACCTCGTCTCAGCTGCGGTTCAACGC
GGAGCTGCTCAGCTTGCGGAACCACTGCGAGATCGCGCTGCGCCCACTCGGCCCGGGGCATGCGGCCGAGCTGGCCC
GCGCCACCCTCGGCCCCGGCCTCTCCGACGAAACACTCACGGAGCTGTACCGGGTGACCGGAGGCAACCTGAGTCTC
AGCCGCGGGCTGATCGACGATGTGCGGGACGCCTGGGCACGAGGGGAAACGGGCGTCCAGGTGGGCCGGGCGTTCCG
15 GCTGGCCTACCTCGGTTCCCTCCACCGCTGTGGTCCGCTGGCGTTGCGGGTCGCCCCGCGTAGCCGCCGTACTGGGCC
CGAGCGCCACCAGCGTCCTGGTGCGCCGGATCAGTGGGCTCAGCGCGGAGGCCATGGCCCAGGCGACCGATATCCTC
GCTGACGGCGGCCTCCTGCGCGACCAGCGGTTACACATCCAGCGGCCCGCTCGGTGGTGCTCGACGACATGTCCGC
CGAGGAACGACGCAGCGTGCACAGCCTCGCCCTGGAACCTGCTGGACGAGGCACCGGCCGAGATGCTCGCGCACCACC
GGGTGCGCGCCGGTCTCGTGCACGGGCCGAAGGCCGCGGAGACATTCACCGGGGCCGGCCGGGCACTGGCCGTTTCGC
20 GGCATGCTGGGCGAGGCAGCCGACTACCTGCAACTGGCGTACCGGGCCTCCGGCGACGCCGCTACCAAGGCCGCGAT
ACGCGTCGAGTCCGTGGCGGTCGAGCGCCGACGCAATCCGCTGGTCGTAGTCGCCATTGGGACGAGCTGAGCGTCG
CGGCCCGCGCCGCTCTGCTCTCCTGCGAGCACGTGTCCAGGACGGCCCGCTGGCTGACCGTCGGTGGGCGGCCCGGC
GAGGCGGCCAGGGTGCTGGCGTCGCAACACCGACGGGTCGTACCGATCAGGACCGGGCCCACCTGCGGGTCGCCGA
GTTCTCGCTCGCGCTGCTGTACCCCGGTACGTCCGGCTCGGACCGGCGCCCGCACCCGCTCACGTGCGACGAACTCG
25 CGGCCCTACCGACTGCGACCAGACACTGCGCGATCGCCGATAACGCTGTATGGCTGCCTTGCGTGGTCATCCGGAG
CTTGCCACCGCCGAGGCAGAAGCCGTTCTGCAGCAAGCCGACGCGGCGGACGGCGCTGCTCTACCGCGCTGATGGC
CCTGCTGTACGCGGAGAGCATCGAGGTGCTGAAGTCTGGGCGGACAAGCTGGCGGCAGAGGCCGGAGCATCGAACG
GGCAGGACGCGGAGTACGCCGGTATACGCGCCGAAATCGCCCTGCGGCGCGGCGATCTGACCGCGGCCGTCGAGACC
GCCGGCATGGTCCTGGACGGCCGGCCGCTGCCGTGCTCGACATCACCGCCACGTTGCTGT'TGGCCGGCAGGGCGTC
30 CGTCGCCGTCGGGCTGGGCGAACTCGACCACGCGGAGGAGCTGTTCCGCCGCGCCGCCGGAGGACGCCTTCCAGGACA
GCCTCTTCGGTCTGCATCTGCTCTCGGCGCACGGCCAGTACAGCCTCGCGACAGGCCGGGCCGAGTCGGCATAACGG
GCCTTTTCGTGCCTGCGGCGAACGTATGCGCGAT'TGGGGCTTCGACGCGCCCGGTGTGGCCCTGTGGCGCGTCGGCGC
CGCCGAGGCGCTGCTCGGCCTCGACCGGAACGAGGGCCGACGGCTCATCGACGAACAGCTGAGCCGGACGATGGCCC
CCCGGTCCCACGCGT'TGACGCTGCGGATAAAAGCGGCGTACATGCCGGAGCCGAAGCGGGTTCGACCTGCTCTACGAA
35 GCGGCTGAGCTGCTGCTCTCCTGCCGGGACCAGTATGAGCGAGCGCGGGTGCTCGCCGATCTGGGCGAGGCGCTCAG
CGCGCTCGGGAACTACCGGCAGGCGCGAGGTGTGCTCCGGCAGGCTCGGCATCTGGCCA'TGCGAACCGGCGCGGACC
CGCTGCTGCGCCGGCTCGGAATCAGGCCCGGCCGGCAGGACGACCCCGACCCGCAGCCGCGGAGCAGATCGCTGACC
AACGCTGAGCGGCGTGCGGCGTCGCTGGCCGCGACCGGACTGACCAACCGGGAGATCGCCGACCGGCTCTTCGTAC
CGCCAGCACCGTGGAGCAGCACCTCACCAACGTCTTCCGCAAGCTGGGCGTCAAGGGCCGCAAGCAGCTGCCGGCCG
40 AGTTGGACGACATGGAATAG

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MPAVECYELDARDDELRKLEEVVTGRANGRGVVVTITGPIACGKTELLDAAAAKADAITLRAVCSAEEQALPYALIG
QLIDNPALASHALEPACPTLPGEHLSPEAENRLRSDLTRTLLALAAERPVLIGIDESHANALCLLHLARRVGSARIA
MVLTELRRRLTPAHSQFQAELLSLGHHREIALRPLSPKHTAELVRAGLGPDVDEDVLTGLYRATGGNLTGLINDV
REAWETGGTGISAGRAYRLAYLGSLYRCGPVPLRVARVAAVLGQSANTTLVRWISGLNADAVGEATEILTEGGLLHD
5 LRFPHPAARSVVLNDMSAQERRRLHRSALVLDLDDVPVEVVAHHQVVGAGLLHGPKAAEIFAKAGQELHVRGELDTASD
YLQLAHQASDDAVTGMRAEAVAIERRRNPLASSRHLDELTVVARAGLLFPEHTALMIRWLGVGGRSGEAAAGLLASQR
PRAVTDQDRAHMRAAEVSLALVSPGTSGPDRRPRPLTPDELANLPKAARLCAIADNAVMSALRGRPELAAAEAEENVL
QHADSAAAGTTALAALTALLYAENTDTAQLWADKLVSETGASNEEEAGYAGPRAEAALRRGDAAA VEAGSTVLDHR
RLSTLGITAALPLSSAVAAAIRLGETERAEKWLAQPLPQAIQDGLFGLHLLSARGQYSLATGQHE SAYTAFRTCGER
10 MRNWGVDVPGLSLWRVDAAEALLHGRDRDEGRRLVDEQLTRAMGPRSRALT LRVQAAYSPPAKRVDLLDEAADLLLS
CNDQYERARVLADLSETFSALRHHSRARGLLRQARHLAAQRGAIPLLRRLGAKPGPGWLEESGLPQRIKSLTDAER
RVASLAAGGQTNRVIADQLFVTASTVEQHLTDVSTGSRPPAPAAELV

SEQ ID NO: 194

15 MVPEVRAAPDELIARDDELSRLQORALTRAGSGRGGVVAITGPIASGKTALLDAGAAKSGFVALRAVCSWEERTLPYG
MLGQLFDHPELAAQAPDLAHFTASCESPQAGTDNRLRAEFTRTLLALAADWPVLIGIDDVHHADAESLRCLLHLARR
IGPARIAVVLTELRRPTPADSRFQAELLSLSYQEIALRPLTEAQTGELVRRHLGAETHEDVSADTFRATGGNLLLG
HGLINDIREARTAGRPGVVAGRAYRLAYLSSLYRCGPSALRVARASAVLGASAEAVLVQRM TGLNKDAVEQVYEQLN
EGRLLQGERFPHPAARSIVLDDLSALERNNLHESALELLRDHGVAGNVLARHQIGAGRVHGEEAVELFTGAAREHHL
20 RGELDDAAGYLELAHRASDDPVTRAALRVGAAAIERLCNPVRAGRHLPELLTASRAGLLSSEHAVSLADWLAMGGRP
GEAAEVLATQORPAADSEQHRALLRSGELSLALVHPGAWDPLRRTDRFAAGGLGSLPGPARHRAVADQAVIAALRGRL
DRADANAESVLQHTDATADRTTAIMALLALLYAENTDAVQFWVDKLAGDEGTRTPADEAVHAGFNAEIALRRGDLMR
AVEYGEAALGHRHLPTWGMAAALPLSSTVVAAIRLGDLDRERWLAEPLPQQTPESLFGLHLLWARGQHHLATGRHG
AAYTAFRECGERMRRWAVDVPGLALWRVDAAESLLLGRDRAEGLRLVSEQLSRPMRPRARVQTLRVQAAYSPPPQR
25 IDLLEEADLLVTCNDQYELANVLSDLAEASSMVRQHSRARGLLRRARHLATQCGAVPLLRLRGAEPDIDGGAWDAT
LGQRIASLTESERRVAALAAVGRTNREIAEQLFVTASTVEQHLTNVFRKLAVKGRQQLPKELADVGEPADRDRRCG

SEQ ID NO: 195

30 MIARLSPPDLIARDDEFGLHRLALTRAGGGRGVVAAVTGPIACGKTELLDAAAAKAGFVTLRAVCSMEERALPYGML
GQLLDQPELAARTPELVRLTASCENLPADVDNRLGTELTRTVLTLAAERPVLIGIDDVHHADAPSLRCLLHLARRIS
RARVAIVLTELLRPTPAHSQFRAALLSLRHYQEIALRPLTEAQTTELVRRLHGLQDAHDDVVAQAFRATGGNLLLGHG
LIDDIAREARTRTSGCLEVVAGRAYRLAYLGSLYRCGPAALSVARASAVLGESVELTLVQRM TGLDTEAVEQAHEQLV
EGRLLREGRFPHPAARSVVLDDLSAAERRGLHELALELLRDRGVASKVLARHQMG TGRVHGAEVAGLFTDAAREHHL
RGELDEAVTYLEFAYRASDDPAVHAALRVDTAAIERLCDPARSGRHVPELLTASRERLLSSEHAVSLACWLAMDGRP
35 GEAAEVLAAQRSAAPSEQGRAHLRVADLSLALIYPGAADPPRPADPPAEDEVASFSGAVRHRAVADKALSNALRGWS
EQAEAKAEYVLQHSRVTTDRTTTMMALLALLYAEDTDAVQSWVDKLAGDDNMRTPADEAVHAGFRAEAALRRGDLTA
AVECGEALAPRVVPSWGMAAALPLSSTVAAAIRLGDLDRERWLAEPLPEETS DSLFGLHVMVWARGQHHLAAGRYR
AAYNAFRDCGERMRRWSVDVPGLALWRVDAAEALLLGRGRDEGLRLISEQLSRPMGSRARVMTLRVQAAYSPPAKR
IELLDEAADLLIMCRDQYELARVLADMGEACGMLRRHSRARGLFRRARHLATQCGAVPLLRLRGGESSDADGTQDVT
40 PAQRITSLTEAERRVASHAAVGRTNKEIASQLFVTSSTVEQHLTNVFRKLGVKGRQQLPKELSDAG

SEQ ID NO: 196

MEFYDLVARDDELRRLDQALGRAAGGRGVVVTVTGPGVCGKTELLDAAAAEEEFITLRAVCSAEERALPYAVIGQLL
DHPVLSARAPDLACVTAPGRTL PADTENRLRRDLTRALLALASERPVLICIDDVHQADTASLNCLLHLARRVASARI
AMILTELRRLTPAHSRFEAEALLSLRHRHEIALRPLGPADTAELARARLGAGVTADELAQVHEATSGNPNLVGGLVND
5 VREAWAAGGTGIAAGRAYRLAYLSSVYRCGPVPLRIAQAAAVLGPSATVTLVRRISGLDAETVDEATAILTEGGLLR
DHRFPHPAARSVVLDDMSAQERRRLHRSTLDVLDGVPVDVLAHHQAGAGLLHGPQAAEMFARASQELRVRGELDAAT
EYLQLAYRASDDAGARAALQVETVAGERRRNPLAASRHLDELAAAARAGLLSAEHAALVVHWLADAGRPGEEAAEVLA
LQRALAVTDHDRARLRAAEVSLALFHGVPVPCSDPRPLAPEELASLSLSARHGVTADNAVLAALRGRPESAAAEAEENV
LRNADMAASGPTALAALTALLYAENTDAAQLWADKLAAGIGAGEGEAGYAGPRTVAALRRGDLTTAVQAAGAVLDRG
10 RPSSLGITAVLPLSGAVAAAIRLGELERA EKWLAEPLPEAVHDSLFGLHLLMARGRYS LAVGRHEAAYA AFRDCGER
MRRWDVDVPGLALWRVDAAEALLPGDDRAEGRRLLIDEQLTRPMGPRSRALT LRVRAAYAPPAKRIDL LDEAADLLLS
SNDQYERARVLADLSEAFSALRQNGRARGILRQARHLAAQCGAVPLLRRLGVKAGRSGR LGRPPQGIRSLTEAERRV
ATLAAAGQTNREIADQLFVTASTVEQHLTNVFRKLG VKGRQQLPAELADLRPPG

15 SEQ ID NO: 197

MYSGTCREGYELVAREDELGILQRSLEQASSGQGVVVTVTGPIACGKTELLDAAAAKAEAIILRAVCAPEERAMPYA
MIGQLIDDPALAHRAPGLADRIAQGGQLSLRAENRLRRDLTRALLALAVDRPVLIGVDDVHHADTASLNCLLHLARR
VRPARISMIFTELRSLTPTQSRFKAELLSLPYHHEIALRPF'GPEQSAELARAAFGPGLAEDVLVGLYKTTTRGNLSLS
RGLISDVREALANGESAFEAGRAFRLAYLGSLYRCGPVALRVARVAAVLGPSATTTLVRRLSGLSAETIDRATKILT
20 EGGLLLDQQFPHPAARSVVLDDMSAQERRGLHTLALELLDEAPVEVLAHHQVGAGLIHGPKAAEMFAKAGKALVVRN
ELGDAAEYLQLAHRASDDVSTRAALRVEAVAIERRRNPLASSRHMDLSAAGRAGLLSPKHAALAVFWLADGGRSGE
AAEVLASERPLATTDQNRHLRFVEVTLALFSPGA'GSDRRPPPLTPDELASLPKAAWQCAVADNAAMTALHGHPEL
ATAQAETVLRQADSAADAIPAALIALLYAENTESAHIWADKLGSTNGGVSNEAEAGYAGPCAEIALRRGDLATAFEA
GSTVLDDRS LPSLGITAALLSSKTAAAVRLGELERA EKLLAEPLPNGVQDSLFGLHLLSAYGQYSLAMGRYESALR
25 AFHTCGERMRSWDVDVPGLALWRVDAAEALLSLDRNEGQRLIDEQLTRPMGPRSRALT LRKAAYLPRTKRIPLLHE
AAELLLPCPDPIEQARVLADLGD TLSALRRYSRARGVLRQARHLAAQCGAVPLLRRLGGEPGRIDDAGLPQRSTSLT
DAERRVAALAAAGQTNREIAKQLFVTASTVEQHLTSVFRKLG VKGRKQLPTALADVEQT

SEQ ID NO: 198

30 MPAVESYELDARDDELRRLEEAVGQAGNGRGVVVTITGPIACGKTELLDAAAAKSDAITLRAVCSEEERALPYALIG
QLIDNPAVASQLPDPVSMALPGEHLSPEAENRLRGDLTRTLLALAAERPVLIGIDDMHHADTASLNCLLHLARRVGP
ARIAMVLTELRRLTPAHSQFHAELLSLGHHR EIALRPLGPKHIAELARAGLGPDVDEDVLTGLYRATGGN LNLGHGL
IKDVREAWATGGTGINAGRAYRLAYLGSLYRCGPVPLRVARVAAVLGQSANTTLVRWISGLNADAVGEATEILTEGG
LLHDLRFPHPAARSVVLNDLSARERRRLHRSAL EVLDDVPVEVVAHHQAGAGFIHGPKAAEIFAKAGQELHVRGELD
35 AASDYLQLAHHASDDAVTRAALRVEAVAIERRRNPLASSRHLDELTVAAARAGLLSLEHAALMIRWLALGGRSGEAAE
VLAAQRPRAVTDQDRAHLRAAEVSLALVSPGASGVSPGASGPDRRPRPLPPDELANLPKAARLCAIADNAVISALHG
RPELASAEAEENVLKQADSAADGATALSALTALLYAENTDTAQLWADKLVSETGASNEEEGAGYAGPRAETALRRGDL
AAAVEAGSAILDHRRGSL LGITAALPLSSAVAAAIRLGETERAEKWLAEPLPEAIRDSLFGLHLLSARGQYCLATGR
HESAYTAFRTCGERMRNWGVDVPGLSLWRVDAAEALLHGRDRDEGRRLIDEQLTHAMGPRSRALT LRVQAAYSPQAAQ
40 RVDLLEEAAADLLLS CNDQYERARVLADLSEAFSALRHHSRARGLLRQARHLAAQCGATPLLRRLGAKPGGPWLEES
GLPQRIKSLTDAERRVASLAAGGQTNRVIADQLFVTASTVEQHLTNVFRKLG VKGRQHLP AELANAE

SEQ ID NO: 199

MPAVKRNDLVARDGELRWMQEILSQASEGRGAVVTITGAIACGKTVLLDAAAASQDVIQLRAVCSAEEQELPYAMVG
QLLDNPFVLAARVPALGNLAAAGERLLPGTENRIRRELTRTLLALADERPVLIGVDDMHADPASLDCLLHLARRVGP
ARIAIVLTELRRLTPAHSRFQSELLSLRYHHEIGLQPLTAEHTADLARVGLGAEVDDDLTELYEATGGNPSLCCGL
5 IRDVRQDWEAGVTGIHVGRAYRLAYLSSLYRCGPAALRTARAAAVLGDSADACLIRRVSGLGTEAVGQAIQQLTEGG
LLRDQQFPHPAARSVVLDDMSAQERHAMYRSAREAAAEQADPGTPGEPRAATAYAGCGEQAGDYPEPAGRACVDGA
GPAEYCGDPHGADDDPDELVAALGGLLPSRLVAMKIRRLAVAGRPGAAAELLTSQRLHAVTSEDRA SLRAAEVALAT
LWPGATGPD RHPLTEQEAA SLPEGPRL LAAADDAVGAALRGRAEYAAAEAEENVLRHADPAAGCDAYAAMIALLYTEH
PENVLFWADKLDAGRPDEETSY PGLRAETAVRLGDLETAMELGRTVLDQRR LPSLGVAAGLLLGAVTAAIRLGDL D
10 RAEKWLAEP IPDAIRTS LYG LHVLAARGRLDLAAGRYEAA YTA FR LCGERMAGWDADV SGLALWRVDAAEALLSAGI
RPDEGRKLIDDQLTREMGARSRALTLRAQAAYS L P VHRVGLLDEAAGLL LACHDGYERARVLADLGETLRTL RHTDA
AQRVLRQAEQAAARCGSVPLLRRLGAEPVRIGTRRGEPGLPQRI RL L TDAERRVAAMAAAGQTNREIAGRLFVTAST
VEQHLTSVFRKLG VKGRRFLPTELAQAV

15 SEQ ID NO: 200

MYSGTCREGYELVAREDELGILQRSLEQASSGQGVVTVTGPIACGKTELLDAAA AKAEAI ILRAVCAPEERAMPYA
MIGQLIDDPALAHRA PGLADRIA QGGQLSLRAENRLRRDLTRALLALAVDRPVLIGVDDVHHADTASLNCLLHLARR
VRPARISMIFTELRS LTPTQSRFKAELL SLPYHHEIALRPF GPEQSAELARAAFGPGLAEDVLAGLYKTTRGNLSLS
RGLISDVREALANGESAFEAGRAFR LAYLSSLYRCGPVALRVARVAAVLGPSATTTLVRRLSGLSAETIDRATKILT
20 EGGLLLDQQFPHPAARSVVLDDMSAQERRSLHTLALELLDEAPVEVLAHHQVGAGLIHGPKAAEMFAKAGKALVVRN
ELGDAAEYLQLAHRASDDVSTRAALRVEAVAIERRRNPLASSRHMD ELSAAGRAGLLSPKHAALAVFWLADGGRSGE
AAEVLASERPLATTDQNR AHLRFVEVTLALFSPGAFGSDRRPPPLTPDELASLPKAAWQCAVADNAAMTALHGHPEL
ATAQAETVLRQADSAADAIPAALIALLYAENTESAHIWADKLGSTNAGVSNEAEAGYAGPCAEIALRRGDLATAFEA
GSAVLDDRS LPSLGITAALLLSSKTAAAVRLGELERA EKLLAEPLPNGVQDSLFGLHLLSAYGQYSLAMGRYESAHR
25 AFRTCGERMRSWDVDVPGLALWRVDAAEALLSLDRNEGQRL IDEQLTRPMGPRSHALT LRIKAAYLPRTKRIPLLHE
AAELLLPCPD PYEQARVLADLGD TLSALRRYSRARGVLRQARHLATQCGAVPLLRRLGGEPGRIDDAGLPQRSTSLT
DAERRVAALAAAGQTNREIAEQLFVTASTVEQHLTSVFRKLG VKGRKQLPTALADVEQT

SEQ ID NO: 201

30 MYSGTCREGYELVAREDELGILQRSLEEAGSGQGAVVTVTGPIACGKTELLDAAA KADAI ILRAVCAPEERAMPYA
MIGQLIDDPALAHRAPELADRIA QGGHLSLRAENRLRRDLTRALLALAVDRPVLIGVDDVHHADTASLNCLLHLARR
VRPARISMIFTELRS LTPTQSRFKAELL SLPYHHEIALRPLGPEQSAELAHAAFGPGLAEDVLAGLYGMTRGNLSLS
RGLISDVREAQANGESAFEVGRAFR LAYLSSLYRCGP IALRVARVAAVLGPSATTTLVRRLSGLSAETIDRATKILT
EGGLLLDHQFPHPAARSVVLDDMSAQERRSLHTLALELLDEAPVEVLAHHQVGAGLIHGPKAAEIFARAGQALVVRN
35 ELGDAAEYLQLAHRASDDVSTRAALRVEAVAIERRRNPLASSRHMD ELSAAGRAGLLSPKHAALAVFWLADGGRSGE
AAEVLASEHPLATTDQNR AHLRF AEVTLALFCPGA FGSDRRPPPLAPDELASLPKAAWQCAVADNAVMTALHAHPEL
ATAQAETVLRQADSAADAIPAALIALLYAENTESAQI WADKLGSTNAGVSNEAEAGYAGPCAEIALRRGDLATAFEA
GGTVLDDRPLPSLGITAALLLSSKTAAAVRLGELERA EKLLAEPLPNGVQDSLFGLHLLSAHGQYSLAMGRYESAHR
AFHTCGERMRSWGVDPGLALWRVDAAEALLSLDRNEGQRL IDEQLARPMGPRSRALT LRIKAAYLPRTKRIPLLHE
40 AAELLLSCPD PYEQARVLADLGD TLSALRRYSRARGVLRQARHLATQCGAVPLLRRLGGEPGRIDDAGLPQRSTSLT
DAERRVSALAAAGQTNREIAKQLFVTASTVEQHLTSVFRKLG VKGRRQLPTALADVE

SEQ ID NO: 202

MYSGTCREGYELVAREDELGILQRSLEQASSGQGVVTVTGPIACGKTELDDAAAAKAEAIILRAVCAPEERAMPYA
MIGQLIDDPALAHRAPGLADRIAQGGQLSLRAENRLRRDLTRALLALAVHRPVLIGVDDVHHADTASLNCLLHLARR
VRPARISMIFTELRSLTPTQSRFKAELLSLPYHHEIALRPFGEQSAELARAAFGPGLAEDVLAGLYKTTRGNLSLS
5 RGLISDVREALANGESAFEAGRAFRLAYLSSLYRCGPVALRVARVAAVLGPSATTTLVRRLSGLSAETIDRATKILT
EGGLLLDQQFPHPAARSVVLDDMSAQERRGLHTLALELLDEAPVEVLAHHQVGAGLIHGPKAAEMFAKAGKALVVRN
ELGDAAEYLQLAHRASDDVSTRAALRVEAVAIERRRNPLASSRHMDLSAAGRAGLLSPKHAALAVFWLADGGRSGE
AAQVLASERPLATTDQNRHLRFVEVTLALFSPGAFGSDRRPPPLTPDELASLPKAAWQCAVADNAAMTALHGHPEL
ATAQAETVLRQADSAADAIPAALIALLYAENTESAHIWADKLGSMNAGVSNEAEAGYAGPCAEIALRRGDLATAFEA
10 GSTVLDDRSPLSLGITAAALLSSKTAAAVRLGELERA EKLLAEPLPNGVQDSLFGHLHLLSAYGQYSLAMGRYESAHR
AFRTCGERMRSWDVDVPGLALWRVDAAEALLSLDRNEGQRLIDEQLTRPMGPRSRALT LRIKAAYLPRTKRIPLHE
AAELLPCPDPIEQARVLADLGD TLSALRRYSRARGVLRQARHLATQCGAVPLLRRRLGGEPGRIDDAGLPQRSTSLT
DAERRVAALAAAGQTNREIAEQLFVTASTVEQH LTSVFRKLG VKGRKQLPTALADVEQT

SEQ ID NO: 203

MRAINASDTGPPELVAREDELGRVRSALNRANGGQGVLI SITGPIACGKTELLEAAASEVDAITLRAVCAAEERAIPY
ALIGQLIDNPALGIPVPDPAGLTAQGGRLSSSAENRLRRDLTRALLTLATDRLVLICVDDVQHADNASLSCLLYLAR
RLVPARIALVFTELRLVTSSQLRFNAELLSLRNHCEIALRPLGPGHAAELARATLGPGLSDETLT ELYRVTGGNLSL
SRGLIDDVRDAWARGETGVQVGRAFRLAYLGSLHRCGPLALRVARVAAVLGPSATSVLVRRISGLSAEAMAQATDIL
20 ADGGLLRDQRFTHPAARSVVLDDMSAEERRSVHSLALELLDEAPAEMLAHHRVGAGLVHGPKAAETFTGAGRALAVR
GMLGEAADYLQLAYRASGDAAATKAAIRVESVAVERRRNPLVVSRRHWDELSVAARAGLLSCEHVSRTARWLT VGGRPG
EAARVLASQHRRVVT DQDRAHLRVAEFSLALLYPGTSGSDRRPHPLTSDELAALPTATRHCAIADNAVMAALRGHPE
LATAEAEAVLQQADAADGAALTALMALLYAESIEVAE VWADKLAAEAGASNGQDAEYAGIRAEIALRRGDLTAAVET
AGMVLDGRPLPSLDITATLLLAGRASVAVRLGELDHAEELFAAPPEDAFQDSLFGHLHLLSAHGQYSLATGRPESAYR
25 AFRACGERMRDWGFDAPGVALWRVGAAEALLGLDRNEGRRLIDEQLSRTMAPRSHALT LRIKAAYMPEPKRVDLLYE
AAELLSCRDQYERARVLADLGEALSALGN YRQARGVLRQARHLAMRTGADPLLRRRLGIRPGRQDDPD PQPRSRSLT
NAERRAASLAATGLTNREIADRLFVTASTVEQH LTNVFRKLG VKGRKQLPAELDDME

LAL Binding Sites

30 In some embodiments, a gene cluster (e.g., a PKS gene cluster) includes one or more promoters
that include one or more LAL binding sites. The LAL binding sites may include a polynucleotide
consensus LAL binding site sequence (e.g., as described herein). In some instances, the LAL binding
site includes a core AGGGGG (SEQ ID NO: 204) motif. In certain instances, the LAL binding site
includes a sequence having at least 80% (e.g., 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100%)
35 homology to SEQ ID NO: 204. The LAL binding site may include mutation sites that have been restored
to match the sequence of a consensus or optimized LAL binding site. In some embodiments, the LAL
binding site is a synthetic LAL binding site. In some embodiments, synthetic LAL binding sites may be
identified by (a) providing a plurality of synthetic nucleic acids including at least eight nucleotides; (b)
contacting one or more of the plurality of nucleotides including at least eight nucleotides with one or more
40 LALs; (c) determining the binding affinity between a nucleic acid of step (a) and an LAL of step (b),
wherein a synthetic nucleic acid is identified as a synthetic LAL binding site if the affinity between the

synthetic nucleic acid and an LAL is greater than X. The identified synthetic LAL binding sites may then be introduced into a host cell in a compound-producing cluster (e.g., a PKS cluster).

In some embodiments, a pair of LAL binding site and a heterologous LAL or a heterologous LAL binding site and an LAL that have increased expression compared to a natural pair may be identified by

5 (a) providing one or more LAL binding sites; (b) contacting one or more of the LAL binding sites with one or more LALs; (c) determining the binding affinity between a LAL binding site and an LAL, wherein a pair having increased expression is identified if the affinity between the LAL binding site and the LAL is greater than the affinity between the LAL binding site and its homologous LAL and/or the LAL at its homologous LAL binding site. In some embodiments, the binding affinity between the LAL binding site

10 and the LAL is determined by determining the expression of a protein or compound by a cell which includes both the LAL and the LAL binding site.

Constitutively active LALs

In some embodiments, the recombinant LAL is a constitutively active LAL. For example, the

15 amino acid sequence of the LAL has been modified in such a way that it does not require the presence of an inducer compound for the altered LAL to engage its cognate binding site and activate transcription of a compound producing protein (e.g., polyketide synthase). Introduction of a constitutively active LAL to a host cell would likely result in increased expression of the compound-producing protein (e.g., polyketide synthase) and, in turn, increased production of the corresponding compound (e.g., polyketide).

20

Engineering Unidirectional LALs

FK gene clusters are arranged with a multicistronic architecture driven by multiple bidirectional promoter-operators that harbor conserved (in single or multiple, and inverted to each other and/or directly repeating) GGGGGT (SEQ ID NO: 170) motifs presumed to be LAL binding sites. Bidirectional LAL

25 promoters may be converted to unidirectional ones (UniLALs) by strategically deleting one of the opposing promoters, but maintaining the tandem LAL binding sites (in case binding of LALs in the native promoter is cooperative, as was demonstrated for MalT). Functionally this is achieved by removal of all sequences 3' of the conserved GGGGGT (SEQ ID NO: 170) motif present on the antisense strand (likely containing the -35 and -10 promoter sequences), but leaving intact the entire sequence on the sense

30 strand. As a consequence of this deletion, transcription would be activated in one direction only. The advantages of this feed-forward circuit architecture would be to tune and/or maximize LAL expression during the complex life cycle of *Streptomyces* vegetative and fermentation growth conditions.

Host cells

35 In some embodiments, the host cell is a bacteria such as an Actiobacterium. For example, in some embodiments, the host cell is a *Streptomyces* strain. In some embodiments, the host cell is *Streptomyces anulatus*, *Streptomyces antibioticus*, *Streptomyces coelicolor*, *Streptomyces peucetius*, *Streptomyces sp. ATCC 700974*, *Streptomyces canus*, *Streptomyces nodosus*, *Streptomyces (multiple sp.)*, *Streptoalloteicus hindustanus*, *Streptomyces hygroscopicus*, *Streptomyces avermitilis*, *Streptomyces*

40 *viridochromogenes*, *Streptomyces verticillus*, *Streptomyces chartruensis*, *Streptomyces (multiple sp.)*, *Saccharothrix mutabilis*, *Streptomyces halstedii*, *Streptomyces clavuligerus*, *Streptomyces venezuelae*,

Streptomyces roseochromogenes, *Amycolatopsis orientalis*, *Streptomyces clavuligerus*, *Streptomyces rishiriensis*, *Streptomyces lavendulae*, *Streptomyces roseosporus*, *Nonomuraea sp.*, *Streptomyces peucetius*, *Saccharopolyspora erythraea*, *Streptomyces filipinensis*, *Streptomyces hygroscopicus*, *Micromonospora purpurea*, *Streptomyces hygroscopicus*, *Streptomyces narbonensis*, *Streptomyces kanamyceticus*, *Streptomyces collinus*, *Streptomyces lasaliensis*, *Streptomyces lincolnensis*, *Dactosporangium aurantiacum*, *Streptomyces toxitricini*, *Streptomyces hygroscopicus*, *Streptomyces plicatus*, *Streptomyces lavendulae*, *Streptomyces ghanaensis*, *Streptomyces cinnamomensis*, *Streptomyces aureofaciens*, *Streptomyces natalensis*, *Streptomyces chattanoogensis* L10, *Streptomyces lydicus* A02, *Streptomyces fradiae*, *Streptomyces ambofaciens*, *Streptomyces tendae*, *Streptomyces noursei*, *Streptomyces avermitilis*, *Streptomyces rimosus*, *Streptomyces wedmorensis*, *Streptomyces cacaoi*, *Streptomyces pristinaespiralis*, *Streptomyces pristinaespiralis*, *Actinoplanes sp.* ATCC 33076, *Streptomyces hygroscopicus*, *Lechevalieria aerocolonigenes*, *Amycolatopsis mediterranei*, *Amycolatopsis lurida*, *Streptomyces albus*, *Streptomyces griseolus*, *Streptomyces spectabilis*, *Saccharopolyspora spinosa*, *Streptomyces ambofaciens*, *Streptomyces staurosporeus*, *Streptomyces griseus*, *Streptomyces (multiple species)*, *Streptomyces acromogenes*, *Streptomyces tsukubaensis*, *Actinoplanes teichomyceticus*, *Streptomyces glaucescens*, *Streptomyces rimosus*, *Streptomyces cattleya*, *Streptomyces azureus*, *Streptoalloteicus hindustanus*, *Streptomyces chartreusis*, *Streptomyces fradiae*, *Streptomyces coelicolor*, *Streptomyces hygroscopicus*, *Streptomyces sp.* 11861, *Streptomyces virginiae*, *Amycolatopsis japonicum*, *Amycolatopsis balhimycini*, *Streptomyces albus* J1074, *Streptomyces coelicolor* M1146, *Streptomyces lividans*, *Streptomyces incarnates*, *Streptomyces violaceoruber*, or *Streptomyces griseofuscus*. In some embodiments, the host cell is an *Escherichia* strain such as *Escherichia coli*. In some embodiments, the host cell is a *Bacillus* strain such as *Bacillus subtilis*. In some embodiments, the host cell is a *Pseudomonas* strain such as *Pseudomonas putida*. In some embodiments, the host cell is a *Myxococcus* strain such as *Myxococcus xanthus*.

25

Examples

Example 1. Single module swapping to produce an engineered PKS

Inter-module residue covariation analysis and evolutionary trace analysis were used to predict 10 heterologous donor modules that would successfully replace module 3 of the PKS that produces Compound 1 (FIG. 3A). Seven of the 10 predicted donor modules, ranging in length from 4-6kb, were selectively amplified in their entirety using a GC-rich long PCR method. In parallel, a bacterial artificial chromosome (BAC) that harbored the PKS that produces Compound 1 was converted to a module swap acceptor for heterologous donor modules by introducing the restriction sites *Afl*I and *Spe*I to the flanking intermodule sequence of module 3. The modified acceptor BAC was linearized by digestion with *Afl*I and *Spe*I, and the 7 donor modules were gel-purified and subcloned by Gibson cloning. The resulting constructs were subjected to Sanger sequencing of region of interest, PCR-based analysis to confirm cluster integrity, and Illumina NGS to sequence the entire BAC. The PCR-mediated error rate of the module amplification protocol was determined to be approximately 1bp per 5000bp, or approximately 1 mutation per module.

A single module was swapped to produce an engineered PKS by replacing module 3 of the PKS that produces Compound 1 with module 3 of *Streptomyces* strain S317. The donor S317 module 3 was

PCR amplified and Gibson cloned into position 3 of the PKS that produces Compound 1 (FIG. 3B). The resulting clone was conjugated into a *Streptomyces* expression host and fermented. Production of compound was analyzed by LC-TOF mass spectrometry analysis by co-injecting purified native FKBP12, the protein to which both compounds are expected to bind, with either the product of the native PKS, Compound 1, or the compound produced by the engineered PKS cluster, Compound 2. Comparative LC-TOF analysis of indicated that Compound 2 had the expected mass of 611.38, corresponding to the conversion of the module 3 alkene to a fully reduced module at that position. Compound 2 was re-fermented at large scale, purified to homogeneity and the structure was confirmed by NMR spectroscopy.

To replace module 4 in the PKS that produces Compound 1, module swapping prediction algorithms based on inter-module covariation were used to generate a list of 16 modules encoding 4 chemistries. Gibson-based subcloning into module 4 was not as efficient as module 3. Gibson cloning, which involves a ssDNA intermediate, is difficult in high GC-rich regions, and direct ligation of donor modules to restriction sites with 4bp overhangs may not be sensitive to local GC content. Therefore *Afl*I and *Spe*I sites were introduced at new positions in the inter-module flanking region to generate a direct ligation acceptor BAC. This direct ligation acceptor BAC was linearized by digestion with *Afl*I and *Spe*I, and 12 donor modules were gel-purified, digested with *Afl*I and *Xba*I and subcloned by ligation.

Single module swaps of either module 3 or module 4 in the PKS that produces Compound 1 generated novel Compounds 2-5 (FIG. 3C). Therefore, single module swapping was used to introduce a range of module encoded chemistries and generate novel compounds. LC-TOF mass spectrometry analysis indicated that of the module swaps at module 3 and module 4, the resulting hybrid clusters yielded a range of compound expression.

Example 2. Library construction by combinatorial dimodule swapping

Pooled transfer of dimodule libraries was used to simultaneously replace modules 3 and 4 in the PKS that produces Compound 1 and generate a plurality of engineered PKS clusters (FIG. 4A). A total of 31 modules were amplified for transfer to the module 3 position and 25 modules for the module 4 position. To optimize Gibson dimodule assembly cloning, phosphothiorate-modified DNA oligos were synthesized for PCR amplification of the donor modules. Phosphothiorate-capped module ends function by constraining the exonuclease step of the Gibson cloning protocol, which resulted in a dramatic increase in Gibson capture of GC-rich DNA (FIG. 4B). An intermediate plasmid-based dimodule capture protocol was developed to assemble, capture, amplify, and enrich the dimodule units (FIG. 4C). Pooled module 3 and module 4 amplicons were mixed with a linear backbone amplicon based on pBR322 for a 3-part Gibson assembly reaction. Shuttle vectors containing dimodule assemblies could be resolved from empty vector by fractionating on a preparative 0.4% agarose gel. After dimodule capture, the assembled dimodule fragments were released from the shuttle vector by digestion with *Afl*I and *Xba*I and subcloned by direct ligation to an expression vector containing the PKS that produces Compound 1, in which the PKS lacked the native module 3 and module 4.

Replicate BACs encoding single module and dimodule swaps were conjugated to optimized *Streptomyces* producer strain S2441 and solid-phase extracted samples were subjected to LC-TOF mass spectrometry with the expected protein binding partner, purified FKBP12 protein. Further analysis confirmed that dimodule library generation is capable of engineering PKS clusters that express novel

compounds in high yield (FIG. 4D). As a representative example, Compound 6 was generated by dimodule swapping of a module encoding mDEK chemistry at module 3 and K chemistry at module 4 of the PKS that produced Compound 1. The expected mass of Compound 6 was observed by LC-TOF analysis, confirming that the dimodule assembly protocol yields engineered derivatives Compound 1.

5 A 650-member combinatorial library of engineered derivatives of the PKS that produces Compound 1 was produced by dimodule swapping. A total of 31 modules were amplified for transfer the module 3 position and 25 modules for the module 4 position of the PKS that produces Compound 1 (FIG. 4E). Clusters were cloned onto BACs, and the cloned BACs were subsequently used as templates to PCR modules of diverse sources from multiple heterologous donors.

10 A subset of the library corresponding to 15 different donor modules at the module 3 position and 15 different donor modules at the module 4 position produced a potential combinatorial library of 225 novel PKS clusters and resulting novel compounds (the 15x15 dimodule library). Because the dimodule library was assembled as a pool, rarefaction analysis was performed to determine how many clones needed to be conjugated, fermented, and extracted to effectively sample >90% of the diversity of the library. Rarefaction analysis indicated that 650 clones corresponded to a statistical sampling >90% of the dimodule library (FIG. 4F). 650 clones were prosecuted and subjected to LC-TOF mass spectrometry analysis. 115 of the 650 sampled clones expressed compounds with novel masses.

20 **Example 3. Characterization of a combinatorial dimodule library by single-molecule long-read sequencing**

A library corresponding to 15 different donor modules at the module 3 position and 15 different donor modules at the module 4 position (the 15x15 dimodule library), produced according to the methods of Example 2, was characterized by Nanopore sequencing (FIG. 4G). The dimodules present in the 15x15 dimodule library were excised from the PKS clusters using CRISPR/Cas9 (NEB). The resulting excised dimodules each had a length of approximately 7-12 kilobases. The dimodules were purified by 96-well column purification, and well-specific adaptors were ligated to the dimodules. The resulting dimodules were normalized and pooled and prepared for sequencing according to the standard ligation preparation protocol for Nanopore sequencing of oligonucleotides. Nine 96-well plates (864 dimodule clones total) were sequenced by Nanopore and the resulting sequencing data was analyzed according to the informatics workflow provided in FIG. 4H, with 73.1% of clones being called. The comparison of the resulting sequencing data against the table of input of the donor modules allows the deconvolution of the resulting combinatorial library by identification of the resulting dimodules. The results of Nanopore sequencing of the 15x15 dimodule library are provided in Table 1.

Table 1.

Library Plate IDs	NoCall	Ambiguous	Single Read	Called	Grand Total
163846	45	4	11	36	96
163848	14	10	14	58	96
163851		16		80	96
163896	5	8	5	78	96
163897		21	1	74	96
163898	3	10	11	72	96
163899	4	6	2	84	96
163900	1	26	3	66	96
50066321		12		84	96
Grand Total	72	113	47	632	864
%	8.3%	13.1%	5.4%	73.1%	

Example 4. Library construction by combinatorial trimodule swapping

The combinatorial module swap protocols were modified to generate trimodule assemblies in the PKS that produces Compound 7 (FIG. 5A). Increasing the number of module swaps increases the size, and therefore diversity, of a PKS library. For example, given a collection of 13 different module-encoded chemistries, increasing size and diversity is based on the number of modules that are swapped such that the maximal library size of a single mod swap is 13; with a dimodule swap the maximal library size is 13²=169,; and for a trimodule swap, the maximal library is 13³ = 2197.

Trimodule assembly leverages the technical advances of the dimodule protocol with an additional “proof-reading” Gibson cloning step to insert the captured trimodule assembly into the PKS that produces Compound 7 (FIG. 5B). As before, phosphorothioate chemistry was used to constrain the ssDNA intermediate for the first round of Gibson cloning into a shuttle vector. Shuttle vector clones harboring trimodule assemblies were enriched by preparative gel fractionation and isolation. Finally, Gibson-mediated “error correction” was used to trim restriction sites for scarless cloning in the expression vector. First, flanking PmeI restriction sites were introduced within the linker regions between Module 3 and Module 4, as well as between Module 6 and Module7. Sites with reduced GC content and secondary structure (as predicted by DNAFold; <8 kcal/ml) were selected for optimal Gibson homology arms. A Gibson Assembly Ultra Kit (SGI-DNA) was used to clone the trimodule assembly into the PKS that produces Compound 7 enabling the replacement of Modules 4, 5, and 6 and simultaneously removal of the additional extraneous PmeI sequence retained after digestion. This resulted in >95% correct assembly for the industrial scale production of compounds produced by trimodule swapped PKS clusters (>200 per week).

Example 5. Ring expansion by swapping a single module acceptor with a dimodule donor

A heterologous dimodule donor assembly encoding mDEK chemistry and K chemistry was swapped into module 3, a single module acceptor, of the PKS that produces Compound 1 by the methods described above (FIG. 6A). The compound produced by engineered PKS, Compound 8, was observed in

high yield and had a mass of 655.41, as determined by LC-TOF analysis (FIG. 6B). This corresponds to a ring-expanded compound product in which Compound 8 contains an additional 2-carbon extender unit. Thus reprogramming PKS biosynthesis via module swapping by insertion of a dimodule assembly to replace a single module may produce functional PKS expression.

5

Example 6. Module swapping of a PKS loading module

Rapamycin is a natural product synthesized by a mixed polyketide synthase (PKS)/nonribosomal peptide synthetase (NRPS) system. Rapamycin shares a common structural motif with related natural product FK506 which is responsible for binding to FK506-binding proteins (FKBPs). During biogenesis of Rapamycin, loading modules bind and load a 4,5-dihydroxycyclohexa-1,5-dienecarboxylic acid starter unit via a CaiC domain, which functions as a carboxylic acid ligase (CL) like domain (FIG. 7A). Loading modules may possess similar domain structure as conventional elongation PKS modules, including ketoreductase-like domains and an enoyl-reductase domain, which may or may not be catalytically active. The final chemistry of the starter unit depends on the presence and the sequence of the domains in the loading module, so the resulting "starter unit" can be engineered by swapping the loading module

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The X23 PKS cluster produces Compound 9 and Compound 10 (FIG. 7B). The Rapamycin loading module from *Streptomyces* stain S303 was swapped into the X23 cluster by the methods described previously for a single module swap. The engineered PKS produced Compounds 11 and 12, in which the starter unit is replaced with the starter unit of Rapamycin. Additional single elongation module swaps of Module 2 and Module 7 of X23 produced Compounds 13 and 14, respectively.

20

Other Embodiments

It is to be understood that while the present disclosure has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and alterations are within the scope of the following claims.

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Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

30

In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

35

It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

40

Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, 5 unless the context clearly dictates otherwise.

In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention 10 (e.g., any polynucleotide or protein encoded thereby; any method of production; any method of use) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

What is claimed is:

CLAIMS

1. An engineered polyketide synthase comprising one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the engineered polyketide synthase is capable of producing a polyketide when expressed under conditions suitable to allow expression of a compound by the engineered polyketide synthase and wherein the one or more heterologous modules do not substantially inhibit polyketide translocation during polyketide biosynthesis.
2. An engineered polyketide synthase comprising one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the engineered polyketide synthase is capable of producing a polyketide when expressed under conditions suitable to allow expression of a compound by the engineered polyketide synthase and wherein the one or more heterologous modules comprise linking sequences which are compatible to the linking sequences of the modules adjacent thereto.
3. An engineered polyketide synthase comprising one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the engineered polyketide synthase is capable of producing a polyketide when expressed under conditions suitable to allow expression of a compound by the engineered polyketide synthase and wherein the polyketide expression level of the engineered polyketide synthase is at least 1% of the polyketide expression level of the reference polyketide synthase.
4. The engineered polyketide synthase of any one of claims 1 to 3, wherein the one or more heterologous modules comprise native linking sequences.
5. The engineered polyketide synthase of any one of claims 1 to 4, wherein the engineered polyketide synthase comprises two or more heterologous modules.
6. The engineered polyketide synthase of claim 5, wherein the two or more heterologous modules are adjacent.
7. The engineered polyketide synthase of any one of claims 1 to 6, wherein the engineered polyketide synthase comprises three or more heterologous modules.
8. The engineered polyketide synthase of claim 7, wherein the three or more heterologous modules are adjacent.
9. The engineered polyketide synthase of any one of claims 1 to 8, wherein the heterologous module is an elongation module which modifies a β -carbonyl unit in the variable region of the polyketide.

10. The engineered polyketide synthase of any one of claims 1 to 9, wherein at least one of the one or more heterologous modules comprises a portion having at least 90% identity to any one of SEQ ID NO: 1-165.

11. The engineered polyketide synthase of any one of claims 1 to 10, wherein at least one of the one or more heterologous modules comprises a portion having the sequence of any one of SEQ ID NO: 1-165.

12. A chimeric polyketide synthase, wherein at least one module of the chimeric polyketide synthase has been modified as compared to a polyketide synthase having the sequence of SEQ ID NO: 166-167.

13. The chimeric polyketide synthase of claim 12, wherein the at least one module comprises a portion having at least 90% identity to any one of SEQ ID NO: 1-165.

14. A nucleic acid encoding a polyketide synthase of any one of claims 1 to 13.

15. The nucleic acid of claim 15, wherein the nucleic acid further encodes an LAL, wherein the sequence encoding the LAL is operatively linked to the sequence encoding the polyketide synthase.

16. The nucleic acid of claim 15, wherein the LAL is a heterologous LAL.

17. The nucleic acid of claim 15 or 16, wherein LAL comprises a portion having at least 80% identity to SEQ ID NO: 168.

18. The nucleic acid of claim 17, wherein the LAL comprises a portion having the sequence of SEQ ID NO: 168.

19. The nucleic acid of claim 18, wherein the LAL has the sequence of SEQ ID NO: 168.

20. The nucleic acid of any one of claims 14 to 19, wherein the nucleic acid encoding the LAL lacks a TTA inhibitory codon in an open reading frame.

21. The nucleic acid of any one of claims 14 to 20, wherein the nucleic acid further comprises an LAL binding site, wherein the sequence encoding the LAL binding site is operatively linked to the sequence encoding the polyketide synthase.

22. The nucleic acid of claim 21, wherein the LAL binding site comprises a portion having at least 80% sequence identity to the sequence of SEQ ID NO: 169.

23. The nucleic acid of claim 22, wherein the LAL binding site comprises a portion having the sequence of SEQ ID NO: 169.

24. The nucleic acid of claim 23, wherein the LAL binding site has of the sequence of SEQ ID NO: 169.

25. The nucleic acid of claim 21, wherein the LAL binding site has the sequence GGGGGT (SEQ ID NO: 170).

26. The nucleic acid of any one of claims 21 to 25, wherein the binding of an LAL to the LAL binding site promotes expression of the polyketide synthase.

27. The nucleic acid of any one of claims 14 to 26, wherein the nucleic acid further encodes a nonribosomal peptide synthase.

28. The nucleic acid of any one of claims 14 to 27, wherein the nucleic acid further encodes a first P450 enzyme.

29. The nucleic acid of claim 28, wherein the nucleic acid further encodes a second P450 enzyme.

30. An expression vector comprising a nucleic acid of any one of claims 14 to 29.

31. The expression vector of claim 30, wherein the expression vector is an artificial chromosome.

32. The expression vector of claim 31, wherein the artificial chromosome is a bacterial artificial chromosome.

33. A host cell comprising an expression vector of any one of claims 30 to 32.

34. A host cell comprising a polyketide synthase of any one of claims 1 to 13, wherein the polyketide is heterologous to the host cell.

35. The host cell of claim 33 or 34, wherein the host cell naturally lacks an LAL.

36. The host cell of any one of claims 33 to 35, wherein the host cell naturally lacks an LAL binding site.

37. The host cell of any one of claims 33 to 36, wherein the host cell comprises an LAL capable of binding to an LAL binding site and regulating expression of a polyketide synthase.

38. The host cell of claim 37, wherein the LAL is heterologous.
39. The host cell of claim 37 or 38, wherein the LAL comprises a portion having at least 80% identity to the sequence of SEQ ID NO: 168.
40. The host cell of any one of claims 33 to 39, wherein the host cell is a bacterium.
41. The host cell of claim 40, wherein the bacterium is an actinobacterium.
42. The host cell of claim 41, wherein the actinobacterium is *Streptomyces ambofaciens*, *Streptomyces hygroscopicus*, or *Streptomyces malayensis*.
43. The host cell of claim 42, wherein the actinobacterium is S1391, S1496, or S2441.
44. The host cell of any one of claims 33 to 43, wherein the host cell has been modified to enhance expression of a polyketide synthase.
45. The host cell of claim 44, wherein the host cell has been modified to enhance expression of a compound-producing protein by (i) deletion of an endogenous gene cluster which expresses a compound-producing protein; (ii) insertion of a heterologous gene cluster which expresses a compound-producing protein; (iii) exposure of the host cell to an antibiotic challenge; and/or (iv) introduction of a heterologous promoter that results in an at least 2-fold increase in expression of a compound compared to the homologous promoter.
46. A method of producing a polyketide, the method comprising culturing a host cell of any one of claims 33 to 45 under suitable conditions.
47. A method of producing a polyketide, the method comprising culturing a host cell engineered to express a polyketide synthase of any one of claims 1 to 13 under conditions suitable for polyketide synthase to produce a polyketide.
48. A method of producing a compound, the method comprising:
- a) providing a parent polyketide synthase sequence capable of producing a compound;
 - (b) determining the compatibility of at least one module of a second polyketide synthase with at least two modules of the parent polyketide synthase;
 - (c) producing a nucleic acid encoding a modified polyketide synthase, wherein the modified polyketide synthase comprises at least one module of a second polyketide synthase which has been determined to be compatible with the at least two modules of the parent polyketide synthase.
49. A method of producing a compound, the method comprising:
- (a) providing a parent nucleic acid encoding a parent polyketide synthase;

(b) modifying the parent nucleic acid to create a modified nucleic acid encoding a modified polyketide synthase capable of producing a compound, wherein the modification produces a modified polyketide synthase comprising at least one heterologous module.

50. A method of producing a compound, the method comprising:

- (a) providing a parent polynucleotide sequence capable of producing a compound;
- (b) identifying one or more heterologous modules suitable for replacement of one or more modules in the parent polynucleotide sequence;
- (c) producing a nucleic acid encoding a modified polyketide synthase, wherein the modified polyketide synthase comprises at least one heterologous module identified in step (b).

51. A method of producing a plurality of polynucleotides, wherein each of the plurality of polynucleotides corresponds to an engineered polyketide synthase, and wherein each of the plurality of polynucleotides comprises one or more heterologous modules with altered enzymatic activity relative to a reference polyketide, wherein the method comprises:

- (a) providing a parent polynucleotide sequence encoding a polyketide synthase;
- (b) identifying one or more modules for replacement in the parent polynucleotide sequence;
- (c) identifying two or more heterologous modules suitable for replacement for each of the modules identified in step (b);
- (d) generating a plurality of polynucleotides, wherein each of the plurality of polynucleotides corresponds to an engineered polyketide synthase, and wherein each of the plurality of polynucleotides comprises a heterologous module selected from the two or more heterologous modules identified in step (c) in replacement of each of the one or more modules to be replaced identified in step (b).

FIG. 1A

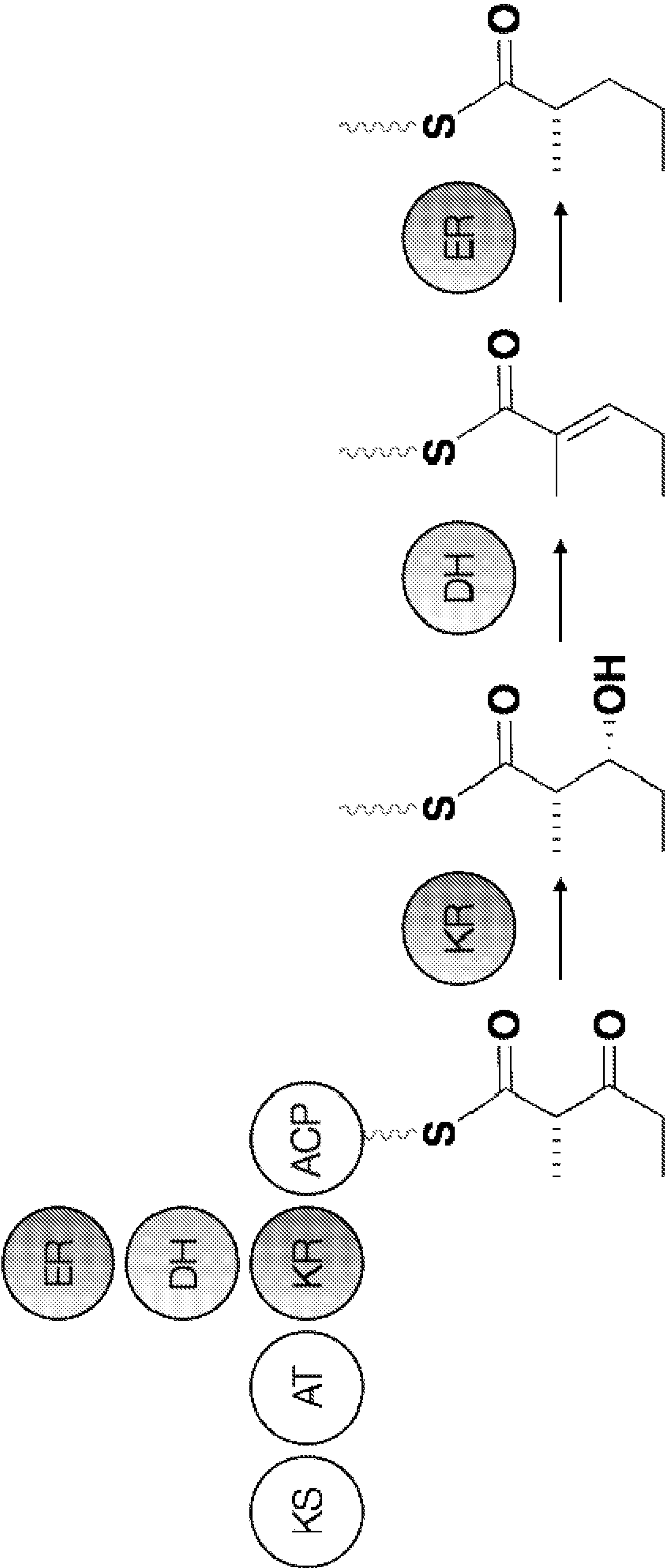


FIG. 1B

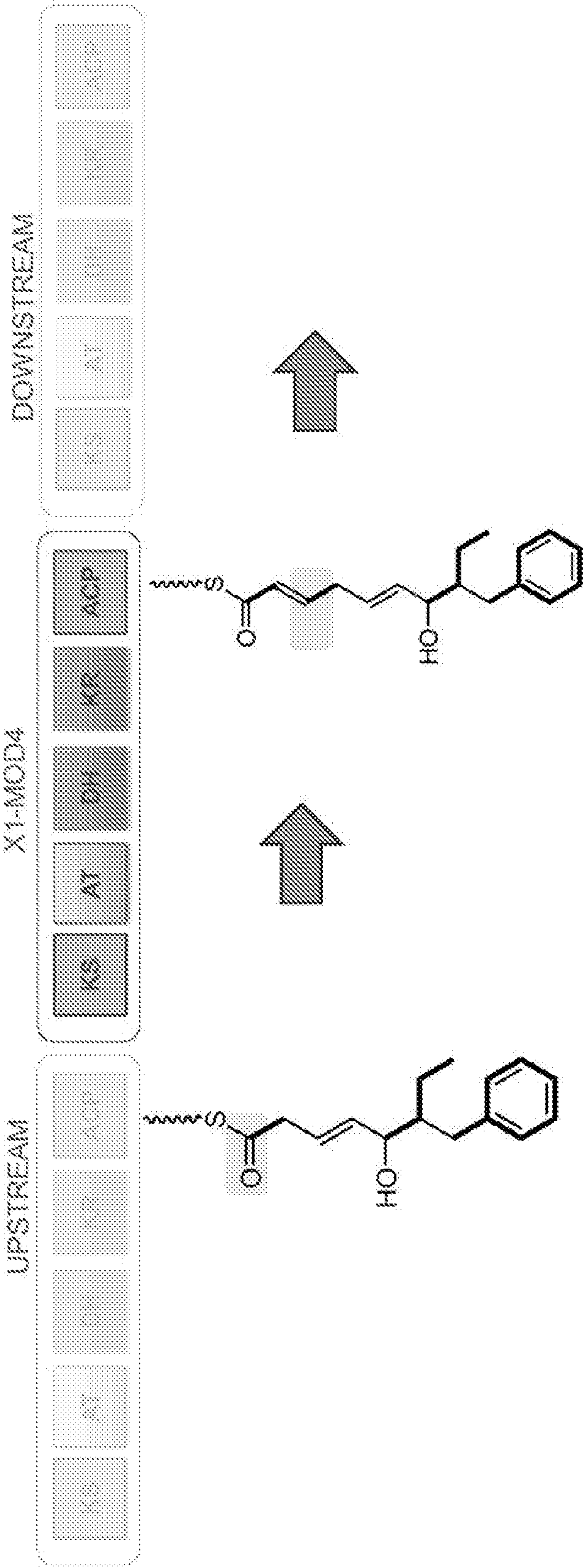


FIG. 2A

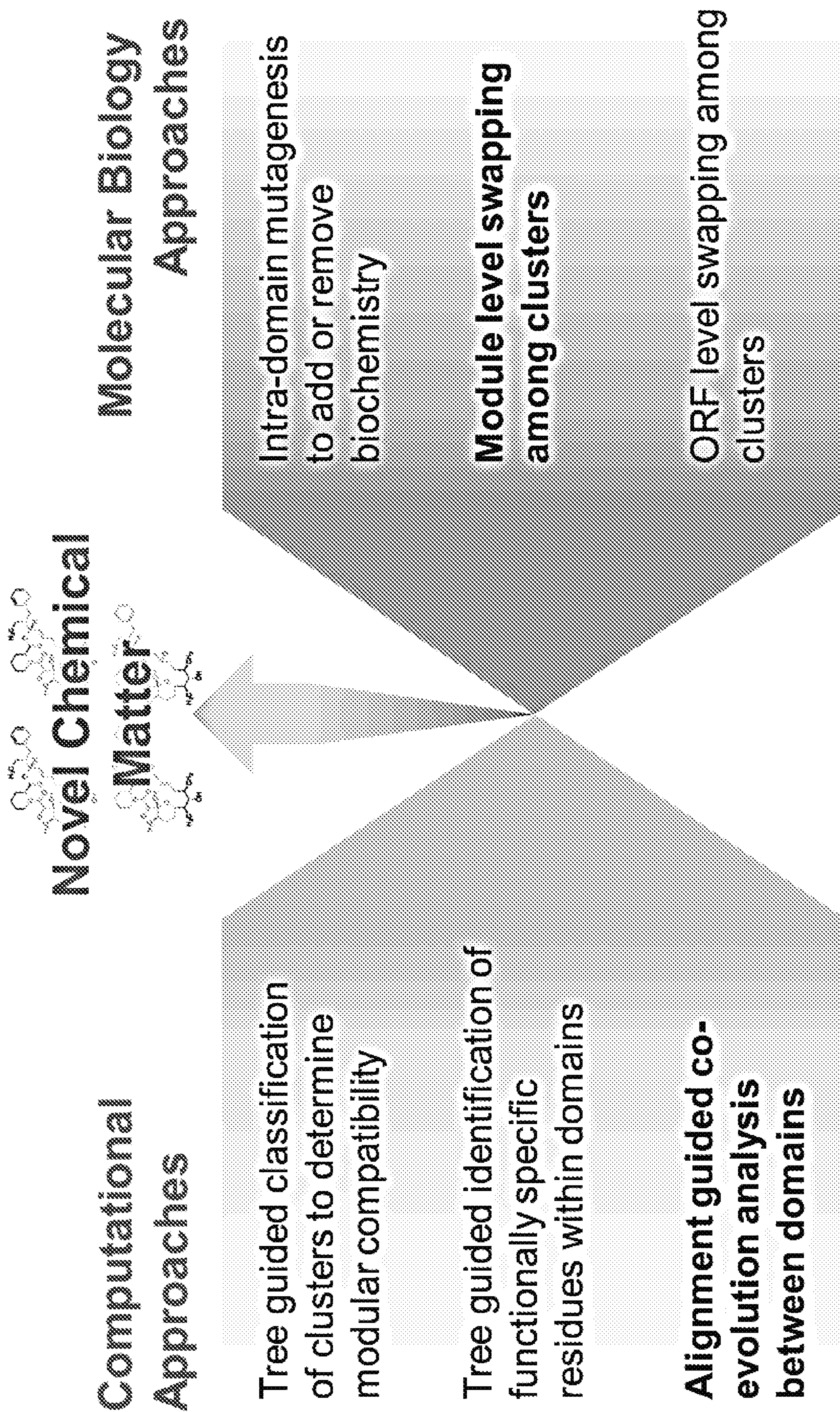


FIG. 2B

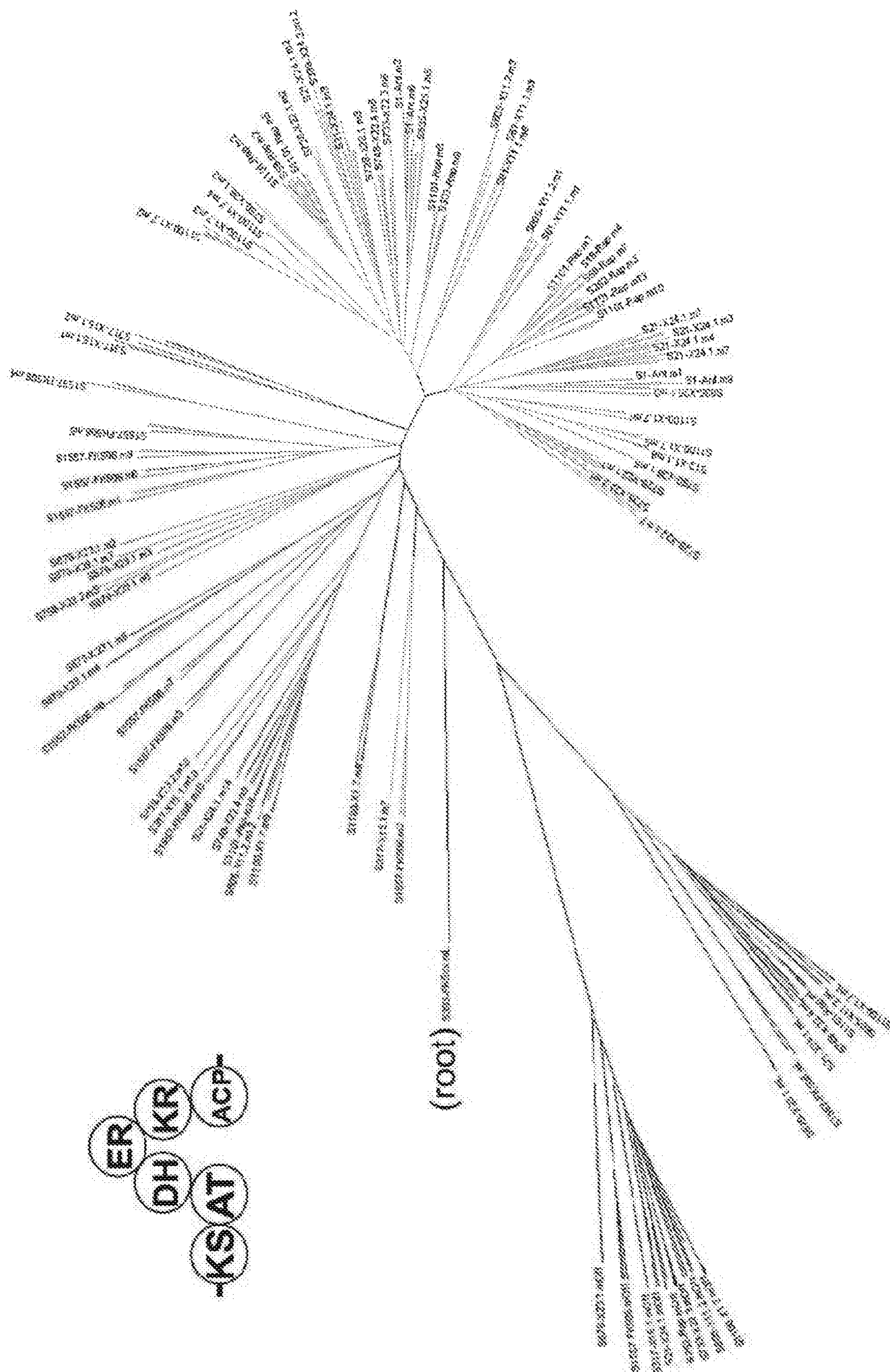
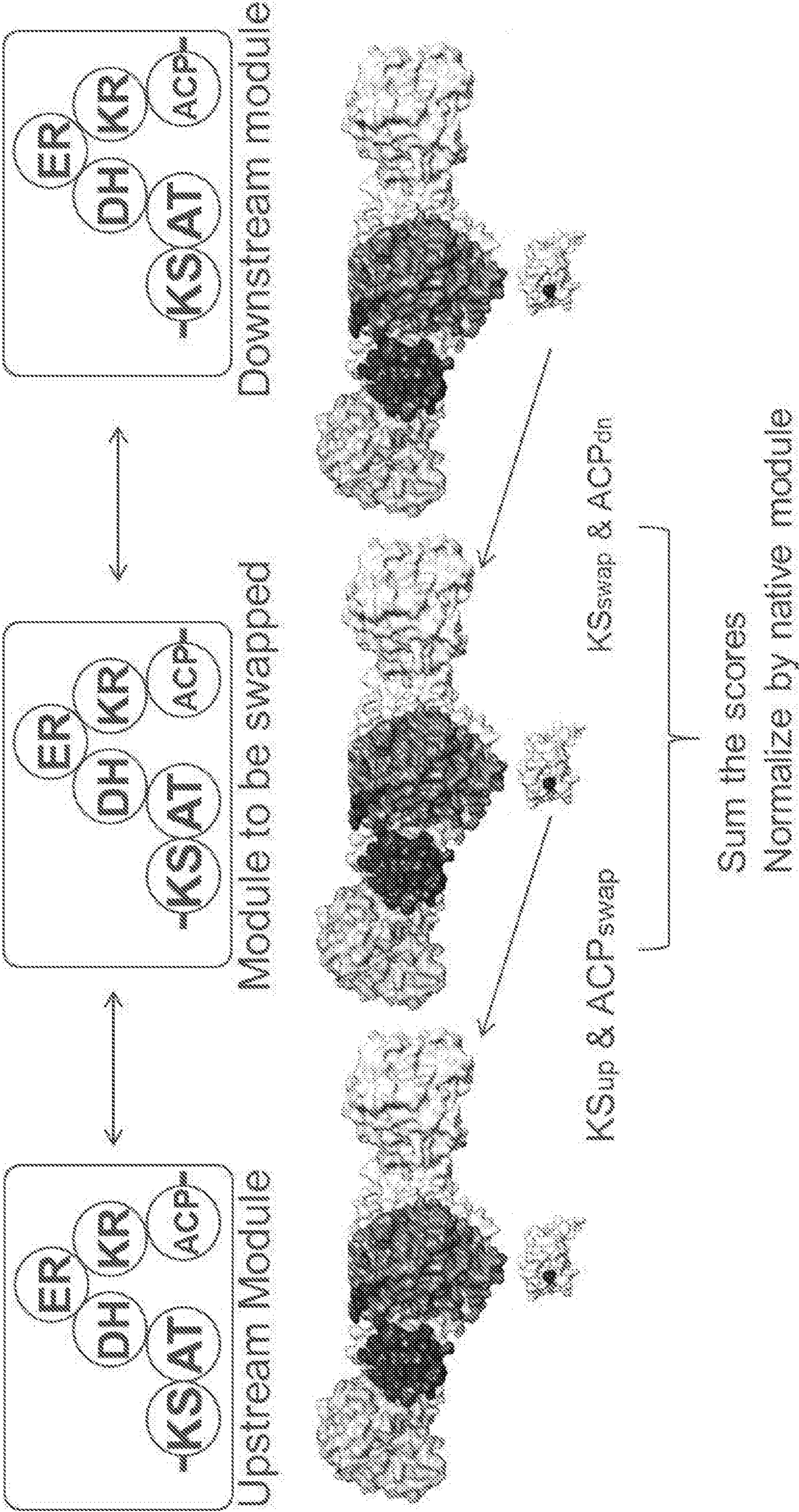


FIG. 2C



Correlation Score**X** High

✦ Medium

✧ Low

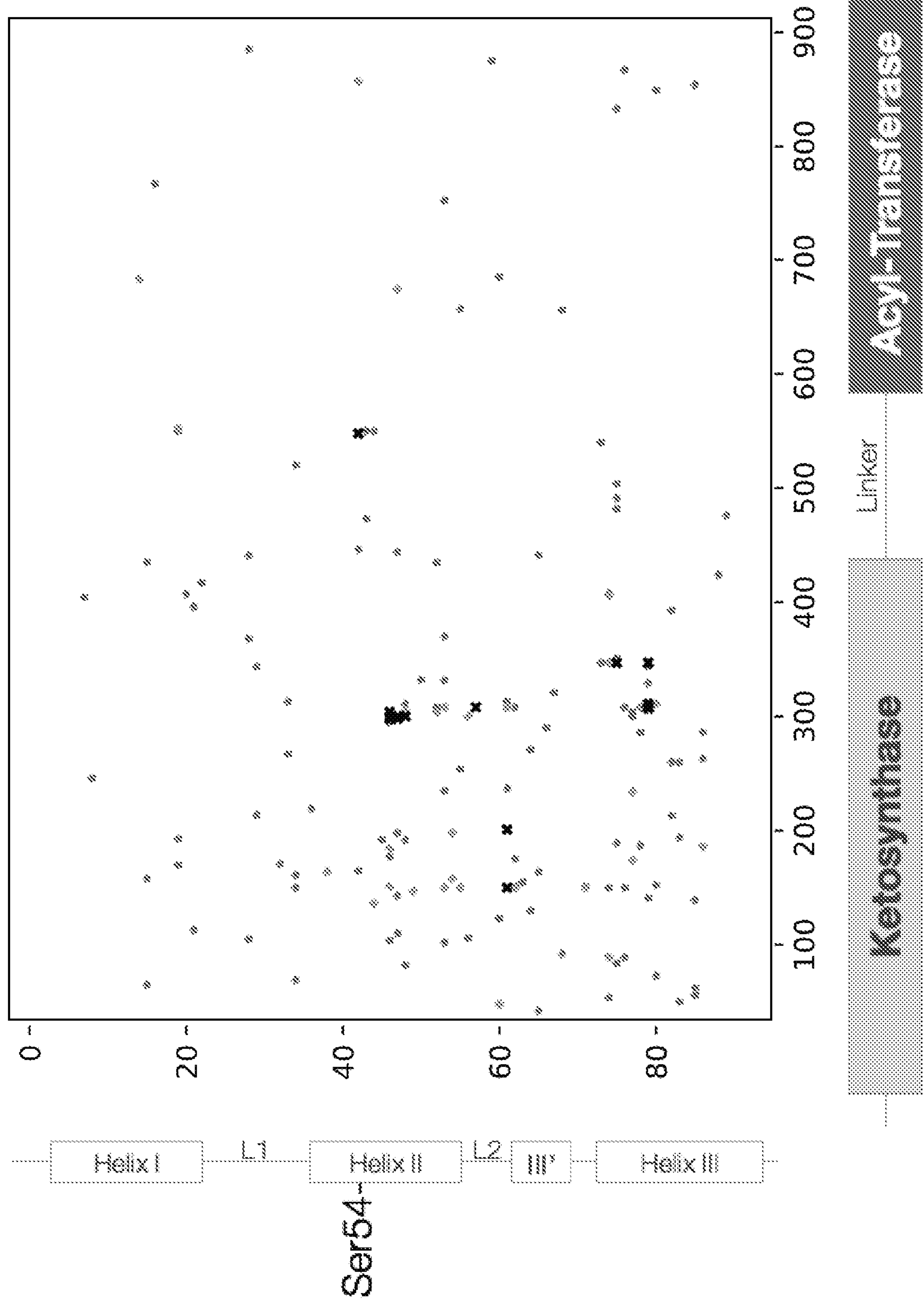
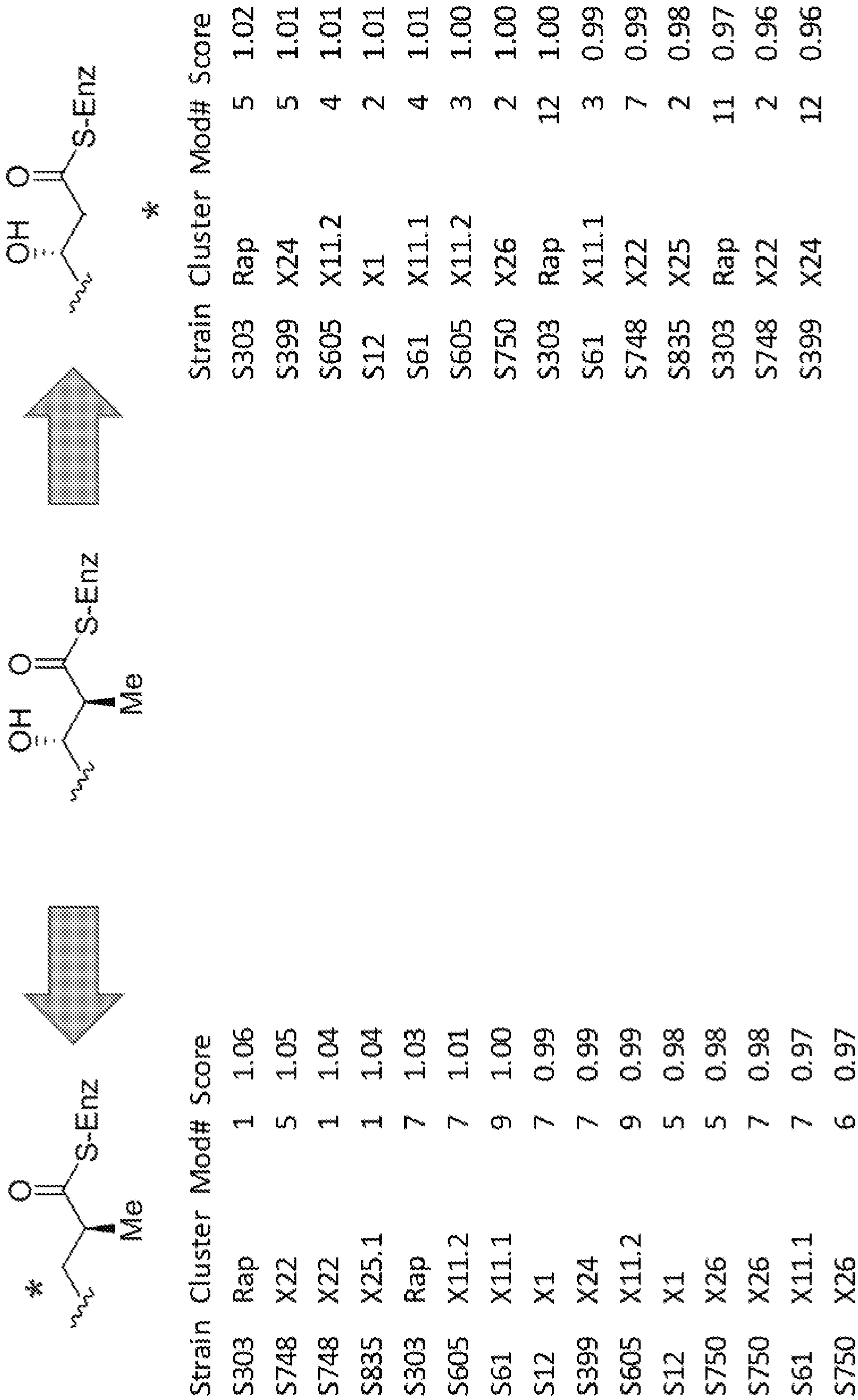
FIG. 2D

FIG. 2E



Score >0.95 from clusters available for plucking

FIG. 2F

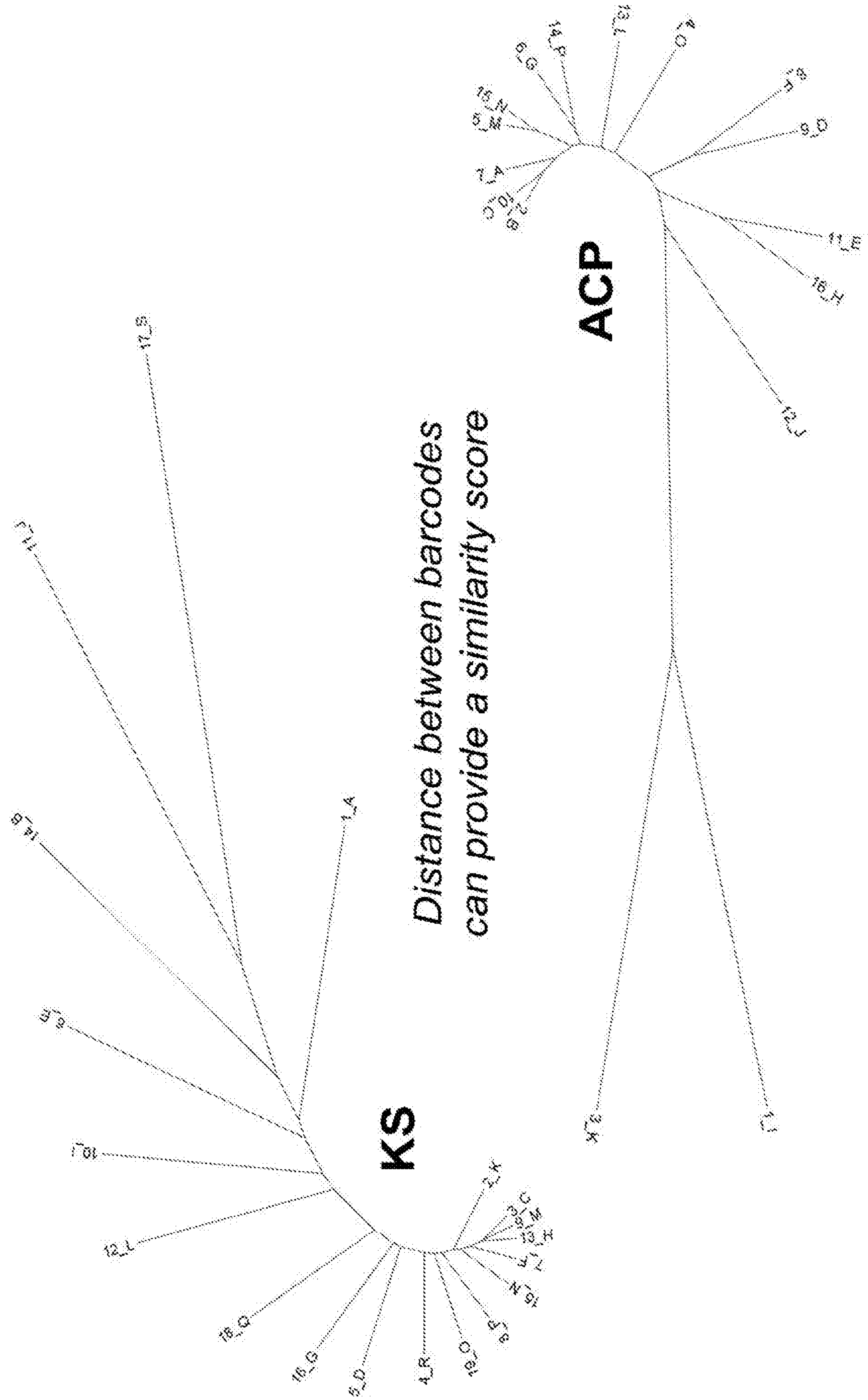


FIG. 2G

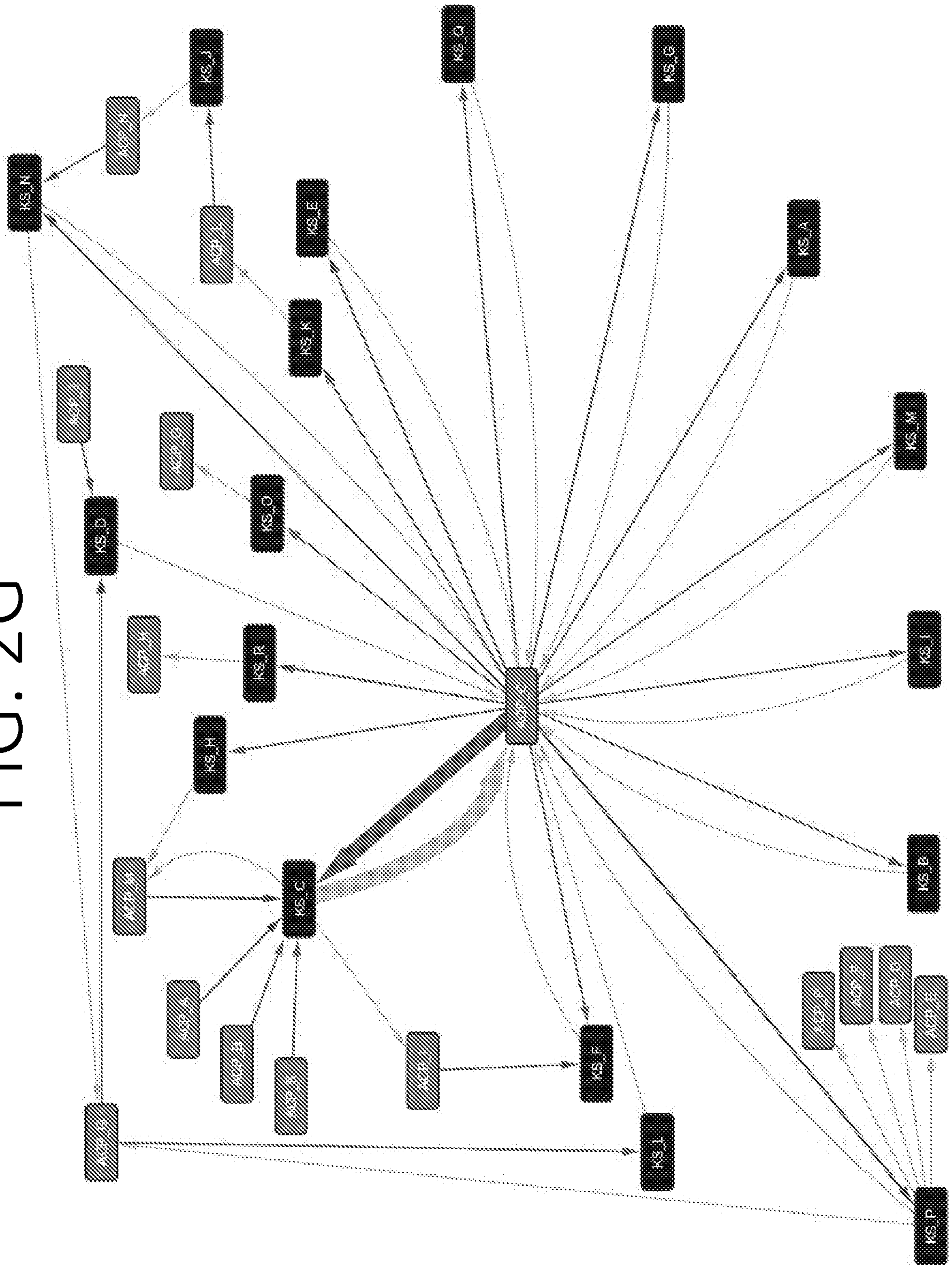


FIG. 3A

Introduce Unique Restriction Sites to BAC

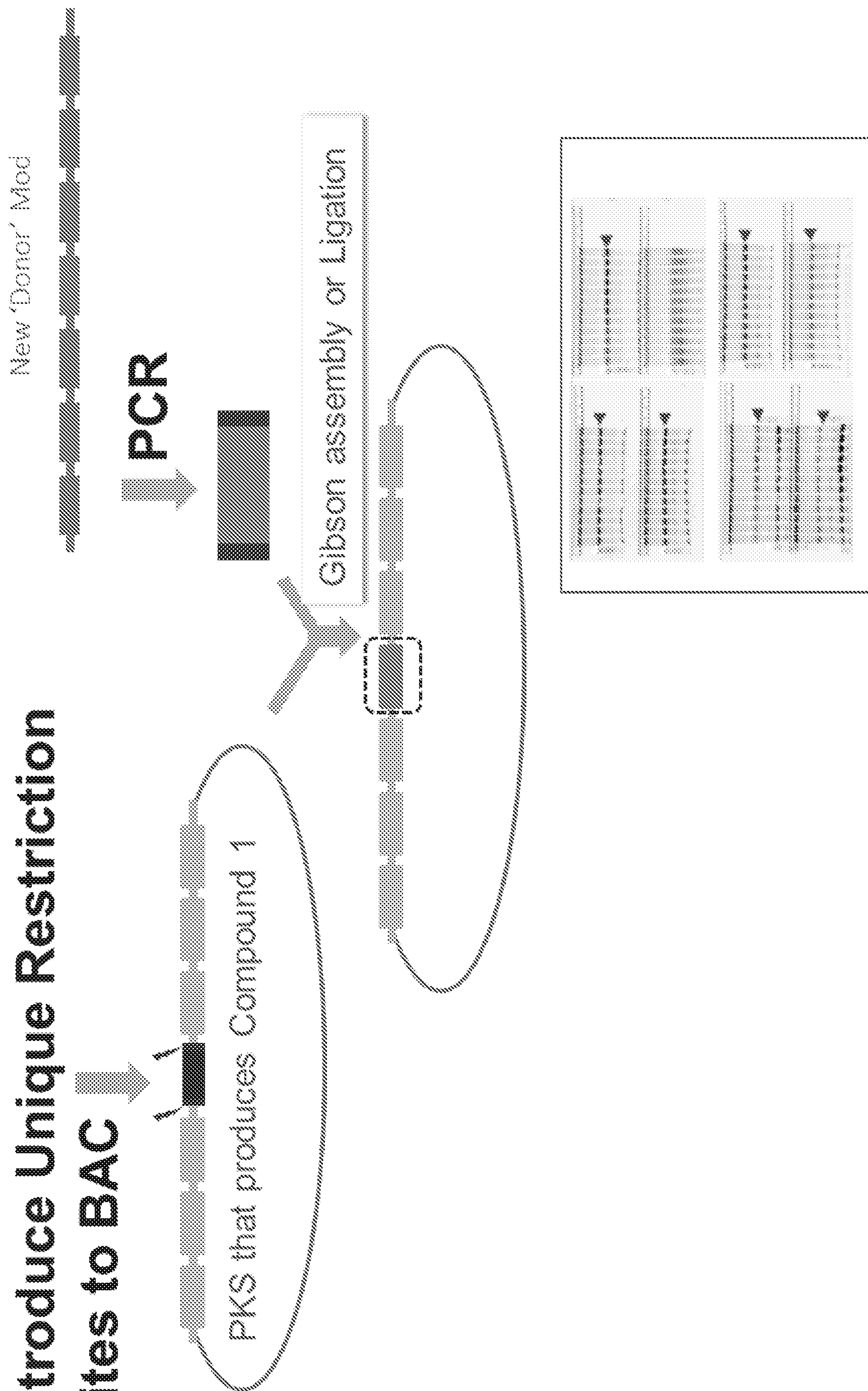


FIG. 3B

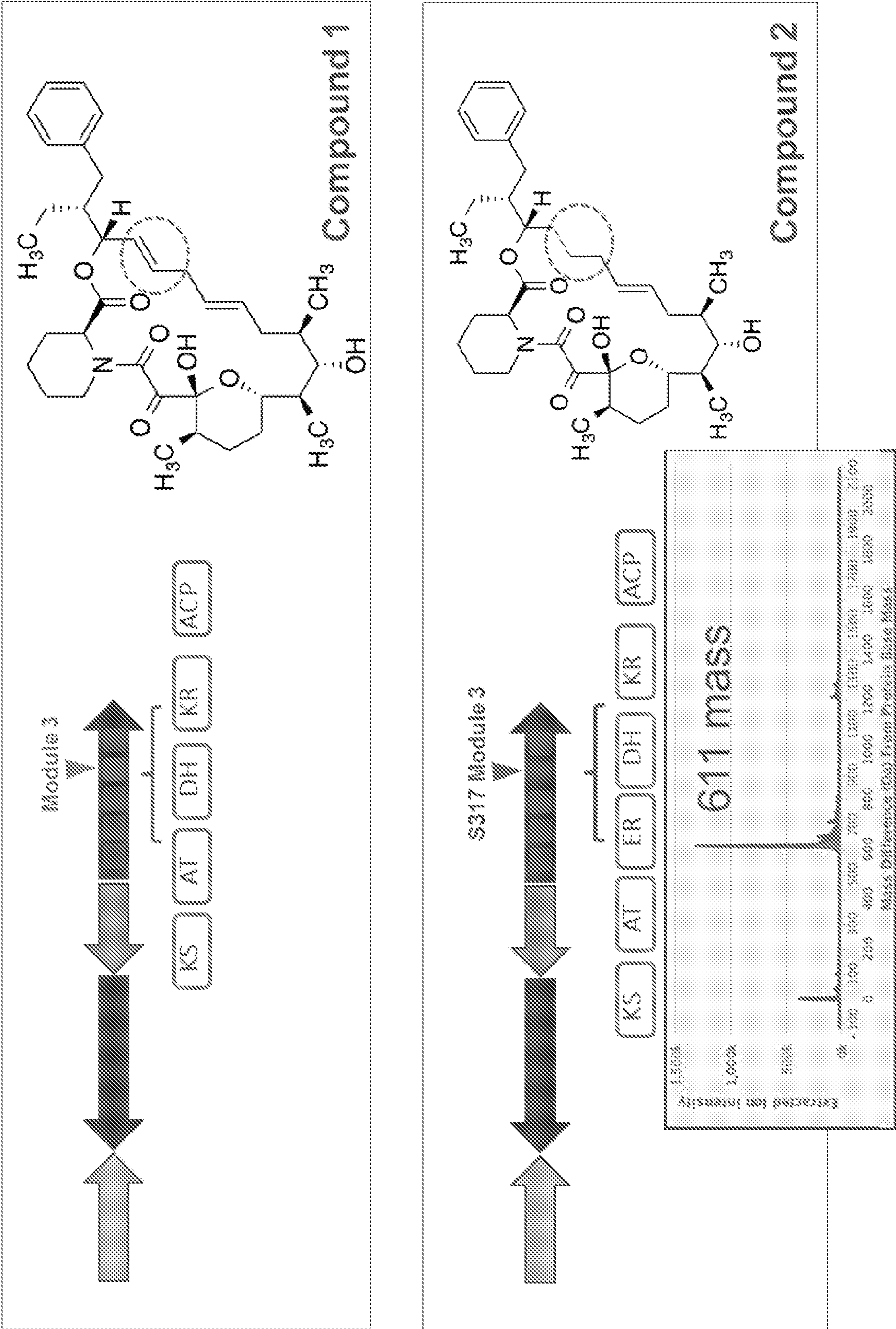
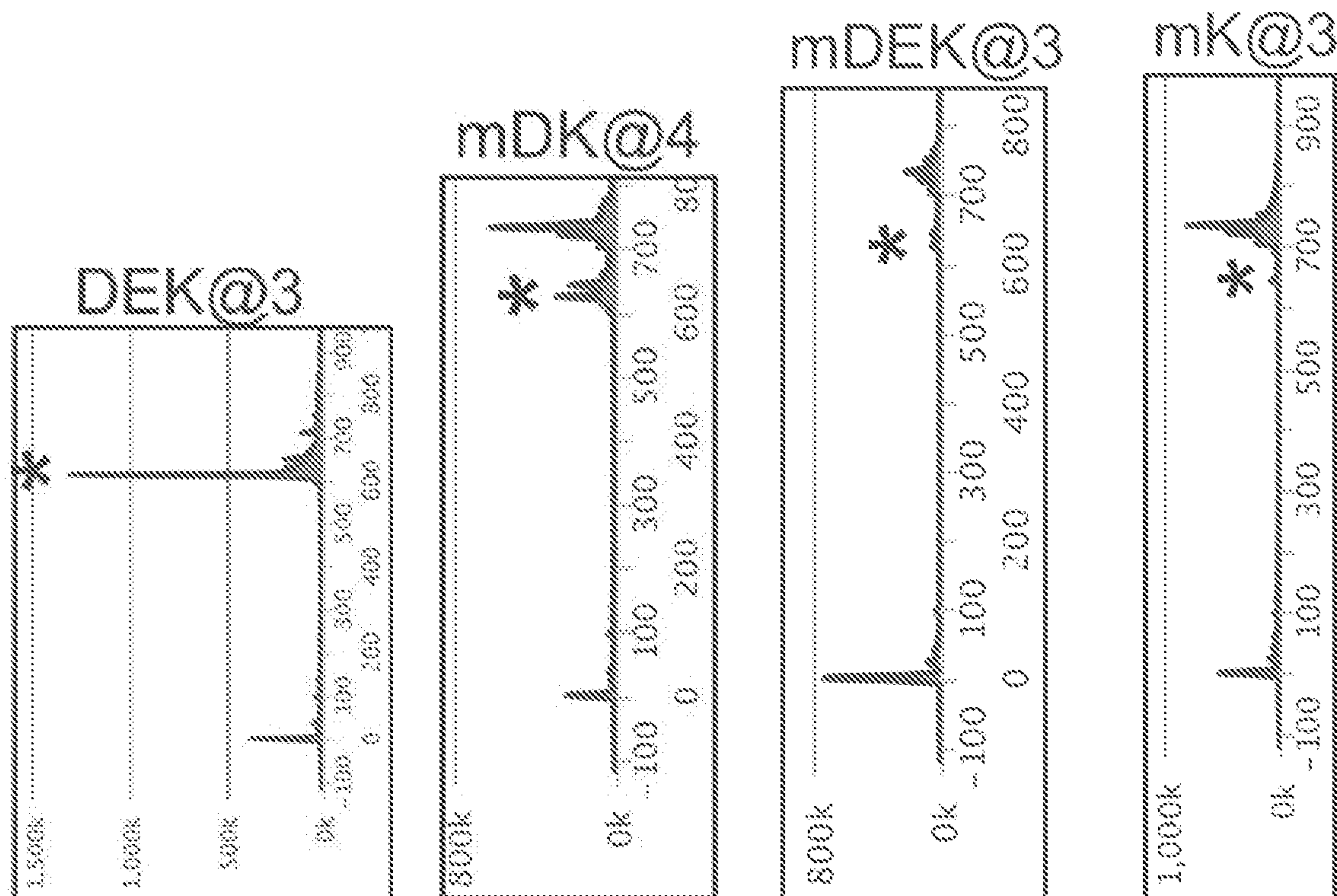
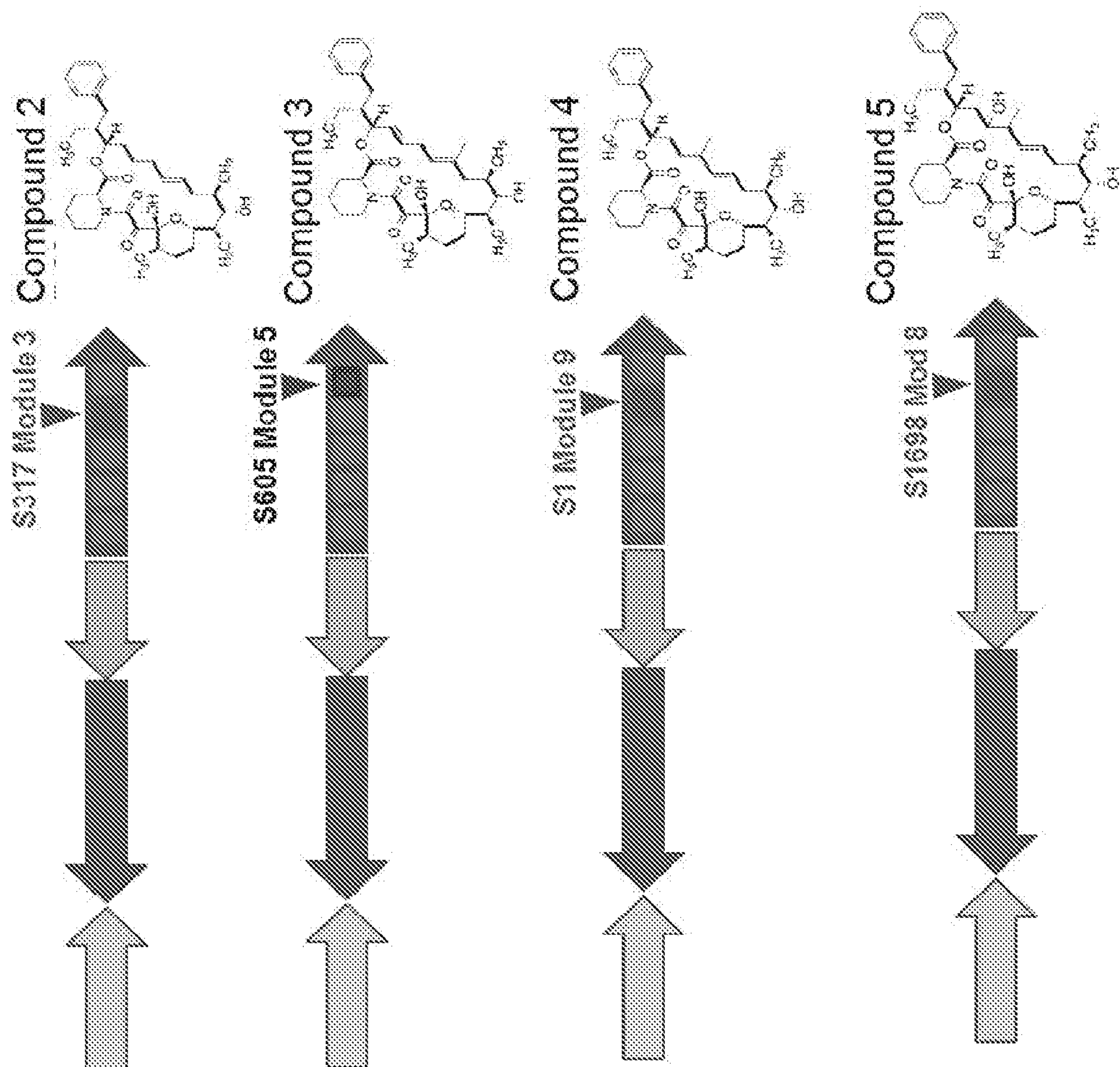


FIG. 3C



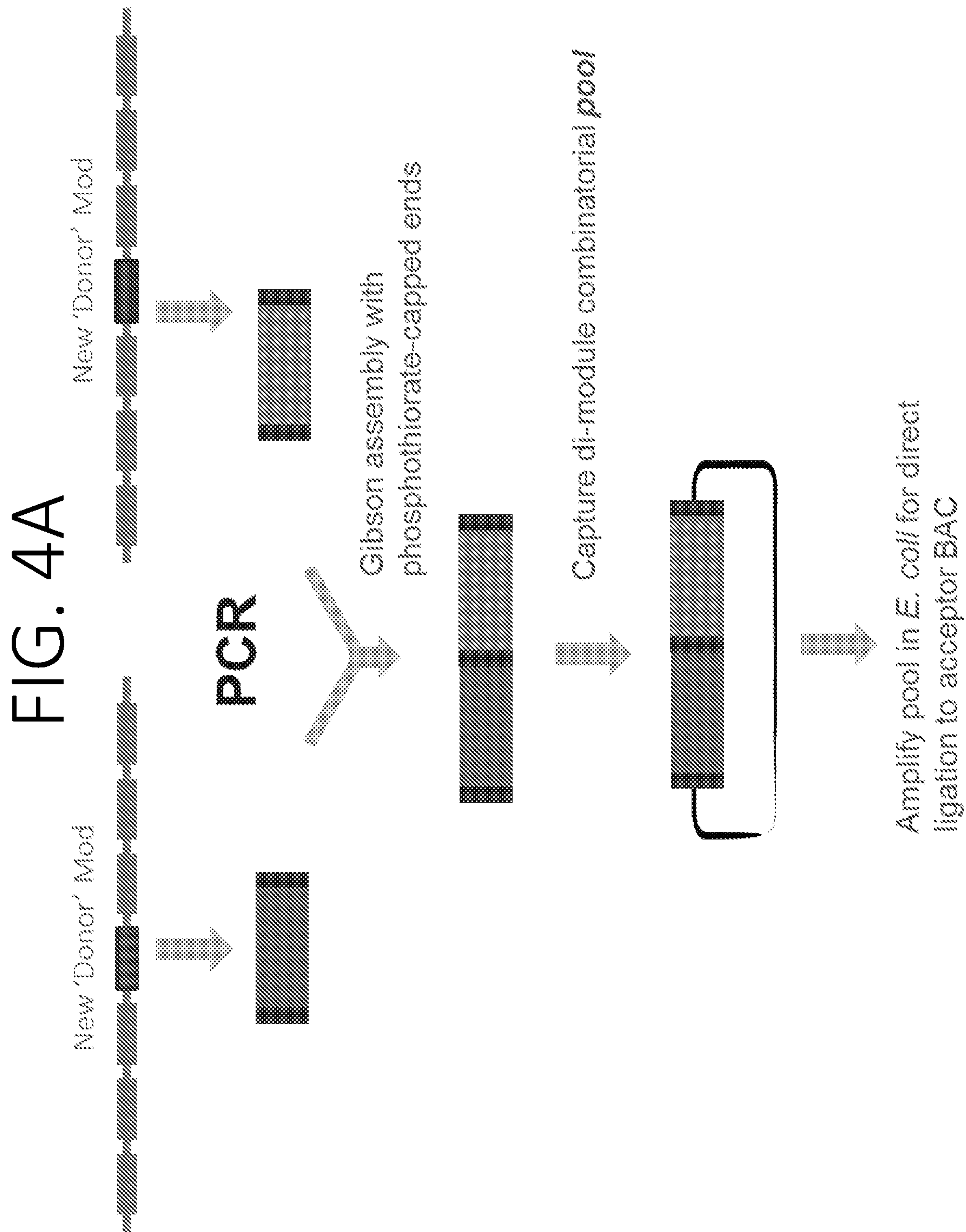


FIG. 4B

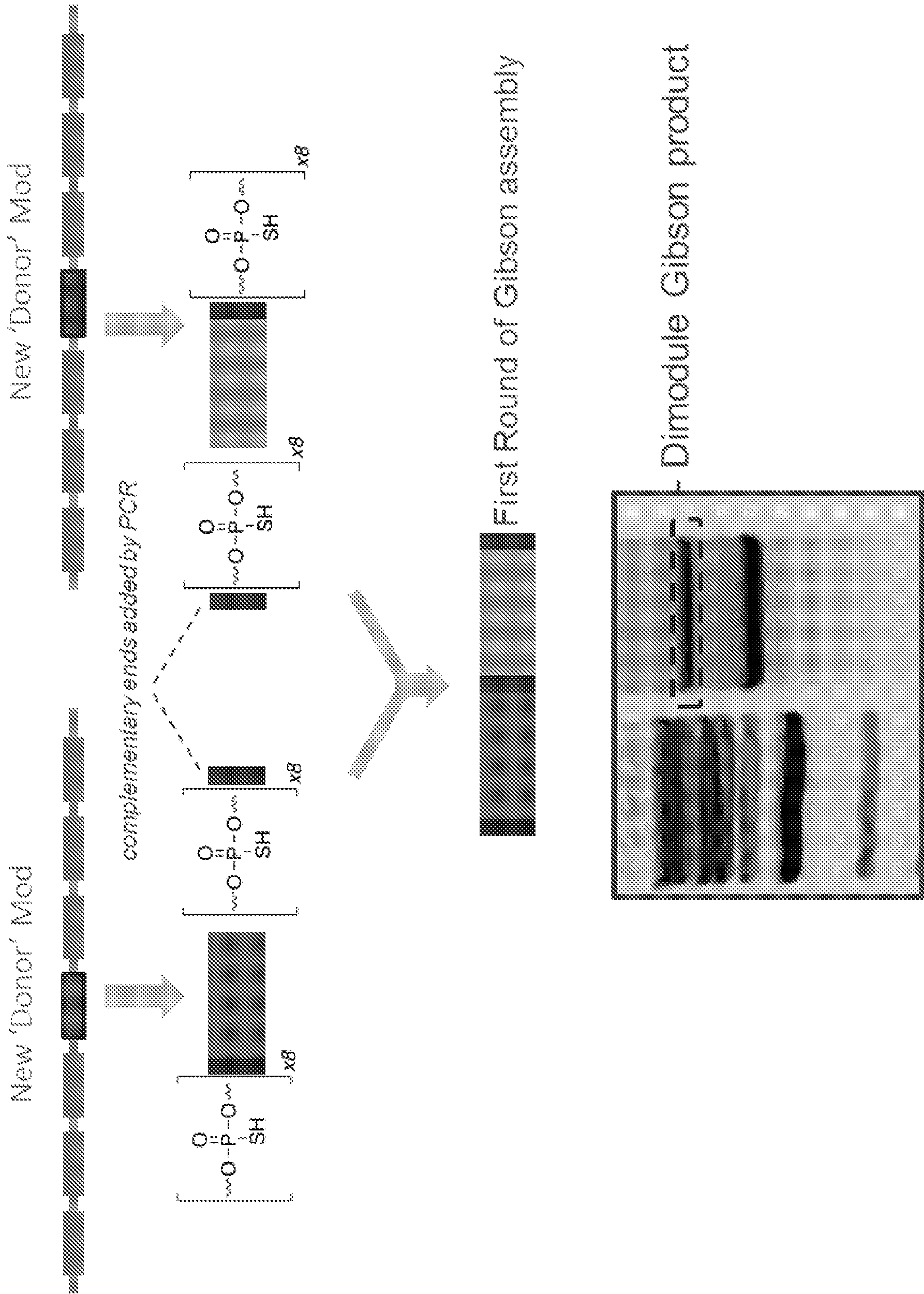


FIG. 4C

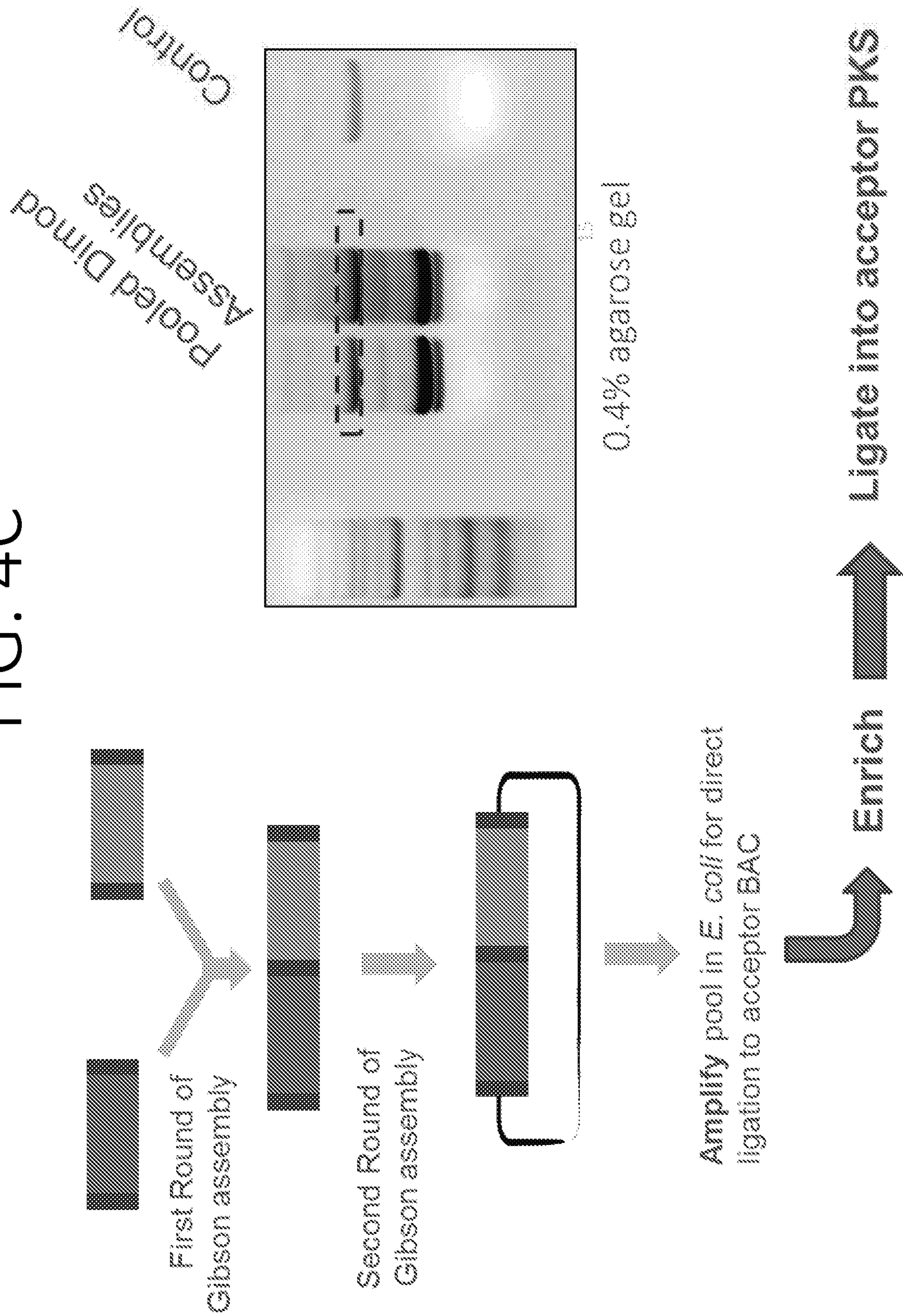
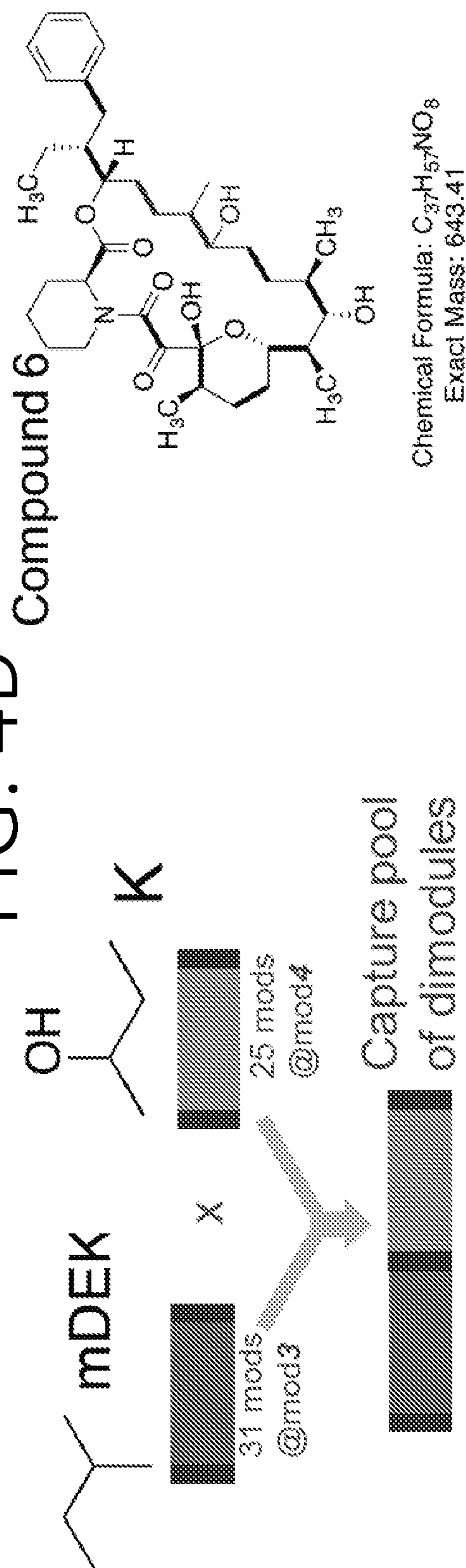
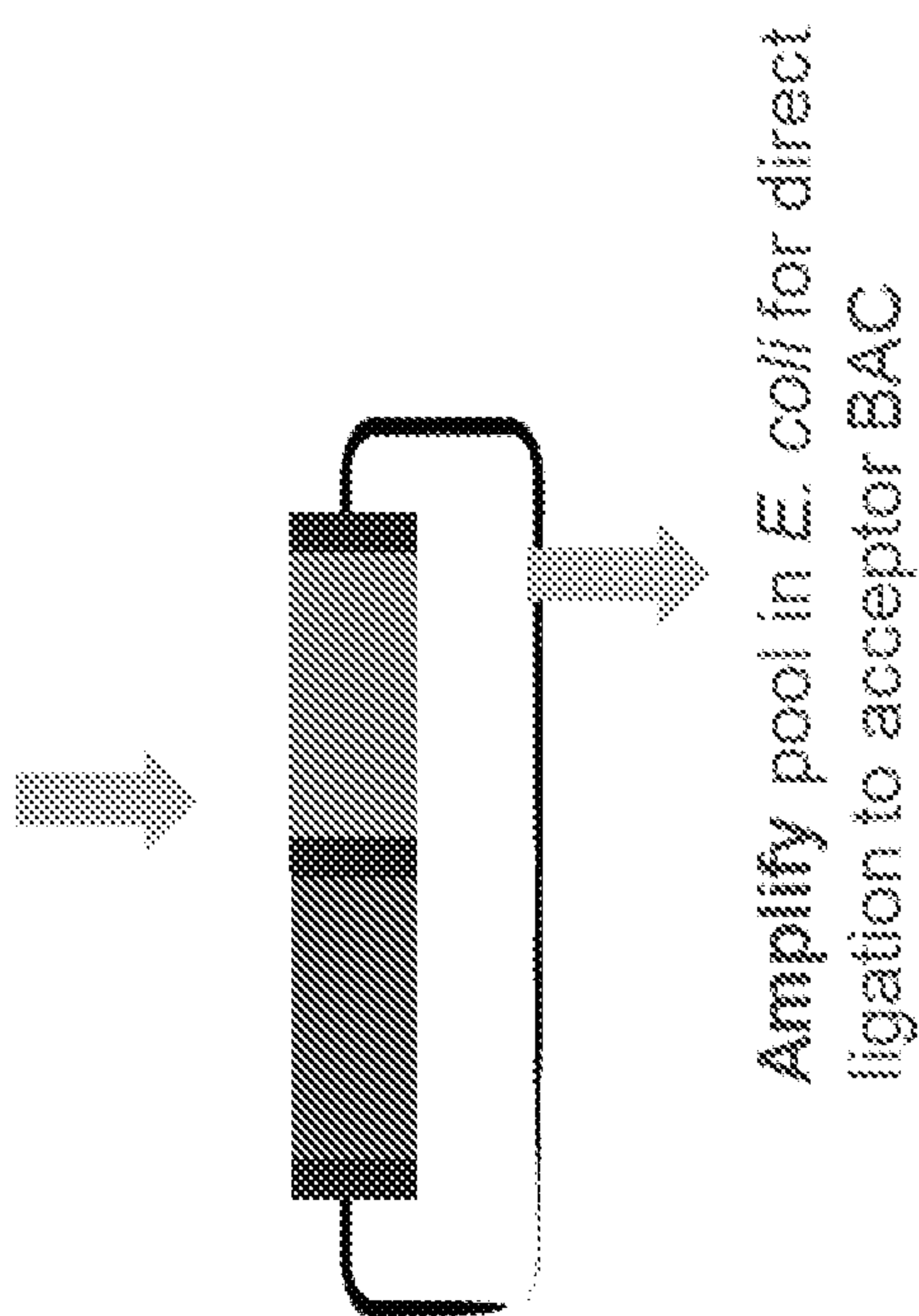


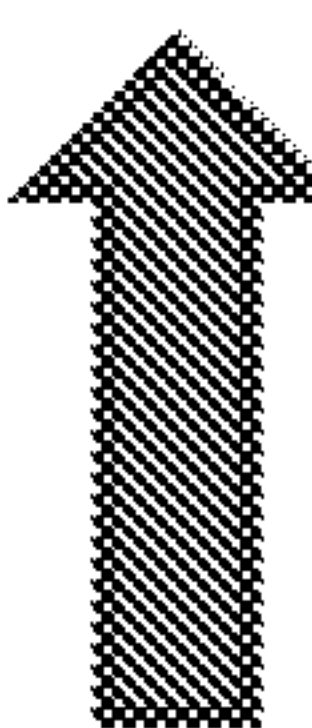
FIG. 4D



Capture pool
of dimodules



Enrich



Ligate into acceptor PKS

Top-Down

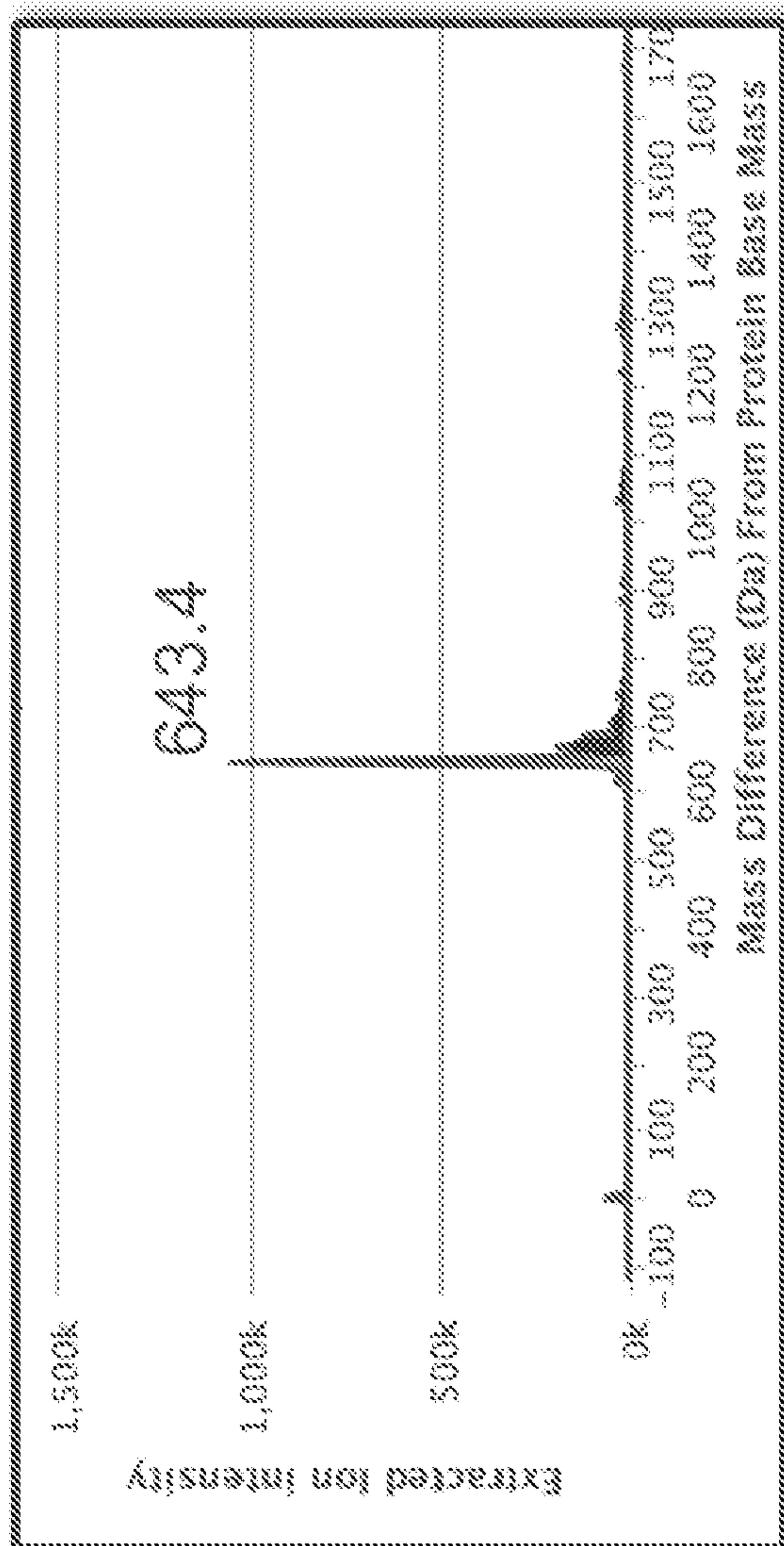
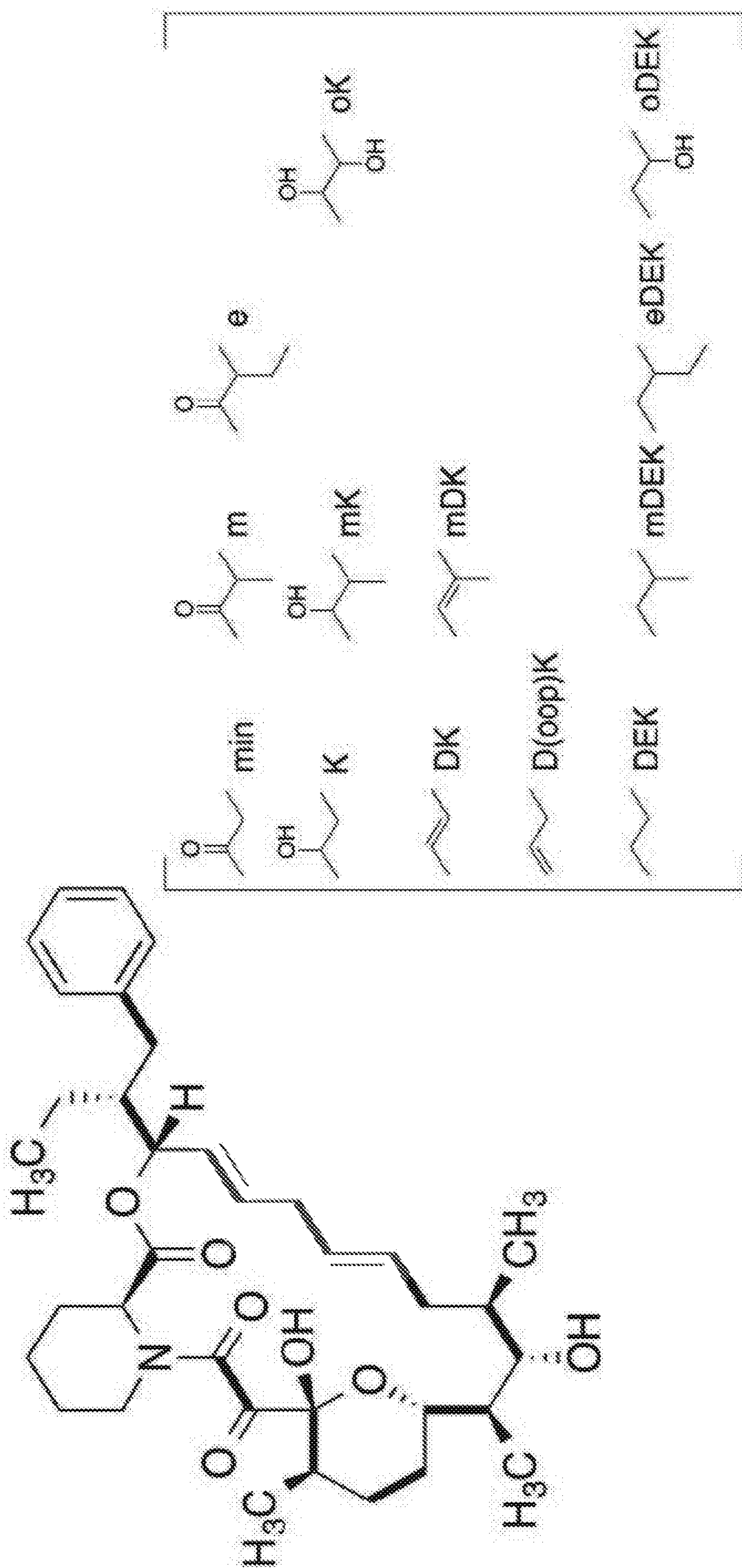


FIG. 4E



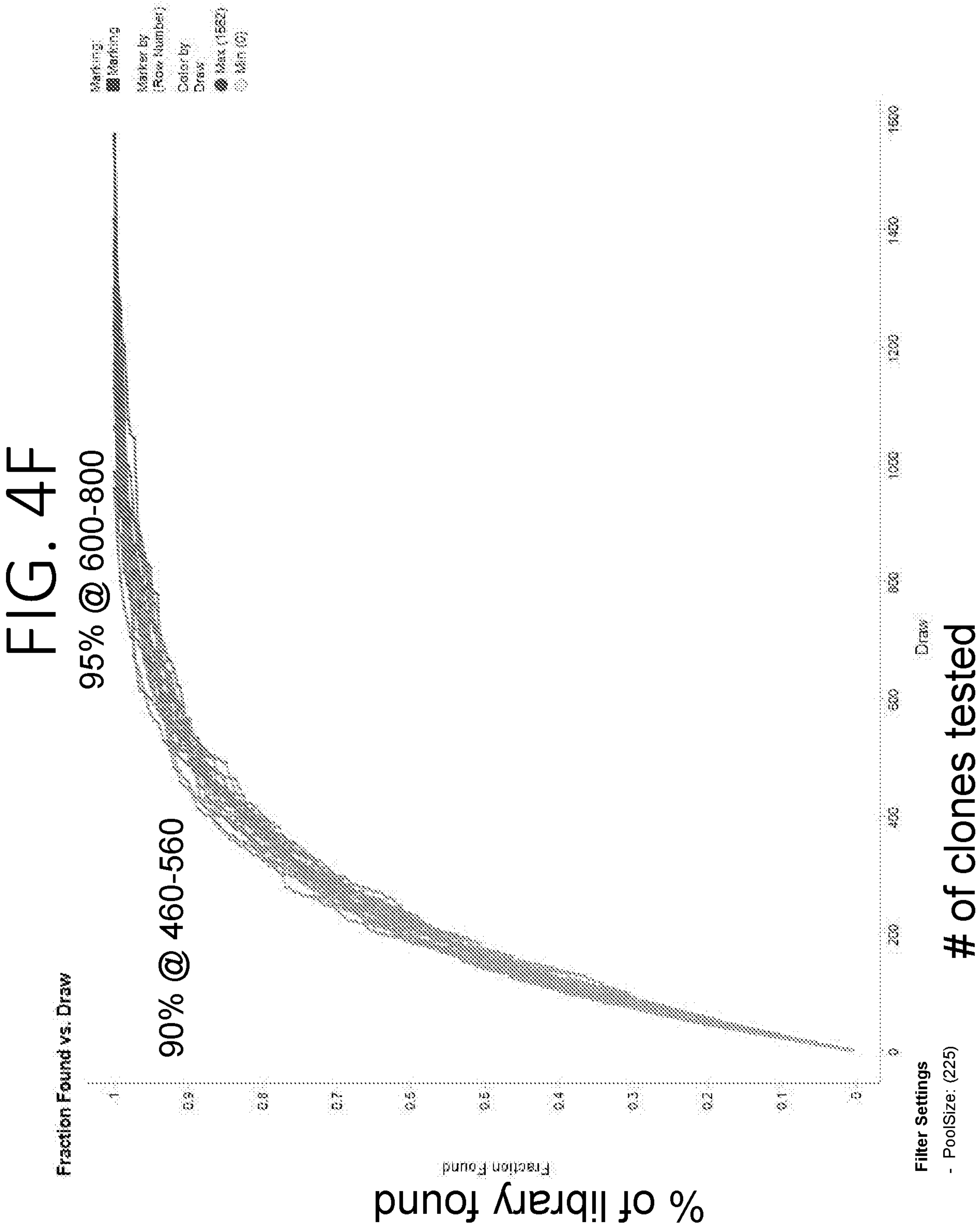


FIG. 4G

In vitro CRIPSR / Cas9 module release for Nanopore Library Preparation

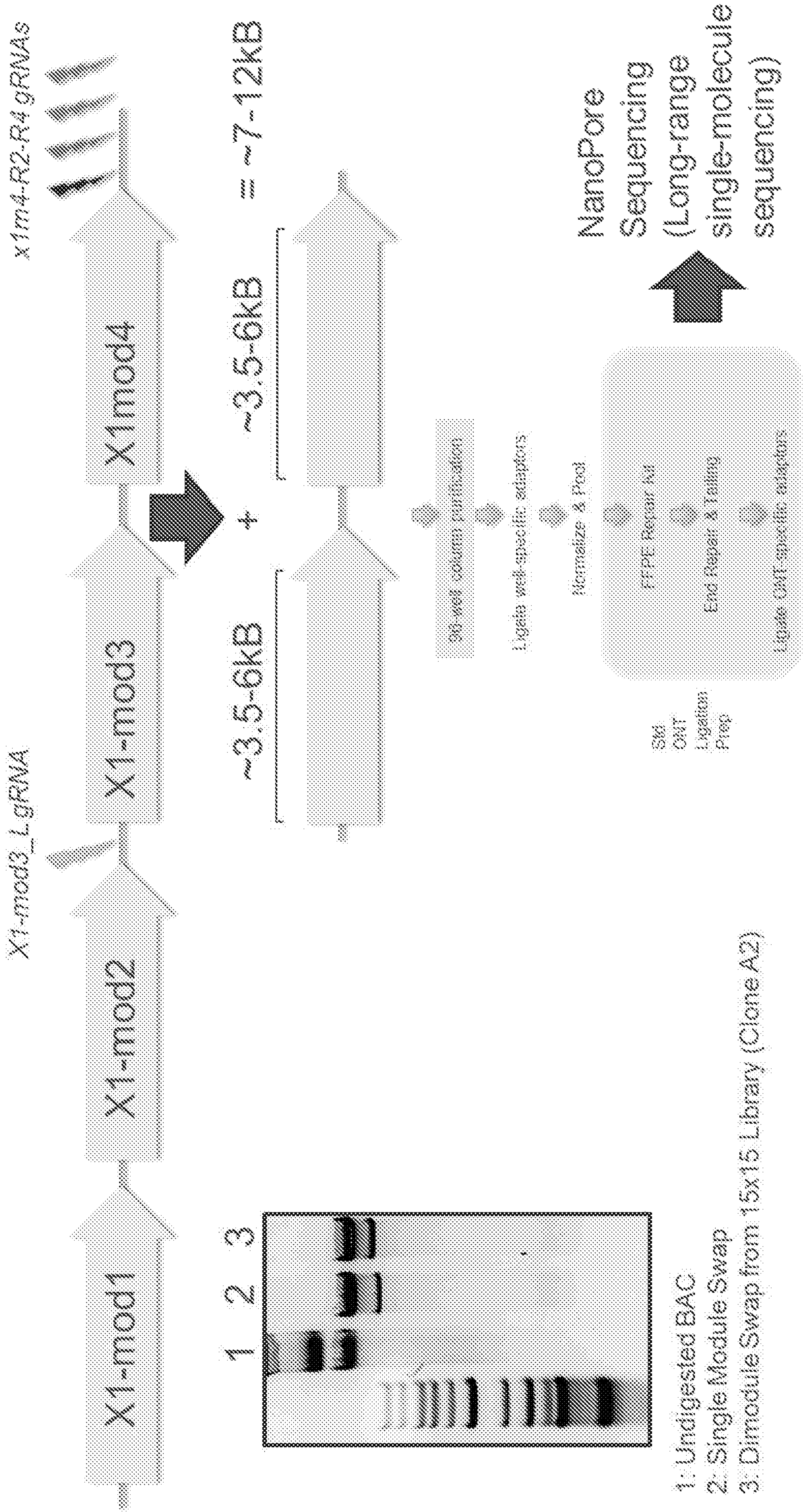


FIG. 4H
Albacore (Oxford Nanopore) basecaller

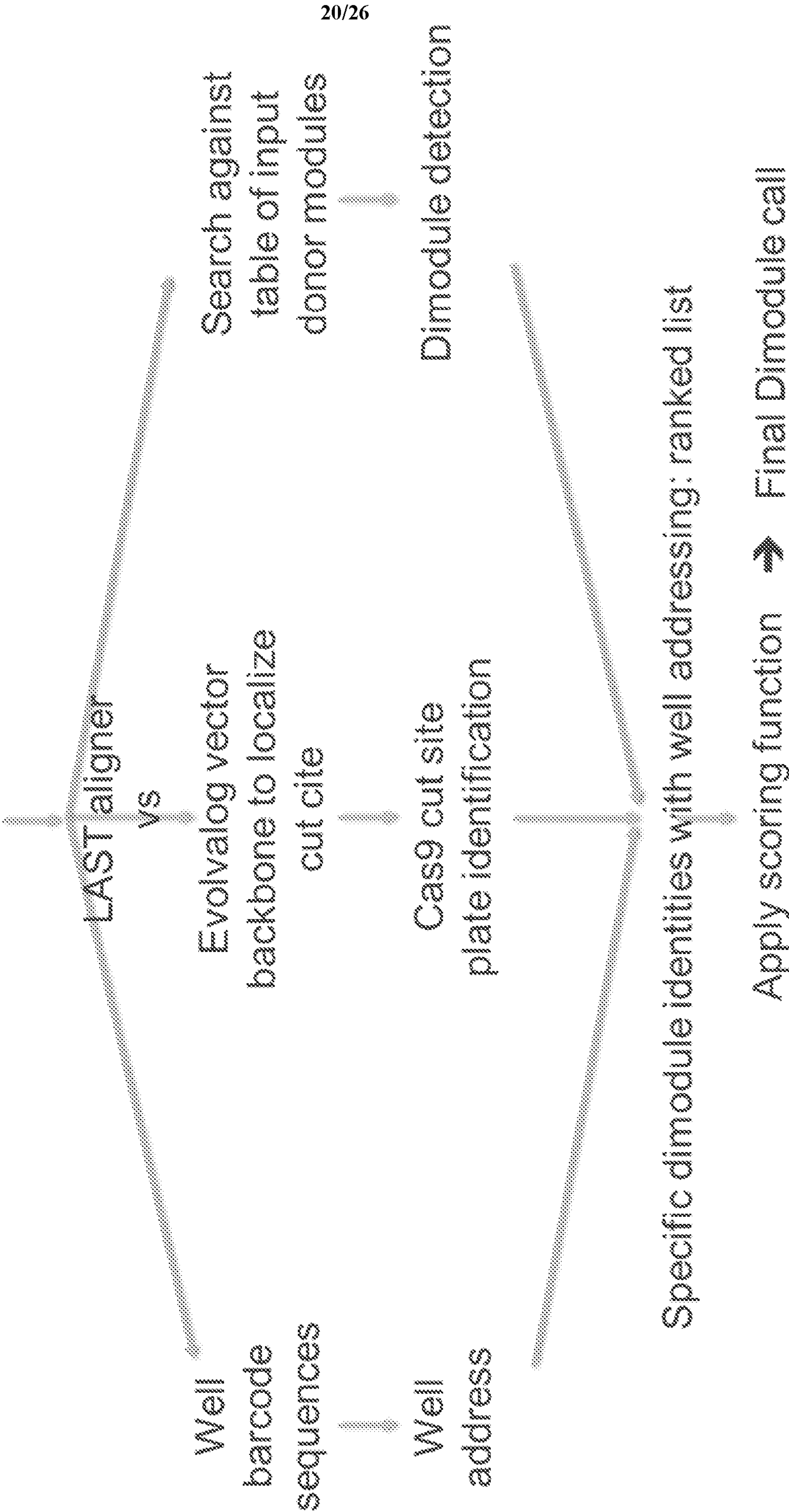


FIG. 5A

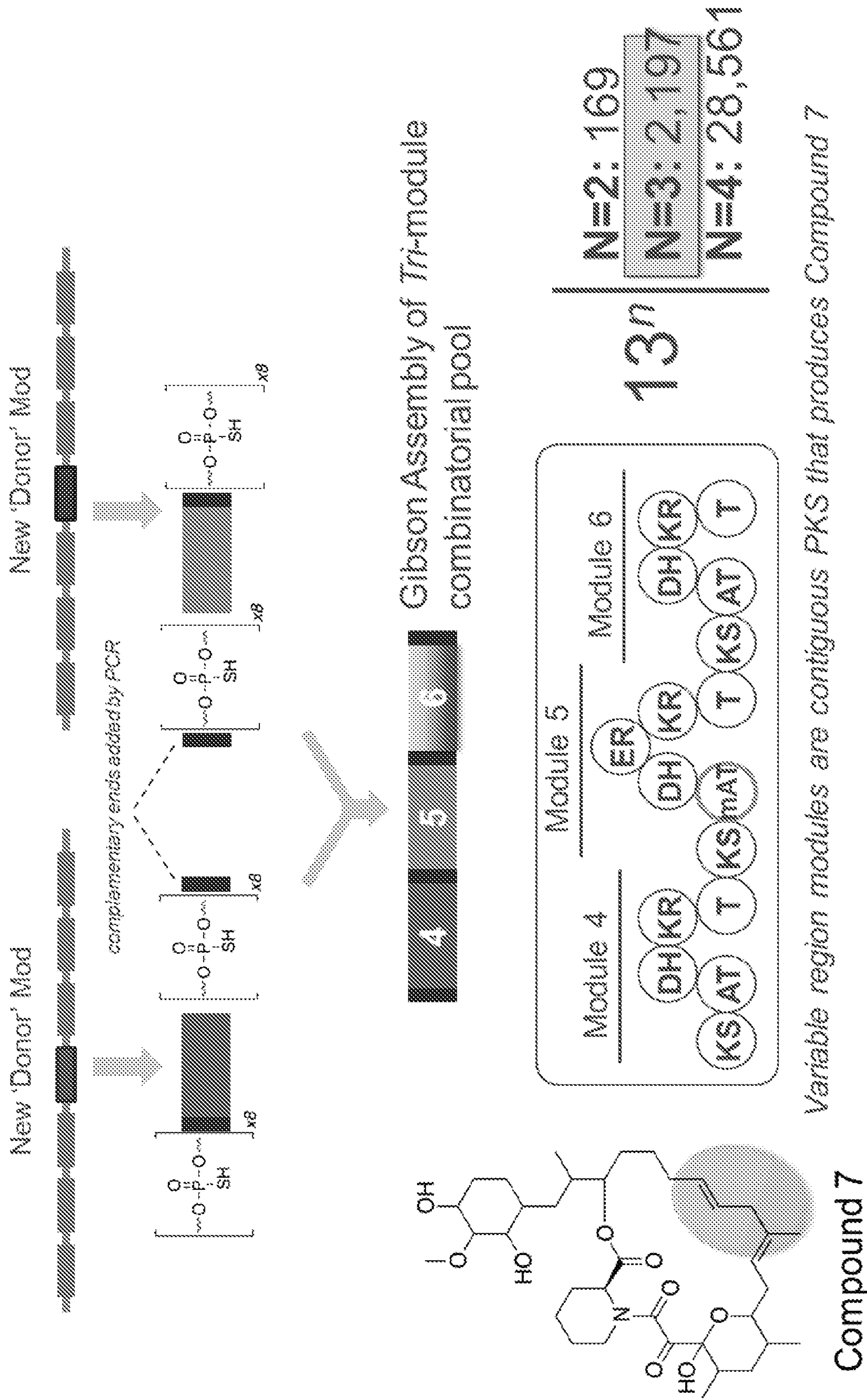


FIG. 5B

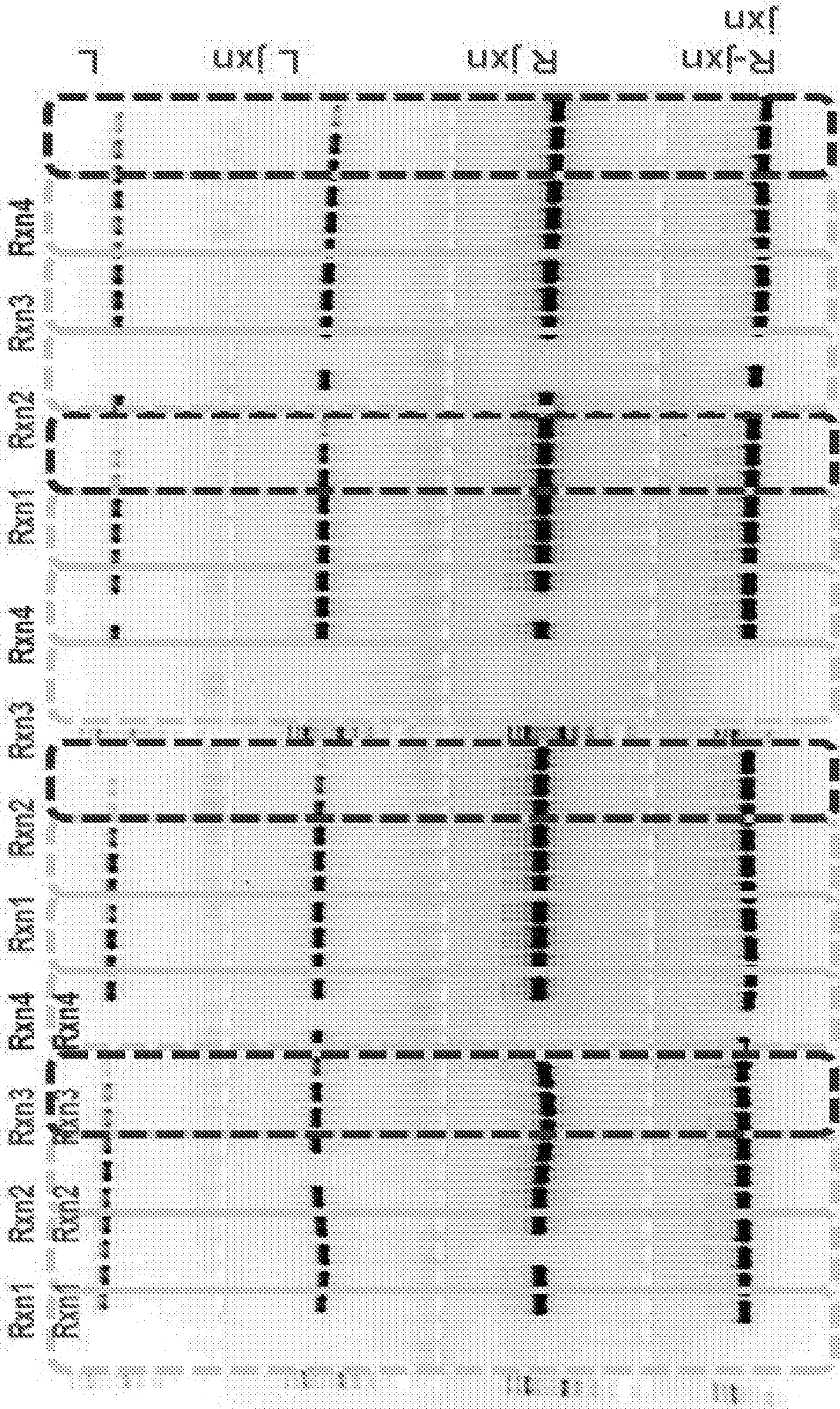


FIG. 6A

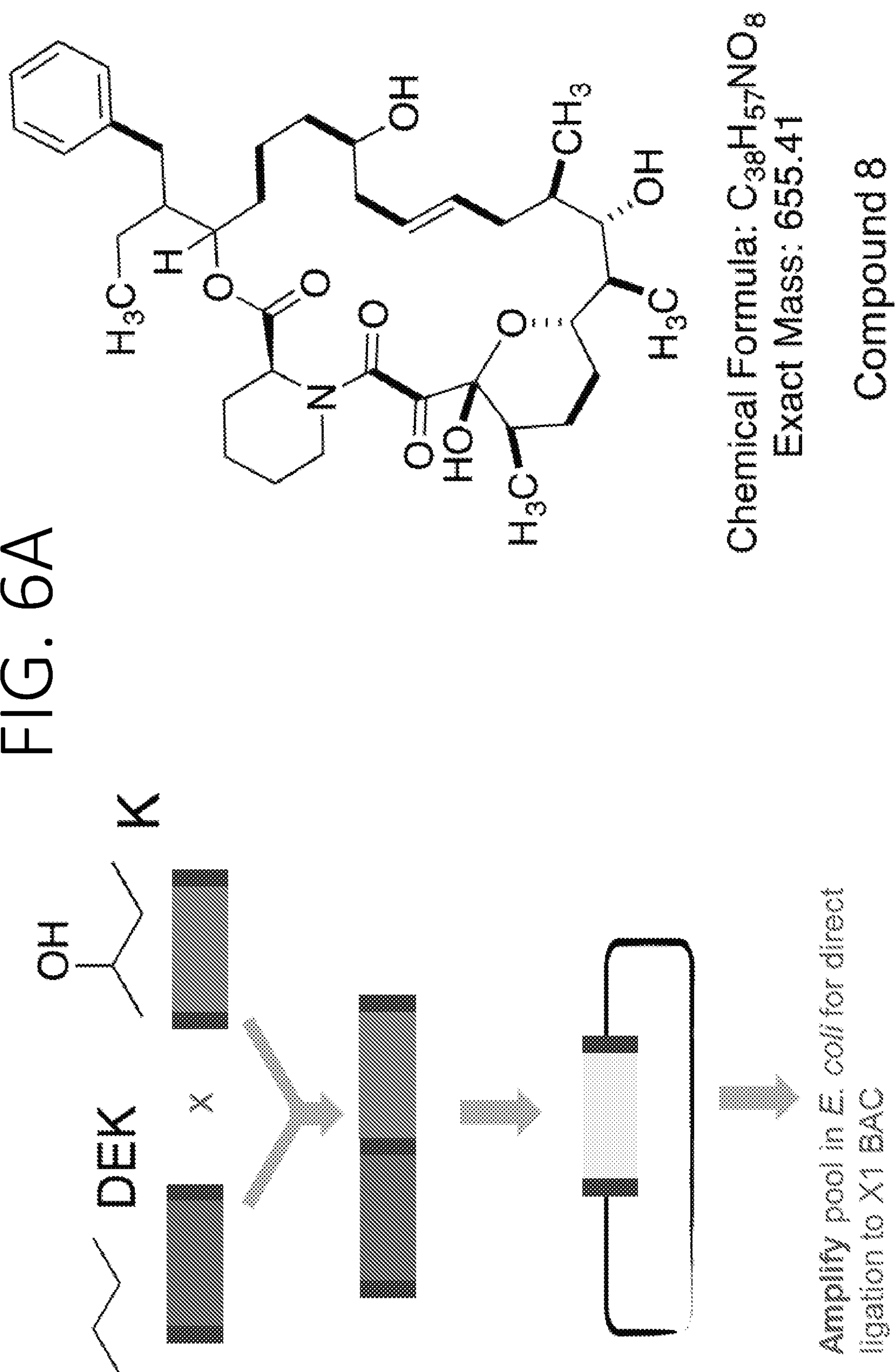


FIG. 6B

WDB 0011752#557-701 RT: 8.97-10.44 AV: 13 NL: 4.58E4
T: FTMS + p NSI Fullms [1975.00-2375.00]
1984.589

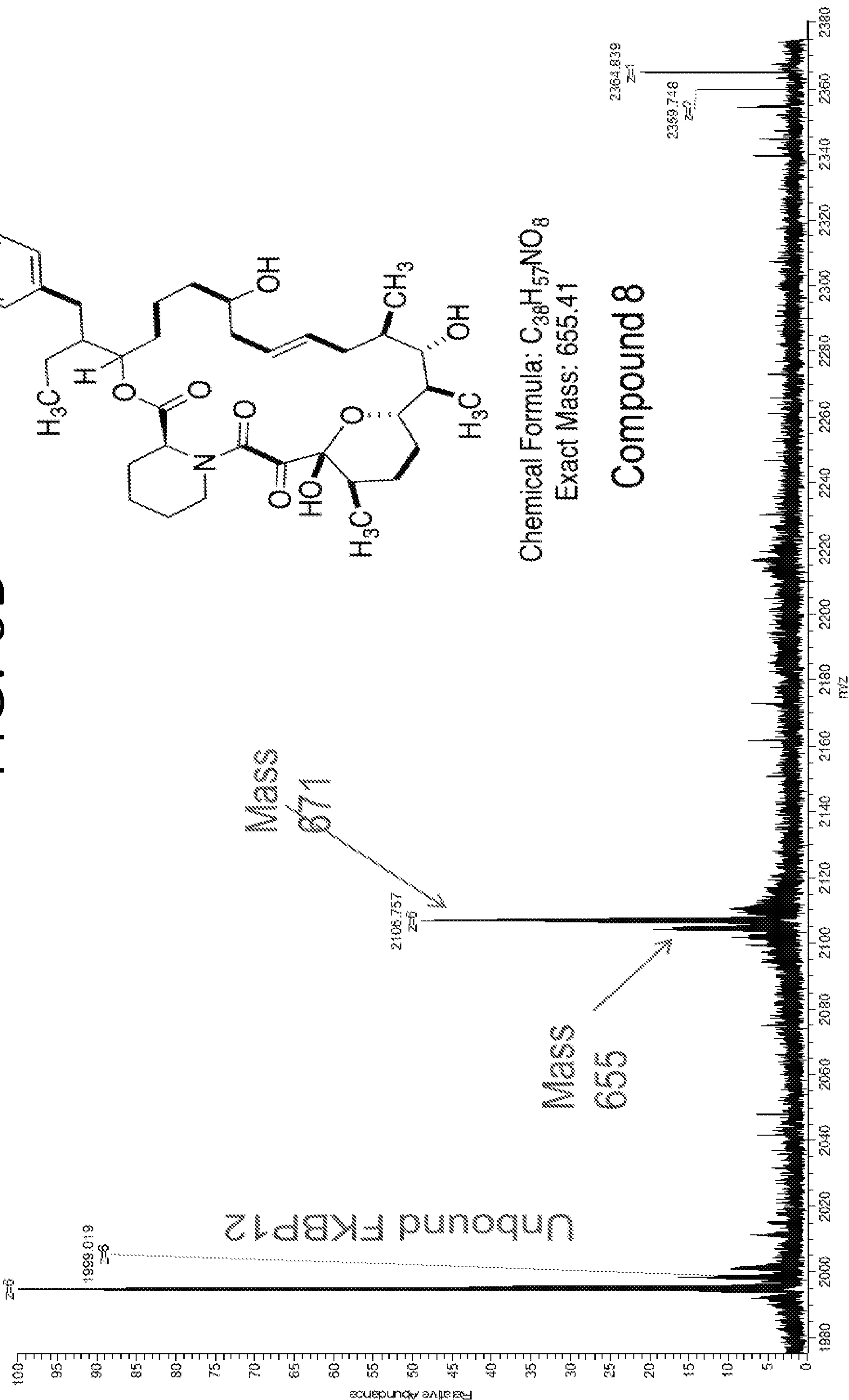


FIG. 7A

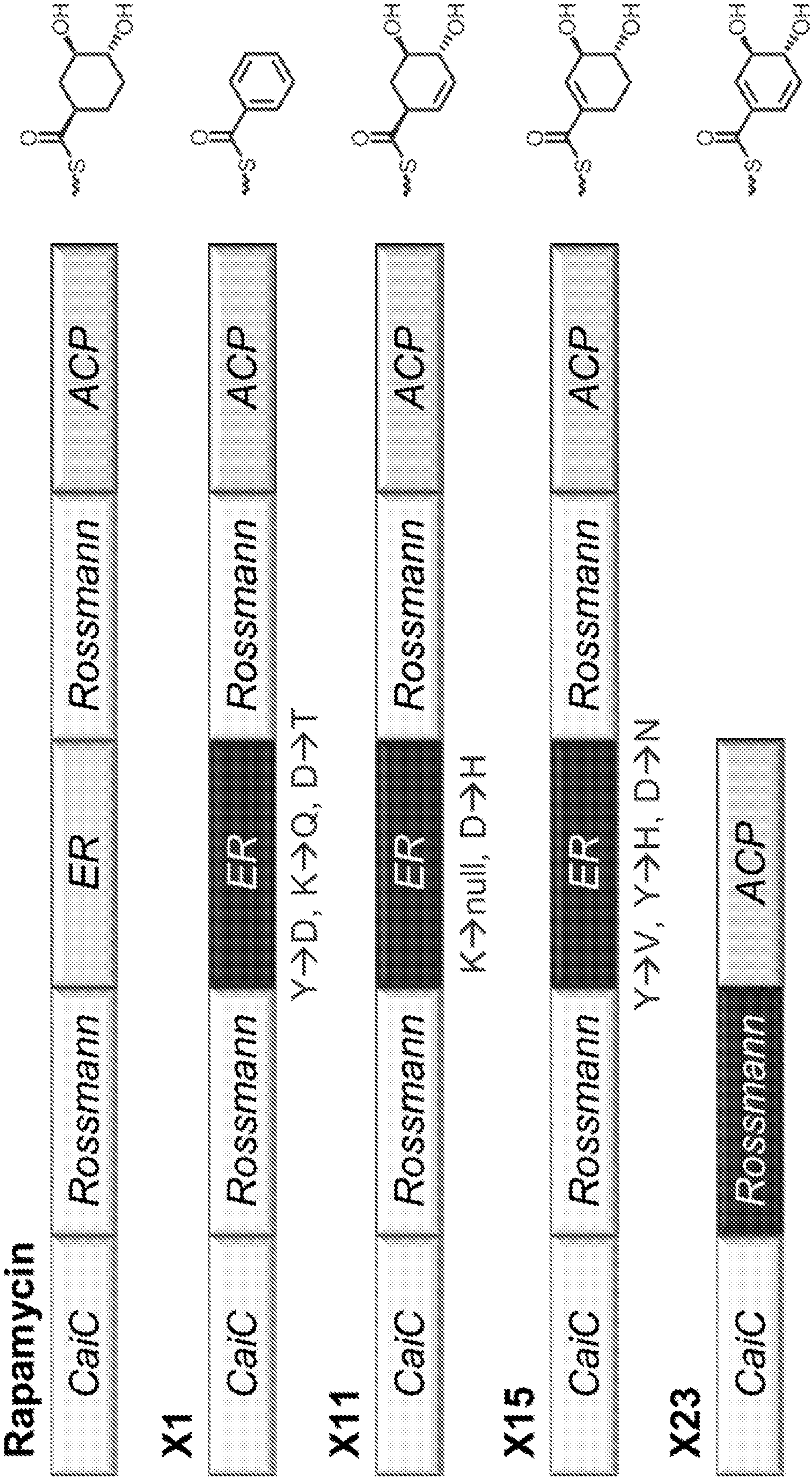


FIG. 7B

