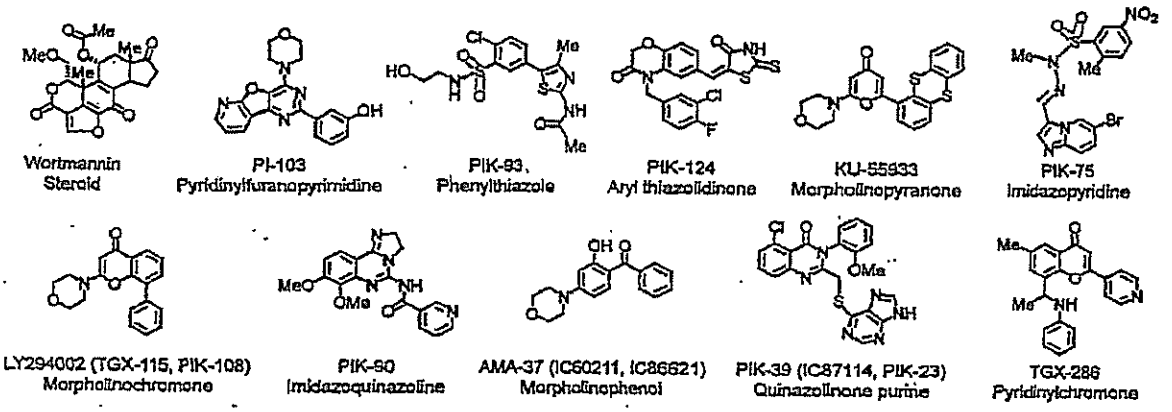

Wortmannin
Steroid
PI-103
Pyridinylfuranopyrimidine
PIK-93,
Phenylthiazole
PIK-124
Aryl thiazolidinone
KU-55933
Morpholinopyranone
PIK-75
Imidazopyridine
LY294002 (TGX-115, PIK-108)
Morpholinochromone
PIK-90
Imidazoquinazoline
AMA-37 (IC60211, IC86621)
Morpholinophenol
PIK-39 (IC87114, PIK-23)
Quinazolinone purine
TGX-286
Pyridinylchromone

FIG. 1

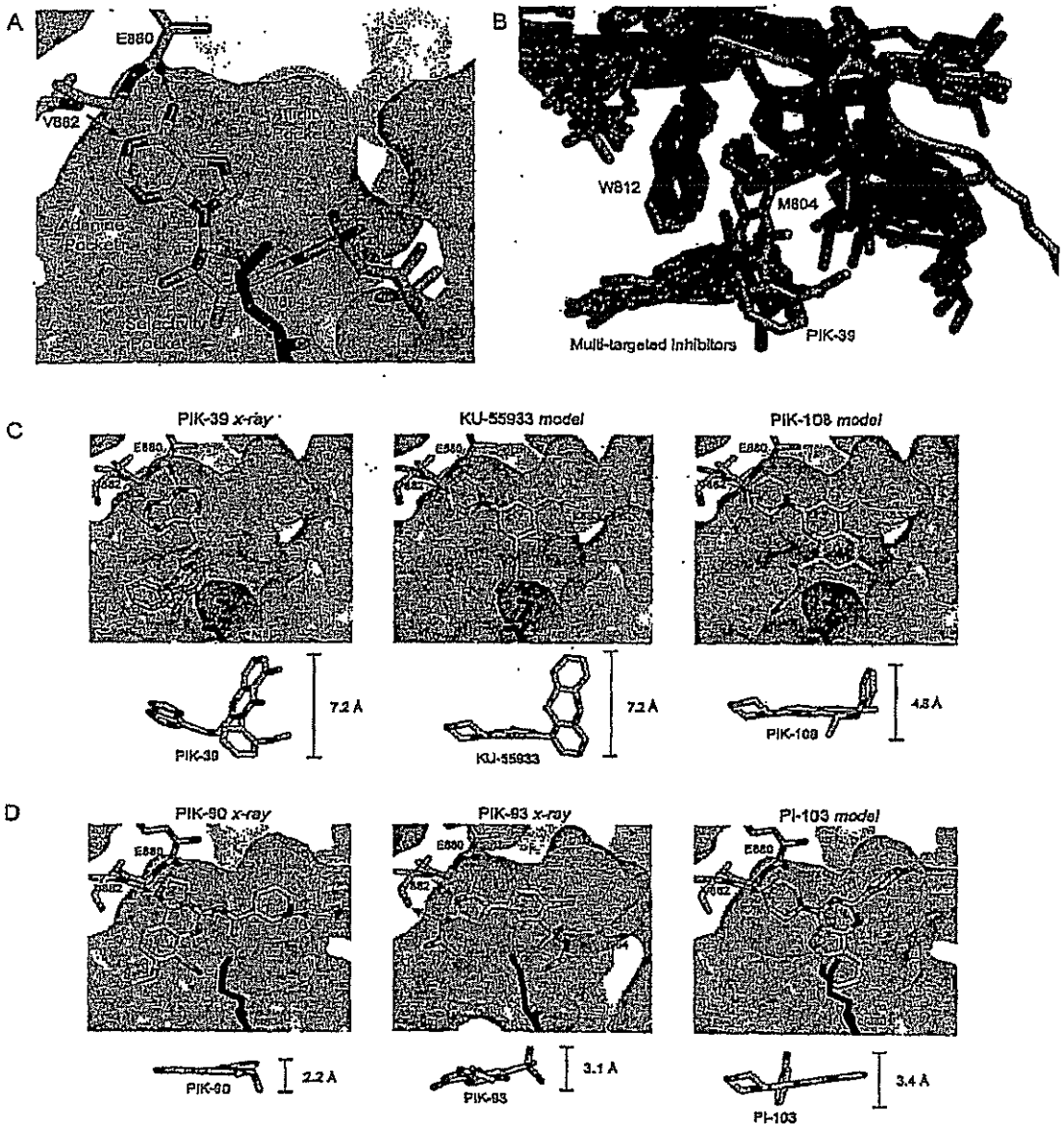

A
E880
V882
Adenine pocket
Affinity pocket
B
W812
M804
PIK-39
Multi-targeted inhibitors
C
PIK-39 x-ray
KU-55933 model
PIK-108 model
7.2 Å
7.2 Å
4.8 Å
PIK-39
KU-55933
PIK-108
D
PIK-90 x-ray
PIK-93 x-ray
PI-103 model
2.2 Å
3.1 Å
3.4 Å
PIK-90
PIK-93
PI-103

FIG. 2

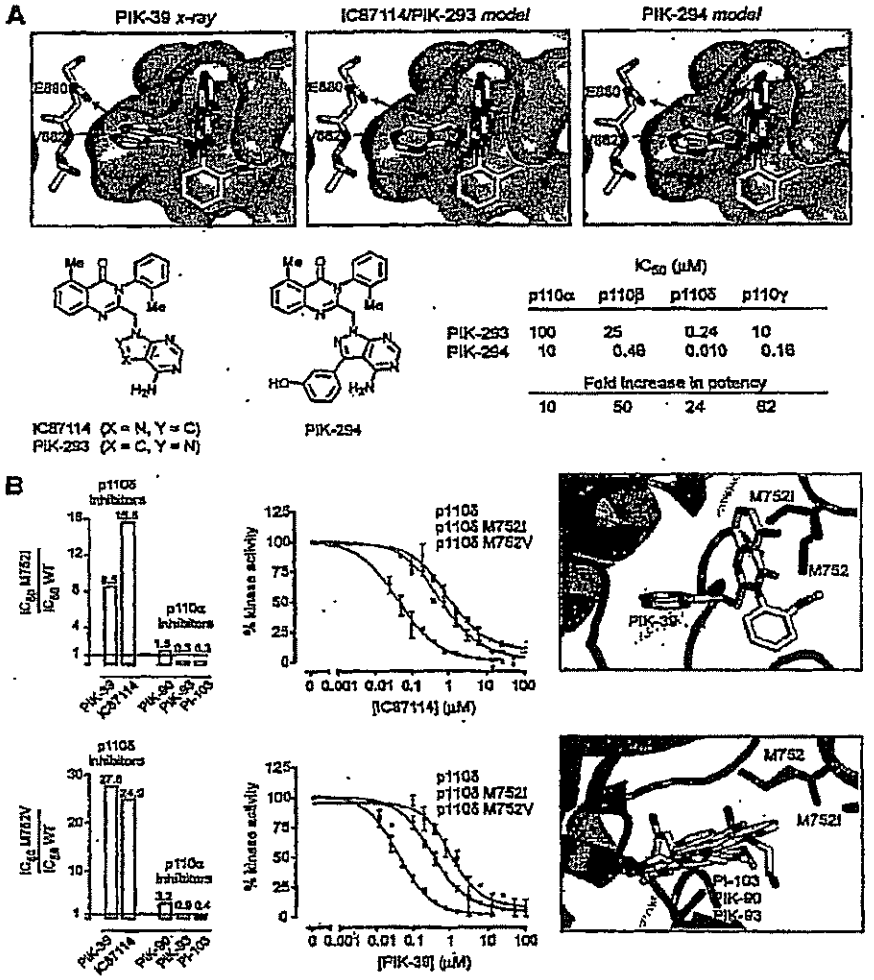
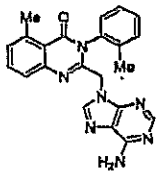

A
PIK-39 x-ray
IC87114/PIK-293 model
PIK-294 model
E880
V882
IC87114 (X = N, Y = C)
PIK-293 (X = C, Y = N)
PIK-294
IC50 (μM)
p110α p110β p110δ p110γ
PIK-293 100 25 0.24 10
PIK-294 10 0.48 0.010 0.16
Fold increase in potency
10 50 24 62
B
p110δ inhibitors
p110α inhibitors
PIK-39
IC87114
PIK-90
PIK-93
PI-103
p110δ
p110δ M752I
p110δ M752V
% kinase activity
[IC87114] (μM)
[PIK-39] (μM)
M752I
M752

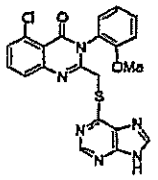
FIG. 3

PI3-K Inhibitor

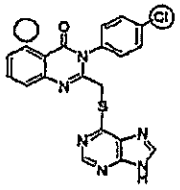
Inactive analog



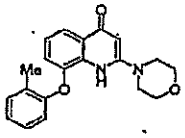
IC87114



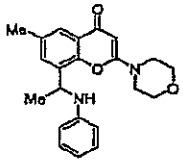
PIK-39



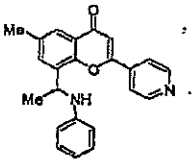
PIK-31



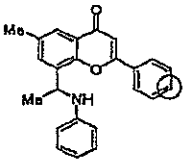
TGX-115



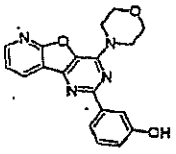
PIK-108



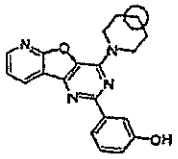
TGX-286



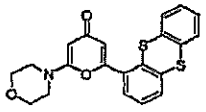
PIK-73



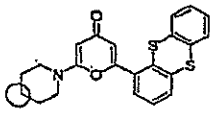
PI-103



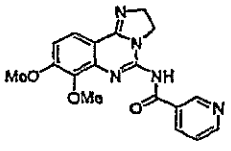
PIK-112



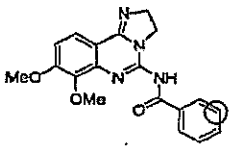
KU-55933



KU-58050



PIK-90



PIK-95

FIG. 4

	PIK23	TGX115	AMA37	PIK39	IC87114	TGX286	PIK75	PIK90	PIK93	PIK108	PI-103	PIK124	KU-55399
PI3Ks													
p110α	*>200*	*61*	*32*	*>200*	*>200*	4.5	0.0058	0.011	0.039	2.6	0.008	0.023	3.3
p110β	*42*	*0.13*	*3.7*	*11*	*16*	0.12	1.3	0.35	0.59	0.057	0.088	1.1	1.2
p110δ	*0.097*	*0.83*	*22*	*0.18*	*0.13*	1	0.51	0.058	0.12	0.26	0.048	0.34	0.72
p110γ	*50*	*100*	*100*	*17*	*61*	10	0.076	0.018	0.016	4.1	0.15	0.054	9.9
PI3KC2α	*>100*	*>100*	*>100*	*>100*	*>100*	>100	~10	0.047	~16	~100	~1	0.14	ND
PI3KC2β	*100*	*50*	*>100*	*100*	*>100*	~100	~1	0.054	0.14	~20	0.026	0.37	ND
PI3KC2γ	*>100*	*100*	*50*	*100*	*>100*	ND	ND	ND	ND	ND	ND	ND	ND
hsVPS34	~50	5.2	>100	>100	>100	3.1	2.6	0.83	0.32	~5	2.3	10	~10
PI4Ks													
PI4KIIα	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
PI4KIIIα	>100	>100	>100	>100	>100	>100	>100	0.83	1.1	~50	>100	>100	>100
PI4KIIIβ	>100	>100	>100	>100	>100	>100	~50	3.1	0.019	>100	~50	>100	>100
PIKKs													
ATR	>100	>100	>100	>100	>100	>100	21	15	17	>100	0.85	2	20
ATM	>100	20	ND	>100	>100	>100	2.3	0.61	0.49	35	0.92	3.9	0.005
DNA-PK	*>100*	*1.2*	*0.27*	*>100*	*>100*	~50	0.002	0.013	0.064	0.12	0.002	1.5	10
mTORC1	*>100*	*>100*	*>100*	*>100*	*>100*	*>100*	*~1*	*1.05*	*1.38*	*~10*	*0.02*	*9*	~20
mTORC2	*>101*	*>100*	*>100*	*>100*	*>100*	*ND*	*~10*	ND	ND	ND	*0.083*	ND	>100
PIPKs													
PI4P5KIα	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
PI4P5KIβ	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
PI5P4KIIβ	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	ND

FIG. 5

	TGX115	AMA37	PIK39	IC87114	TGX286	PIK75	PIK90	PIK93	PI103	PIK124	KU55933
Abl	121.2	126.5	99.9	103.6	100.0	97.9	103.4	99.6	100.8	109.1	100.3
Abl (T315I)	141.2	127.4	110.5	99.4	108.5	121.6	111.3	126.0	108.1	87.5	105.3
Akt1	126.6	125.7	136.4	122.2	114.0	(10)	140.2	112.6	108.5	94.8	114.0
Akt1 (ΔPH)	91.4	77.3	81.0	89.6	94.7	(10)	122.4	122.2	123.1	93.3	116.5
Akt2	98.8	115.0	110.5	116.5	109.7	80.7	119.8	117.4	114.7	114.7	98.2
Akt2 (ΔPH)	104.4	94.4	111.3	117.8	117.3	95.0	108.5	110.7	112.6	98.7	100.2
Akt3	97.6	106.6	94.2	111.0	102.9	(2.9)	113.3	96.4	103.5	93.0	95.1
CamKII	111.4	121.9	122.1	115.4	118.8	119.8	116.1	120.4	127.6	135.5	121.8
CDK1/cyc.B	103.0	114.0	115.5	116.0	120.3	61.6	126.8	124.5	142.3	110.7	101.2
CDK2/cyc.A	105.3	99.7	105.6	102.4	103.1	(1.2)	100.9	98.1	98.5	104.9	97.4
Chk1	119.9	104.0	105.2	103.0	104.1	98.4	102.9	99.7	92.3	107.9	81.4
CK1	99.7	99.2	100.1	98.1	91.3	(3.0)	97.8	100.2	84.8	104.6	94.1
CK2	103.3	106.6	99.6	111.7	111.2	82.2	103.1	113.2	108.1	78.5	105.4
Erk1	96.7	99.3	97.6	93.7	99.0	77.9	98.8	98.6	92.0	97.8	104.6
Erk2	107.7	102.5	109.2	104.7	106.9	94.3	102.0	103.2	98.8	98.0	102.1
FAK	105.5	105.5	106.4	110.1	102.8	(10)	100.0	101.8	101.8	102.8	107.3
Fyn	145.7	131.3	115.7	105.3	111.3	(10)	126.1	127.2	114.2	113.4	116.0
GRK2	113.5	117.3	112.6	118.7	118.1	115.6	120.2	110.9	110.3	87.8	108.6
GSK3β	114.0	107.3	101.5	104.7	96.1	(4.4)	85.6	104.0	105.5	97.6	102.0
Hck	104.9	102.2	101.1	93.0	84.9	(10)	94.7	94.9	94.9	87.2	104.1
Insulin R.	108.4	113.4	113.6	115.7	112.1	99.5	102.8	109.8	106.0	109.9	109.7
JNK1α1	99.9	95.5	92.1	88.5	93.8	97.8	94.2	87.2	83.6	96.9	99.6
JNK2α1	104.8	104.8	116.7	107.1	88.1	88.1	90.5	88.1	81.0	85.7	85.7
JNK2α2	95.4	101.6	90.8	87.7	89.3	86.2	83.1	98.5	76.9	89.3	95.4
IRAK4	112.7	98.9	100.1	93.1	95.0	(0.9)	94.9	95.9	105.6	175.4	74.2
NEK2	125.2	99.1	98.6	114.3	126.4	106.9	103.4	110.1	120.0	118.5	108.5
PKA	105.4	94.0	108.1	108.6	107.3	(10)	103.1	105.6	102.5	104.3	104.1
PKCδ	103.9	104.9	103.9	104.6	104.9	114.3	100.7	103.7	101.2	105.5	103.7
PKCε	108.9	111.9	111.9	114.1	111.5	(10)	105.2	103.4	103.4	106.0	104.6
PDK1	111.2	101.9	97.4	113.4	114.4	111.0	110.4	118.7	107.5	109.4	130.7
PLK1	122.7	118.9	117.4	109.6	107.6	93.7	107.6	111.1	106.2	96.0	84.9
p38	101.2	102.8	108.5	104.1	100.9	100.3	98.5	102.9	99.8	102.6	101.4
Src	111.7	109.0	109.6	113.3	98.4	(10)	103.7	116.1	100.6	102.7	114.7
Src (T338I)	112.8	101.3	97.9	95.7	96.4	80.4	109.5	111.5	113.4	112.5	113.0
WNK1	107.5	108.0	109.6	109.0	119.3	101.1	108.6	110.0	104.1	108.3	104.7
Zap70	123.8	121.1	130.4	110.5	130.0	179.5	115.8	115.4	117.7	100.4	99.3

FIG. 6

```
   1 MPPGVDCPME FWTKEENQSV VVDFLLPTGV YLNFPVSRNA NLSTIKQLLW HRAQYEPLFH
  61 MLSGPEAYVF TCINQTAEQQ ELEDEQRRLC DVQPFLPVLR LVAREGDRVK  KLINSQISLL
 121 IGKGLHEFDS LCDPEVNDFR AKMCQFCEEA AARRQQLGWE AWLQYSFPLQ LEPSAQTWGP
 181 GTLRLPNRAL LVNVKFEGSE ESFTFQVSTK DVPLALMACA LRKKATVFRQ PLVEQPEDYT
 241 LQVNGRHEYL YGNYPLCQFQ YICSCLHSGL TPHLTMVHSS SILAMRDEQS NPAPQVQKPR
 301 AKPPPIPAKK PSSVSLWSLE QPFRIELIQG SKVNADERMK LVVQAGLFHG NEMLCKTVSS
 361 SEVSVCSEPV WKQRLEFDIN ICDLPRMARL CFALYAVIEK AKKARSTKKK SKKADCPIAW
 421 ANLMLFDYKD QLKTGERCLY MWPSVPDEKG ELLNPTGTVR SNPNTDSAAA LLICLPEVAP
 481 HPVYYPALEK ILELGRHSEC VHVTEEEQLQ LREILERRGS GELYEHEKDL VWKLRHEVQE
 541 HFPEALARLL LVTKWNKHED VAQMLYLLCS WPELPVLSAL ELLDFSFPDC HVGSFAIKSL
 601 RKLTDDELFQ YLLQLVQVLK YESYLDCELT KFLLDRALAN RKIGHFLFWH LRSEMHVPSV
 661 ALRFGLILEA YCRGSTHHMK VLMKQGEALS KLKALNDFVK LSSQKTPKPQ TKELMHLCMR
 721 QEAYLEALSH LQSPLDPSTL LAEVCVEQCT FMDSKMKPLW IMYSNEEAGS GGSVGIIFKN
 781 GDDLRQDMLT LQMIQLMDVL WKQEGLDLRM TPYGCLPTGD RTGLIEVVLR SDTIANIQLN
 841 KSNMAATAAF NKDALLNWLK SKNPGEALDR AIEEFTLSCA GYCVATYVLG IGDRHSDNIM
 901 IRESGQLFHI DFGHFLGNFK TKFGINRERV PFILTYDFVH VIQQGKTNNS EKFERFRGYC
 961 ERAYTILRRH GLLFLHLFAL MRAAGLPELS CSKDIQYLKD SLALGKTEEE ALKHFRVKFN
1021 EALRESWKTK VNWLAHNVSK DNRQ
```

FIG. 7

```
1    melenykqpv vlredncrrr rxmkprsaaa slssmelipi efvlptsqrk ckspetallh
61   vaghgnveqm kaqvwlrale tsvaadfyhr lgphhfllly qkkgqwyeiy dkyqvvqtld
121  clrywkathr spgqihlvqr hppseesqaf qrqltaligy dvtdvsnvhd deleftrrgl
181  vtprmaevas rdpklyamhp wvtskplpey lwkkiannci fivihrstts qtikvspddt
241  pgailqsfft kmakkkslmd ipesqseqdf vlrvcgrdey lvgetpiknf qwvrhclkng
301  eeihvvldtp pdpaldevrk eewplvddct gvtgyheqlt ihgkdhesvf tvslwdcdrk
361  frvkirgidi pvlprntdlt vfveaniqhg qqvlcqrrts pkpfteevlw nvwlefsiki
421  kdlpkgalln lqiycgkapa lsskasaesp sseskgkvql lyyvnlllid hrfllrrgey
481  vlhmwqisgk gedqqgsfnad kltsatnpdk ensmsisill dnychpialp khqptpdpeg
541  drvraempnq lrkqleaiia tdplnpltae dkellwhfry eslkhpkayp klfssvkwgq
601  qeivaktyql larrevwdqs aldvgltmql ldcnfsdenv raiavqkles ledddvlhyl
661  lqlvqavkfe pyhdsalarf llkrglrnkr ighflfwflr seiaqsrhyq qrfavileay
721  lrgcgtamlh dftqqvqvie mlqkvtldik slsaekydvs sqvisqlkqk lenlqnsqlp
781  esfrvpydpg lkagalaiek ckvmaskkkp lwlefkcadp talsnetigi ifkhgddlrq
841  dmlilqilri mesiwetesl dicllpygci stgdkigmie ivkdattiak iqqstvgntg
901  afkdevlnhw lkekspteek fqaaverfvy scagycvatf vlgigdrhnd nimitetgnl
961  fhidfghilg nyksflgink ervpfvltpd flfvmgtsgk ktsphfqkfq dicvkaylal
1021 rhhtnlliil fsmmlmtgmp qltskediey irdaltvgkn eedakkyfld qievcrdkgw
1081 tvqfnwflhl vlgikqgekh sa
```

FIG. 8

```
1    MPPRPSSGEL WGIHLMPPRI LVEQLLPNGM IVTLECLREA TLITIKHELF KEARKYPLHQ
61   LLQDESSYIF VSVTQEAERE EFFDETRRLC DLRLFQPFLK VIEPVGNREE KILNREIGFA
121  IGMPVCEFDM VKDPEVQDFR RNILNVCKEA VDLRDLNSPH SRAMYVYPPN VESSPELPKH
181  IYNKLDKGQI IVVIWVIVSP NNDKQKYTLK INHDCVPEQV IAEAIRKKTR SMLLSSEQLK
241  LCVLEYQGKY ILKVCGCDEY FLEKYPLSQY KYIRSCIMLG RMPNLMLMAK ESLYSQLPMD
301  CFTMPSYSRR ISTATPYMNG ETSTKSLWVI NSALRIKILC ATYVNVNIRD IDKIYVRTGI
361  YHGGEPLCDN VNTQRVPCSN PRWNEWLNYD IYIPDLPRAA RLCLSICSVK GRKGAKEEHC
421  PLAWGNINLF DYTDTLVSGK MALNLWPVPH GLEDLLNPIG VTGSNPNKET PCLELEFDWF
481  SSVVKFPDMS VIEEHANWSV SREAGFSYSH AGLSNRLARD NELRENDKEQ LKAISTRDPL
541  SEITEQEKDF LWSHRHYCVT IPEILPKLLL SVKWNSRDEV AQMYCLVKDW PPIKPEQAME
601  LLDCNYPDPM VRGFAVRCLE KYLTDDKLSQ YLIQLVQVLK YEQYLDNLLV RFLLKKALTN
661  QRIGHFFFWH LKSEMHNKTV SQRFGLLLES YCRACGMYLK HLNRQVEAME KLINLTDILK
721  QEKKDETQKV QMKFLVEQMR RPDFMDALQG FLSPLNPAHQ LGNLRLEECR IMSSAKRPLW
781  LNWENPDIMS ELLFQNNEII FKNGDDLRQD MLTLQIIRIM ENIWQNQGLD LRMLPYGCLS
841  IGDCVGLIEV VRNSHTIMQI QCKGGLKGAL QFNSHTLHQW LKDKNKGEIY DAAIDLFTRS
901  CAGYCVATFI LGIGDRHNSN IMVKDDGQLF HIDFGHFLDH KKKKFGYKRE RVPFVLTQDF
961  LIVISKGAQE CTKTREFERF QEMCYKAYLA IRQHANLFIN LFSMMLGSGM PELQSFDDIA
1021 YIRKTLALDK TEQEALEYFM KQMNDAHHGG WTTKMDWIFH TIKQHALN
```

FIG. 9

```
1    MCFSFIMPPA MADILDIWAV DSQIASDGSI PVDFLLPTGI YIQLEVPREA TISYIKQMLW
61   KQVHNYPMFN LLMDIDSYMF ACVNQTAVYE ELEDETRRLC DVRPFLPVLK LVTRSCDPGE
121  KLDSKIGVLI GKGLHEFDSL KDPEVNEFRR KMRKFSEEKI LSLVGLSWMD WLKQTYPPEH
181  EPSIPENLED KLYGGKLIVA VHFENCQDVF SFQVSPNMNP IKVNELAIQK RLTIHGKEDE
241  VSPYDYVLQV SGRVEYVFGD HPLIQFQYIR NCVMNRALPH FILVECCKIK KMYEQEMIAI
301  EAAINRNSSN LPLPLPPKKT RIISHVWENN NPFQIVLVKG NKLNTEETVK VHVRAGLFHG
361  TELLCKTIVS SEVSGKNDHI WNEPLEFDIN ICDLPRMARL CFAVYAVLDK VKTKKSTKTI
421  NPSKYQTIRK AGKVHYPVAW VNTMVFDFKG QLRTGDIILH SWSSFPDELE EMLNPMGTVQ
481  TNPYTENATA LHVKFPENKK QPYYYPPFDK IIEKAAEIAS SDSANVSSRG GKKFLPVLKE
541  ILDRDPLSQL CENEMDLIWT LRQDCREIFP QSLPKLLLSI KWNKLEDVAQ LQALLQIWPK
601  LPPREALELL DFNYPDQYVR EYAVGCLRQM SDEELSQYLL QLVQVLKYEP FLDCALSRFL
661  LERALGNRRI GQFLFWHLRS EVHIPAVSVQ FGVILEAYCR GSVGHMKVLS KQVEALNKLK
721  TLNSLIKLNA VKLNRAKGKE AMHTCLKQSA YREALSDLQS PLNPCVILSE LYVEKCKYMD
781  SKMKPLWLVY NNKVFGEDSV GVIFKNGDDL RQDMLTLQML RLMDLLWKEA GLDLRMLPYG
841  CLATGDRSGL IEVVSTSETI ADIQLNSSNV AAAAAFNKDA LLNWLKEYNS GDDLDRAIEE
901  FTLSCAGYCV ASYVLGIGDR HSDNIMVKKT GQLFHIDFGH ILGNFKSKFG IKREKVPFIL
961  TYDFIHVIQQ GKTGNTEKFG RFRQCCEDAY LILRRHGNLF ITLFALMLTA GLPELTSVKD
1021 IQYLKDSLAL GKSEEEALKQ FKQKFDEALR ESWTTKVNWM AHTVRKDYRS
```

FIG. 10