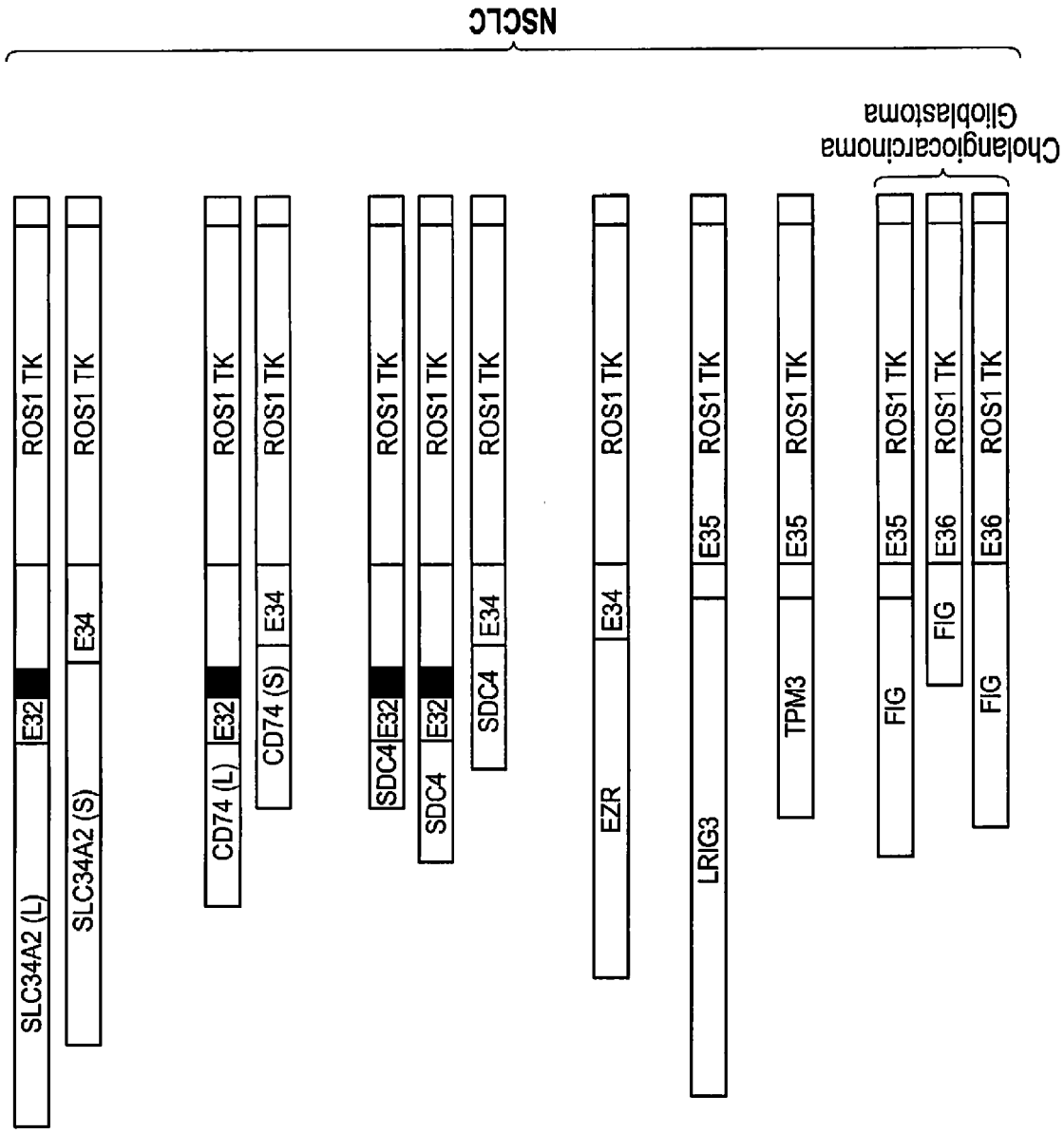

NSCLC
Cholangiocarcinoma
Glioblastoma
SLC34A2 (L)
E32
ROS1 TK
SLC34A2 (S)
E34
ROS1 TK
CD74 (L)
E32
CD74 (S)
E34
SDC4
E32
SDC4
E34
EZR
LRIG3
E35
TPM3
FIG
E36

FIG. 1

FIG. 2

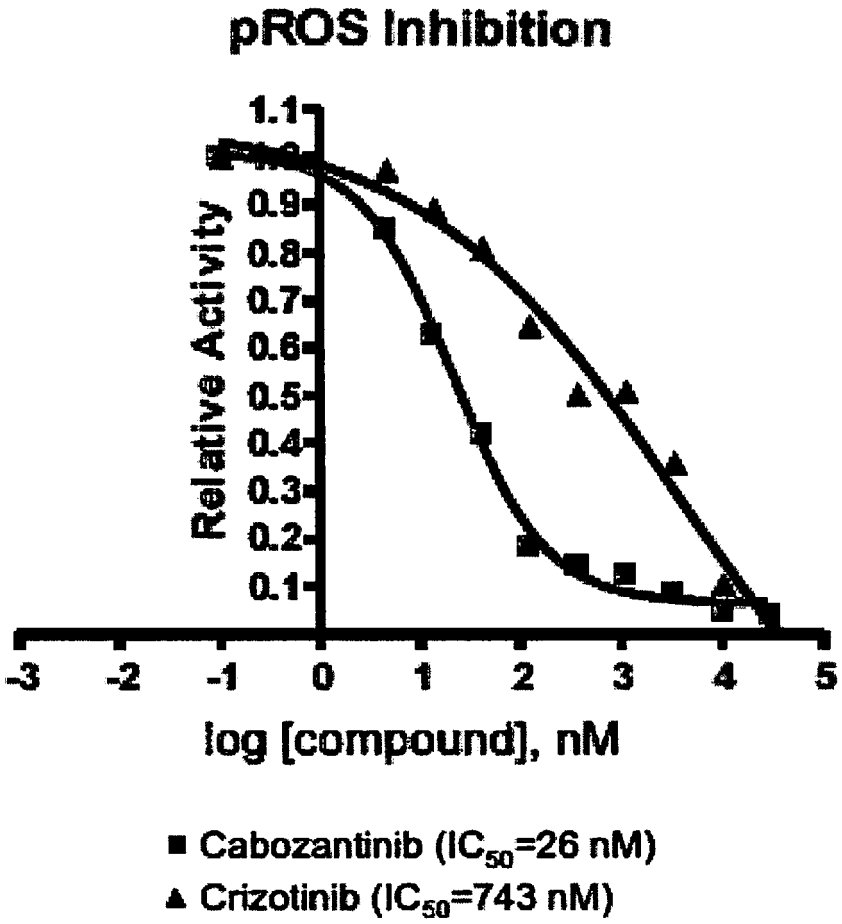

pROS Inhibition
Relative Activity
1.1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
-3
-2
-1
0
1
2
3
4
5
log [compound], nM
Cabozantinib (IC50=26 nM)
Crizotinib (IC50=743 nM)

FIG. 3

```
MKNIYCLIPK LVNFATLGCL WISVVQCTVL NSCLKSCVTN LGQQLDLGTP HNLSEPCIQG CHFWNSVDQK
        10         20         30         40         50         60         70
NCALKCRESC EVGCSSAEGA YEEEVLENAD LPTAPFASSI GSHNMTLRWK SANFSGVKYI IQWKYAQLLG
        80         90        100        110        120        130        140
SWTYTKTVSR PSYVVKPLHP FTEYIFRVVW IFTAQLQLYS PPSPSYRTHP HGVPETAPLI RNIESSSPDT
       150        160        170        180        190        200        210
VEVSWDPPQF PGGPILGYNL RLISKNQKLD AGTQRTSFQF YSTLPNTIYR FSIAAVNEVG EGPEAESSIT
       220        230        240        250        260        270        280
TSSSAVQQEE QWLFLSRKTS LRKRSLKHLV DEAHCLRLDA IYHNITGISV DVHQQIVYFS EGTLIWAKKA
       290        300        310        320        330        340        350
ANMSDVSDLR IFYRGSGLIS SISIDWLYQR MYFIMDELVC VCDLENCSNI EEITPPSISA PQKIVADSYN
       360        370        380        390        400        410        420
GYVFYLLRDG IYRADLPVPS GRCAEAVRIV ESCTLKDFAI KPQAKRIIYF NDTAQVFMST FLDGSASHLI
       430        440        450        460        470        480        490
LPRIPFADVK SFACENNDFL VTDGKVIFQQ DALSFNEFIV GCDLSHIEEF GFGNLVIFGS SSQLHPLPGR
       500        510        520        530        540        550        560
PQELSVLFGS HQALVQWKPP ALAIGANVIL ISDIIELFEL GPSAWQNWTY EVKVSTQDPP EVTHIFLNIS
       570        580        590        600        610        620        630
GTMLNVPELQ SAMKYKVSVR ASSPKRPGPW SEPSVGTTLV PASEPPFIMA VKEDGLWSKP LNSFGPGEFL
       640        650        660        670        680        690        700
SSDIGNVSDM DWYNNSLYYS DTKGDVFVWL LNGTDISENY HLPSIAGAGA LAFEWLGHFL YWAGKTYVIQ
       710        720        730        740        750        760        770
RQSVLTGHTD IVTHVKLLVN DMVVDSVGGY LYWTTLYSVE STRLNGESSL VLQTQPWFSG KKVIALTLDL
       780        790        800        810        820        830        840
SDGLLYWLVQ DSQCIHLYTA VLRGQSTGDT TITEFAAWST SEISQNALMY YSGRLFWING FRIITTQEIG
       850        860        870        880        890        900        910
QKTSVSVLEP ARFNQFTIIQ TSLKPLPGNF SFTPKVIPDS VQESSFRIEG NASSFQILWN GPPAVDWGVV
       920        930        940        950        960        970        980
FYSVEFSAHS KFLASEQHSL PVFTVEGLEP YALFNLSVTP YTYWGKGPKT SLSLRAPETV PSAPENPRIF
       990       1000       1010       1020       1030       1040       1050
ILPSGKCCNK NEVVVEFRWN KPKHENGVLT KFEIFYNISN QSITNKTCED WIAVNVTPSV MSFQLEGMSP
      1060       1070       1080       1090       1100       1110       1120
RCFIAFQVRA FTSKGPGPYA DVVKSTTSEI NPFPHLITLL GNKIVFLDMD QNQVVWTFSA ERVISAVCYT
      1130       1140       1150       1160       1170       1180       1190
ADNEMGYYAE GDSLFLLHLH NRSSSELFQD SLVFDITVIT IDWISRHLYF ALKESQNGMQ VFDVDLEHKV
      1200       1210       1220       1230       1240       1250       1260
KYPREVKIHN RNSTIISFSV YPLLSRLYWT EVSNFGYQMF YYSIISHTLH RILQPTATNQ QNKRNQCSCN
      1270       1280       1290       1300       1310       1320       1330
VTEFELSGAM AIDTSNLEKP LIYFAKAQEI WAMDLEGCQC WRVITVPAML AGKTLVSLTV DGDLIYWIIT
      1340       1350       1360       1370       1380       1390       1400
AKDSTQIYQA KKGNGAIVSQ VKALRSRHIL AYSSVMQPFP DKAFLSLASD TVEPTILNAT NTSLTIRLPL
      1410       1420       1430       1440       1450       1460       1470
AKTNLTWYGI TSPTPTYLVY YAEVNDRKNS SDLKYRILEF QDSIALIEDL QPFSTYMIQI AVKNYYSDPL
      1480       1490       1500       1510       1520       1530       1540
EHLPPGKEIW GKTKNGVPEA VQLINTTVRS DTSLIISWRE SHKPNGPKES VRYQLAISHL ALIPETPLRQ
      1550       1560       1570       1580       1590       1600       1610
SEFPNGRLTL LVTRLSGGNI YVLKVLACHS EEMWCTESHP VTVEMFNTPE KPYSLVPENT SLQFNWKAPL
      1620       1630       1640       1650       1660       1670       1680
NVNLIRFWVE LQKWKYNEFY HVKTSCSQGP AYVCNITNLQ PYTSYNVRVV VVYKTGENST SLPESFKTKA
      1690       1700       1710       1720       1730       1740       1750
GVPNKPGIPK LLEGSKNSIQ WEKAEDNGCR ITYYILEIRK STSNNLQNQN LRWKMTFNGS CSSVCTWKSK
      1760       1770       1780       1790       1800       1810       1820
NLKGIFQFRV VAANNLGFGE YSGISENIIL VGDDFWIPET SFILTIIVGI FLVVTIPLTF VWHRRLKNQK
      1830       1840       1850       1860       1870       1880       1890
SAKEGVTVLI NEDKELAELR GLAAGVGLAN ACYAIHTLPT QEEIENLPAF PREKLTLRLL LGSGAFGEVY
      1900       1910       1920       1930       1940       1950       1960
EGTAVDILGV GSGEIKVAVK TLKKGSTDQE KIEFLKEAHL MSKFNHPNIL KQLGVCLLNE PQYIILELME
      1970       1980       1990       2000       2010       2020       2030
GGDLLTYLRK ARMATFYGPL LTLVDLVDLC VDISKGCVYL ERMHFIHRDL AARNCLVSVK DYTSPRIVKI
      2040       2050       2060       2070       2080       2090       2100
GDFGLARDIY KNDYYRKRGE GLLPVRWMAP ESLMDGIFTT QSDVWSFGIL IWEILTLGHQ PYPAHSNLDV
      2110       2120       2130       2140       2150       2160       2170
LNYVQTGGRL EPPRNCPDDL WNLMTQCWAQ EPDQRPTFHR IQDQLQLFRN FFLNSIYKSR DEANNSGVIN
      2180       2190       2200       2210       2220       2230       2240
ESFEGEDGDV ICLNSDDIMP VALMETKNRE GLNYMVLATE CGQGEEKSEG PLGSQESESC GLRKEEKEPH
      2250       2260       2270       2280       2290       2300       2310
ADKDFCQEKQ VAYCPSGKPE GLNYACLTHS GYGDGSD
      2320       2330       2340    2347
```

– Human ROS1 Protein UniProt Accession No. P08922: SEQ ID. NO: 1

FIG. 4

ROS1 Kinase Domain SEQ ID NO: 2

Leu Thr Leu Arg Leu Leu Leu Gly Ser Gly Ala Phe Gly Glu Val Tyr Glu
Gly Thr Ala Val Asp Ile Leu Gly Val Gly Ser Gly Glu Ile Lys Val Ala
Val Lys Thr Leu Lys Lys Gly Ser Thr Asp Gln Glu Lys Ile Glu Phe Leu
Lys Glu Ala His Leu Met Ser Lys Phe Asn His Pro Asn Ile Leu Lys Gln
Leu Gly Val Cys Leu Leu Asn Glu Pro Gln Tyr Ile Ile Leu Glu Leu Met
Glu Gly Gly Asp Leu Leu Thr Tyr Leu Arg Lys Ala Arg Met Ala Thr Phe
Tyr Gly Pro Leu Leu Thr Leu Val Asp Leu Val Asp Leu Cys Val Asp Ile
Ser Lys Gly Cys Val Tyr Leu Glu Arg Met His Phe Ile His Arg Asp Leu
Ala Ala Arg Asn Cys Leu Val Ser Val Lys Asp Tyr Thr Ser Pro Arg Ile
Val Lys Ile Gly Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asn Asp Tyr
Tyr Arg Lys Arg Gly Glu Gly Leu Leu Pro Val Arg Trp Met Ala Pro Glu
Ser Leu Met Asp Gly Ile Phe Thr Thr Gln Ser Asp Val Trp Ser Phe Gly
Ile Leu Ile Trp Glu Ile Leu Thr Leu Gly His Gln Pro Tyr Pro Ala His
Ser Asn Leu Asp Val Leu Asn Tyr Val Gln Thr Gly Gly Arg Leu Glu Pro
Pro Arg Asn Cys Pro Asp Asp Leu Trp Asn Leu Met Thr Gln Cys Trp Ala
Gln Glu Pro Asp Gln Arg Pro Thr Phe His Arg Ile Gln Asp Gln Leu Gln
Leu Phe Arg Asn Phe Phe