Supporting information

Protein kinase CK-1 inhibitors as new potential drugs for Amyotrophic Lateral Sclerosis

Irene G. Salado,[1] Miriam Redondo,[1] Murilo L. Bello,[1,2] Concepción Perez,[1] Nicole F. Liachko,[3,4] Brian C. Kraemer,[3,4,5] Laetitia Miguel,[6,7] Magalie Lecourtois,[6,7] Carmen Gil,[1] Ana Martinez,[1,*] Daniel I. Perez[1,*]

[1] Instituto de Química Médica-CSIC, Juan de la Cierva 3, 28006 Madrid, SPAIN.
[2] Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, 21949-900, Rio de Janeiro, RJ, BRAZIL.
[3] Geriatric Research Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA.
[4] Department of Medicine, Gerontology Division, University of Washington, Seattle, WA 98104, USA.
[5] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195, USA
[6] Inserm, U1079, Rouen, FRANCE
[7] Normandie Univ (University of Rouen), IRIB Institute for Research and Innovation in Biomedicine, Rouen, FRANCE

Correspondence to:
Dr. Daniel I. Perez (dperez@iqm.csic.es) or Prof Ana Martinez (amartinez@iqm.csic.es);
Tel.: +34 91562900, Fax: +34 915644852

Table S1.- Elemental analyses of *N*-(benzothiazolyl)-phenylacetamides and related compounds.

Table S2.- Kinase profiling for compound **20** (IGS-2.7). Data are expressed in % kinase activity at a concentration of 10 μM for the tested compound.

Table S3.- Kinase profiling for compound **24** (IGS-2.37). Data are expressed in % kinase activity at a concentration of 10 μM for the tested compound.

Figure S1.- Docked poses of selected CK-1δ inhibitors, compounds **24** (A) and **34** (B), on their target (PDB Code: 3UYS).

Figure S2.- Linear correlation between experimental and reported permeability of commercial drugs using the PAMPA-BBB assay.

Table S1. Elemental analysis

Compound	Molecular Formula	Calculated				Found			
		%C	%H	%N	%S	%C	%H	%N	%S
1	$C_{14}H_{13}ClN_2O_2S$	54.46	4.24	9.07	10.38	54.47	4.21	9.06	10.29
2	$C_{16}H_{14}ClN_3O$	64.11	4.71	14.02		63.70	4.35	13.51	
3	$C_{16}H_{14}ClN_3O$	64.11	4.71	14.02		64.02	4.80	13.95	
4	$C_{10}H_8ClN_3OS$	47.34	3.18	15.56	12.64	47.98	3.39	16.80	12.51
5	$C_{12}H_{10}ClN_3O$	58.19	4.07	16.97		58.20	4.09	16.72	
6	$C_{12}H_{10}ClN_3O$	58.19	4.07	16.97		58.10	4.02	16.85	
7	$C_{15}H_{11}ClN_2O_2$	62.84	3.87	9.77		62.78	3.59	9.64	
8	$C_{16}H_{14}N_2O_3$	68.07	5.00	9.92		67.87	4.69	9.74	
9	$C_{15}H_{10}ClNO_2S$	59.31	3.32	4.61		59.56	3.33	4.36	
10	$C_{16}H_{11}F_3N_2O_2S$	54.54	3.15	7.95	9.10	54.21	2.99	7.86	8.98
11	$C_{17}H_{15}F_3N_2OS$	57.94	4.29	7.95	9.10	57.85	4.12	7.70	9.05
12	$C_{21}H_{16}N_2OS$	73.23	4.68	8.13	9.31	73.50	4.72	8.33	9.26
13	$C_{23}H_{20}N_2O_2S$	71.11	5.19	7.21	8.25	71.12	5.31	7.20	8.43
14	$C_{16}H_{13}ClN_2OS$	60.66	4.14	8.84	10.12	60.62	4.09	9.01	9.99
15	$C_{22}H_{18}N_2OS$	73.71	5.06	7.82	8.95	74.00	5.08	7.54	8.76
16	$C_{16}H_{12}F_3N_3O_2S$	52.31	3.29	11.44	8.73	50.27	4.08	11.54	8.85
17	$C_{16}H_{13}ClN_2OS$	60.66	4.14	8.84	10.12	60.90	4.15	8.83	9.87
18	$C_{16}H_{13}ClN_2OS$	60.66	4.14	8.84	10.12	60.90	4.31	8.92	10.12
19	$C_{15}H_{10}Cl_2N_2OS$	53.42	2.99	8.31	9.51	53.74	3.10	8.55	9.41
20	$C_{16}H_{10}ClF_3N_2OS$	51.83	2.72	7.56	8.64	51.72	2.83	7.27	8.56
21	$C_{16}H_{13}ClN_2O_2S$	57.74	3.94	8.42	9.63	57.46	3.90	8.27	9.44
22	$C_{16}H_{10}ClF_3N_2O_2S$	49.68	2.61	7.24	8.29	49.81	2.45	7.32	7.99
23	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	8.08	9.25	59.02	4.18	8.13	8.96
24	$C_{16}H_{10}ClF_3N_2OS$	51.83	2.72	7.56	8.65	51.68	2.54	7.50	8.38
25	$C_{16}H_{13}ClN_2O_2S$	57.74	3.94	8.42	9.63	57.68	3.97	8.42	9.69
26	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	8.08	9.25	58.75	4.31	8.21	9.16
27	$C_{16}H_{10}ClF_3N_2OS$	51.83	2.72	7.56	8.65	52.00	2.71	7.55	8.49
28	$C_{16}H_{13}ClN_2O_2S$	57.74	3.94	8.42	9.63	57.74	3.83	8.20	9.37
29	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	8.08	9.25	58.69	4.22	7.94	9.02
30	$C_{16}H_{13}BrN_2O_2S$	50.94	3.47	7.43	8.50	51.08	3.60	7.31	8.29
31	$C_{16}H_{13}ClN_2O_2S$	57.74	3.94	8.42	9.63	57.69	4.02	8.25	9.48
32	$C_{16}H_{13}FN_2O_2S$	60.75	4.14	8.86	10.14	60.54	3.99	8.74	9.88
33	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97	10.26	65.37	5.40	8.79	10.36

34	$C_{17}H_{13}F_3N_2O_2S$	55.73	3.58	7.65	8.75	56.02	3.61	7.37	8.75
35	$C_{17}H_{16}N_2O_3S$	62.18	4.91	8.53	9.76	62.05	4.79	8.52	10.39
36	$C_{17}H_{13}F_3N_2O_3S$	53.40	3.43	7.33	8.39	53.22	3.28	7.21	8.09
37	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18	9.36	63.19	5.25	8.23	9.35
38	$C_{17}H_{13}F_3N_2O_2S$	55.73	3.58	7.65	8.75	55.80	3.41	7.66	9.02
39	$C_{17}H_{16}N_2O_3S$	62.18	4.91	8.53	9.76	62.53	4.68	8.41	10.00
40	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18	9.36	63.09	5.32	8.19	9.64
41	$C_{17}H_{10}F_6N_2OS$	50.50	2.49	6.93	7.93	50.63	2.71	7.08	8.16
42	$C_{17}H_{13}F_3N_2O_2S$	55.73	3.58	7.65	8.75	55.48	3.31	7.44	8.97
43	$C_{17}H_{16}N_2O_3S$	62.18	4.91	8.53	9.76	62.38	5.10	8.32	9.66
44	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18	9.36	62.95	5.43	8.22	9.61
45	$C_{15}H_{12}N_2OS$	67.14	4.51	10.44	11.95	67.02	4.63	10.31	11.74
46	$C_{16}H_{11}F_3N_2OS$	57.14	3.30	8.33	9.53	57.30	3.28	8.09	9.80
47	$C_{16}H_9F_3Cl_2N_2OS$	47.42	2.24	6.91	7.91	47.28	2.30	7.04	7.38
48	$C_{16}H_{12}Cl_2N_2O_2S$	52.33	3.29	7.63	8.73	52.05	3.09	7.38	8.53
49	$C_{17}H_{14}Cl_2N_2O_2S$	53.55	3.70	7.35	8.41	53.36	3.68	7.09	8.41
50	$C_{16}H_9Cl_2F_3N_2O_2S$	45.62	2.15	6.65	7.62	45.38	1.97	6.48	7.47
51	$C_{18}H_{15}F_3N_2O_3S$	54.54	3.81	7.07	8.09	54.82	3.93	7.38	8.25
52	$C_{19}H_{17}F_3N_2O_5S$	51.58	3.87	6.33	7.25	51.66	3.90	6.45	7.47
53	$C_{19}H_{20}N_2O_5S$	58.75	5.19	7.21	8.25	58.95	5.33	7.38	8.40
54	$C_{20}H_{22}N_2O_5S$	59.69	5.51	6.96	7.97	59.46	5.48	7.05	8.00
55	$C_{19}H_{17}F_3N_2O_4S$	53.52	4.02	6.57	7.52	53.60	4.04	6.62	7.71
56	$C_{16}H_{17}F_3N_2OS$	56.13	5.00	8.18	9.37	56.01	4.97	8.30	9.19
57	$C_{14}H_{15}F_3N_2OS$	53.15	4.78	8.86	10.14	53.36	4.91	9.02	9.90

Table S2.- Kinase profiling for compound **20** (IGS-2.7). Data are expressed in % kinase activity at a concentration of 10 μM for the tested compound.

Target	IGS-2.7	Target	IGS-2.7	Target	IGS-2.7
Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM
AAK1	79	BRK	100	CSNK2A1	100
ABL1(E255K)-phosphorylated	80	BRSK1	100	CSNK2A2	88
ABL1(F317I)-nonphosphorylated	82	BRSK2	84	CTK	100
ABL1(F317I)-phosphorylated	56	BTK	57	DAPK1	100
ABL1(F317L)-nonphosphorylated	100	BUB1	100	DAPK2	82
ABL1(F317L)-phosphorylated	67	CAMK1	100	DAPK3	100
ABL1(H396P)-nonphosphorylated	75	CAMK1D	100	DCAMKL1	48
ABL1(H396P)-phosphorylated	80	CAMK1G	100	DCAMKL2	100
ABL1(M351T)-phosphorylated	100	CAMK2A	85	DCAMKL3	100
ABL1(Q252H)-nonphosphorylated	91	CAMK2B	100	DDR1	100
ABL1(Q252H)-phosphorylated	83	CAMK2D	74	DDR2	100
ABL1(T315I)-nonphosphorylated	58	CAMK2G	97	DLK	92
ABL1(T315I)-phosphorylated	75	CAMK4	100	DMPK	85
ABL1(Y253F)-phosphorylated	73	CAMKK1	97	DMPK2	100
ABL1-nonphosphorylated	73	CAMKK2	74	DRAK1	100
ABL1-phosphorylated	76	CASK	60	DRAK2	87
ABL2	100	CDC2L1	100	DYRK1A	22
ACVR1	72	CDC2L2	100	DYRK1B	11
ACVR1B	72	CDC2L5	88	DYRK2	46
ACVR2A	100	CDK11	100	EGFR	49
ACVR2B	75	CDK2	100	EGFR(E746-A750del)	100
ACVRL1	100	CDK3	100	EGFR(G719C)	100
ADCK3	76	CDK4-cyclinD1	91	EGFR(G719S)	87
ADCK4	78	CDK4-cyclinD3	65	EGFR(L747-E749del, A750P)	72
AKT1	100	CDK5	89	EGFR(L747-S752del, P753S)	91
AKT2	100	CDK7	55	EGFR(L747-T751del,Sins)	100
AKT3	71	CDK8	100	EGFR(L858R)	95
ALK	100	CDK9	93	EGFR(L858R,T790M)	88
ALK(C1156Y)	100	CDKL1	54	EGFR(L861Q)	100
ALK(L1196M)	100	CDKL2	100	EGFR(S752-I759del)	100
AMPK-alpha1	97	CDKL3	80	EGFR(T790M)	36
AMPK-alpha2	100	CDKL5	100	EIF2AK1	37
ANKK1	56	CHEK1	100	EPHA1	100
ARK5	81	CHEK2	97	EPHA2	91
ASK1	100	CIT	81	EPHA3	90
ASK2	85	CLK1	9.9	EPHA4	85
AURKA	84	CLK2	76	EPHA5	82
AURKB	55	CLK3	50	EPHA6	93
AURKC	95	CLK4	11	EPHA7	100
AXL	95	CSF1R	56	EPHA8	100
BIKE	76	CSF1R-autoinhibited	100	EPHB1	100
BLK	100	CSK	100	EPHB2	100
BMPR1A	100	CSNK1A1	16	EPHB3	96
BMPR1B	100	CSNK1A1L	12	EPHB4	98
BMPR2	66	CSNK1D	1.7	EPHB6	75
BMX	100	CSNK1E	0.1	ERBB2	100
BRAF	79	CSNK1G1	84	ERBB3	89
BRAF(V600E)	91	CSNK1G2	32	ERBB4	100
		CSNK1G3	51	ERK1	100

Target	IGS-2.7	Target	IGS-2.7	Target	IGS-2.7
Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM
ERK2	90	IRAK1	94	MEK1	100
ERK3	98	IRAK3	59	MEK2	100
ERK4	100	IRAK4	64	MEK3	100
ERK5	83	ITK	98	MEK4	99
ERK8	77	JAK1(JH1domain-catalytic)	100	MEK5	99
ERN1	97	JAK1(JH2domain-pseudokinase)	100	MEK6	72
FAK	81	JAK2(JH1domain-catalytic)	38	MELK	100
FER	84	JAK3(JH1domain-catalytic)	74	MERTK	68
FES	80	JNK1	70	MET	100
FGFR1	92	JNK2	57	MET(M1250T)	79
FGFR2	81	JNK3	59	MET(Y1235D)	80
FGFR3	78	KIT	19	MINK	33
FGFR3(G697C)	100	KIT(A829P)	87	MKK7	99
FGFR4	95	KIT(D816H)	91	MKNK1	61
FGR	80	KIT(D816V)	65	MKNK2	81
FLT1	28	KIT(L576P)	20	MLCK	5
FLT3	50	KIT(V559D)	14	MLK1	94
FLT3(D835H)	72	KIT(V559D,T670I)	29	MLK2	100
FLT3(D835Y)	72	KIT(V559D,V654A)	46	MLK3	86
FLT3(ITD)	59	KIT-autoinhibited	100	MRCKA	100
FLT3(K663Q)	39	LATS1	64	MRCKB	100
FLT3(N841I)	67	LATS2	100	MST1	100
FLT3(R834Q)	93	LCK	86	MST1R	100
FLT3-autoinhibited	100	LIMK1	82	MST2	100
FLT4	92	LIMK2	100	MST3	100
FRK	100	LKB1	100	MST4	100
FYN	100	LOK	100	MTOR	88
GAK	100	LRRK2	94	MUSK	100
GCN2(Kin.Dom.2,S808G)	100	LRRK2(G2019S)	93	MYLK	81
GRK1	89	LTK	100	MYLK2	60
GRK4	100	LYN	100	MYLK4	74
GRK7	63	LZK	86	MYO3A	100
GSK3A	72	MAK	100	MYO3B	57
GSK3B	92	MAP3K1	62	NDR1	62
HASPIN	82	MAP3K15	100	NDR2	81
HCK	77	MAP3K2	91	NEK1	88
HIPK1	84	MAP3K3	99	NEK10	100
HIPK2	33	MAP3K4	100	NEK11	91
HIPK3	92	MAP4K2	100	NEK2	100
HIPK4	77	MAP4K3	100	NEK3	68
HPK1	100	MAP4K4	100	NEK4	100
HUNK	77	MAP4K5	92	NEK5	100
ICK	77	MAPKAPK2	100	NEK6	82
IGF1R	100	MAPKAPK5	85	NEK7	100
IKK-alpha	36	MARK1	73	NEK9	100
IKK-beta	48	MARK2	100	NIK	97
IKK-epsilon	100	MARK3	100	NIM1	100
INSR	50	MARK4	80	NLK	100
INSRR	100	MAST1	78	OSR1	29

Target	IGS-2.7	Target	IGS-2.7	Target	IGS-2.7
Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM
p38-alpha	100	PKN2	96	SBK1	62
p38-beta	78	PKNB(M.tuberculosis)	67	SGK	53
p38-delta	95	PLK1	100	SgK110	68
p38-gamma	75	PLK2	86	SGK2	97
PAK1	100	PLK3	80	SGK3	90
PAK2	100	PLK4	71	SIK	79
PAK3	89	PRKCD	68	SIK2	100
PAK4	100	PRKCE	49	SLK	82
PAK6	100	PRKCH	100	SNARK	82
PAK7	100	PRKCI	100	SNRK	99
PCTK1	90	PRKCQ	100	SRC	100
PCTK2	91	PRKD1	100	SRMS	86
PCTK3	95	PRKD2	100	SRPK1	75
PDGFRA	100	PRKD3	100	SRPK2	100
PDGFRB	4	PRKG1	82	SRPK3	100
PDPK1	100	PRKG2	51	STK16	77
PFCDPK1(P.falciparum)	82	PRKR	100	STK33	100
PFPK5(P.falciparum)	100	PRKX	100	STK35	100
PFTAIRE2	94	PRP4	99	STK36	100
PFTK1	94	PYK2	100	STK39	100
PHKG1	100	QSK	76	SYK	99
PHKG2	100	RAF1	94	TAK1	92
PIK3C2B	70	RET	100	TAOK1	78
PIK3C2G	79	RET(M918T)	100	TAOK2	100
PIK3CA	100	RET(V804L)	100	TAOK3	99
PIK3CA(C420R)	65	RET(V804M)	100	TBK1	79
PIK3CA(E542K)	84	RIOK1	100	TEC	91
PIK3CA(E545A)	68	RIOK2	97	TESK1	100
PIK3CA(E545K)	71	RIOK3	100	TGFBR1	76
PIK3CA(H1047L)	95	RIPK1	82	TGFBR2	94
PIK3CA(H1047Y)	73	RIPK2	100	TIE1	100
PIK3CA(I800L)	77	RIPK4	95	TIE2	91
PIK3CA(M1043I)	78	RIPK5	66	TLK1	89
PIK3CA(Q546K)	100	ROCK1	64	TLK2	95
PIK3CB	75	ROCK2	74	TNIK	100
PIK3CD	97	ROS1	88	TNK1	79
PIK3CG	98	RPS6KA4(Kin.Dom.1-N-terminal)	79	TNK2	78
PIK4CB	39	RPS6KA4(Kin.Dom.2-C-terminal)	93	TNNI3K	100
PIM1	100	RPS6KA5(Kin.Dom.1-N-terminal)	100	TRKA	100
PIM2	100	RPS6KA5(Kin.Dom.2-C-terminal)	71	TRKB	100
PIM3	100	RSK1(Kin.Dom.1-N-terminal)	94	TRKC	96
PIP5K1A	87	RSK1(Kin.Dom.2-C-terminal)	100	TRPM6	96
PIP5K1C	78	RSK2(Kin.Dom.1-N-terminal)	90	TSSK1B	100
PIP5K2B	63	RSK2(Kin.Dom.2-C-terminal)	100	TTK	100
PIP5K2C	100	RSK3(Kin.Dom.1-N-terminal)	100	TXK	100
PKAC-alpha	100	RSK3(Kin.Dom.2-C-terminal)	100	TYK2(JH1domain-catalytic)	75
PKAC-beta	81	RSK4(Kin.Dom.1-N-terminal)	100	TYK2(JH2domain-pseudokinase)	100
PKMYT1	98	RSK4(Kin.Dom.2-C-terminal)	100	TYRO3	66
PKN1	100	S6K1	92	ULK1	41

Target	IGS-2.7
Gene Symbol	%Ctrl @ 10000nM
ULK2	76
ULK3	42
VEGFR2	100
VRK2	72
WEE1	87
WEE2	100
WNK1	70
WNK3	87
YANK1	46
YANK2	100
YANK3	100
YES	90
YSK1	75
YSK4	100
ZAK	100
ZAP70	100

%Ctrl Legend

0≤x<.1	.1≤x<1	1≤x<10	10≤x<35	x≥35

Table S3.- Kinase profiling for compound **24** (IGS-2.37). Data are expressed in % kinase activity at a concentration of 10 μM for the tested compound.

Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM
AAK1	96
ABL1(E255K)-phosphorylated	92
ABL1(F317I)-nonphosphorylated	100
ABL1(F317I)-phosphorylated	100
ABL1(F317L)-nonphosphorylated	100
ABL1(F317L)-phosphorylated	100
ABL1(H396P)-nonphosphorylated	90
ABL1(H396P)-phosphorylated	97
ABL1(M351T)-phosphorylated	100
ABL1(Q252H)-nonphosphorylated	100
ABL1(Q252H)-phosphorylated	100
ABL1(T315I)-nonphosphorylated	100
ABL1(T315I)-phosphorylated	100
ABL1(Y253F)-phosphorylated	100
ABL1-nonphosphorylated	96
ABL1-phosphorylated	88
ABL2	100
ACVR1	98
ACVR1B	87
ACVR2A	100
ACVR2B	100
ACVRL1	81
ADCK3	70
ADCK4	71
AKT1	100
AKT2	98
AKT3	100
ALK	100
ALK(C1156Y)	95
ALK(L1196M)	100
AMPK-alpha1	100
AMPK-alpha2	98
ANKK1	98
ARK5	100
ASK1	98
ASK2	99
AURKA	96
AURKB	98
AURKC	84
AXL	100
BIKE	48
BLK	100
BMPR1A	97
BMPR1B	100
BMPR2	90
BMX	93
BRAF	100
BRAF(V600E)	100

Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM
BRK	99
BRSK1	100
BRSK2	75
BTK	97
BUB1	96
CAMK1	100
CAMK1D	88
CAMK1G	100
CAMK2A	87
CAMK2B	96
CAMK2D	96
CAMK2G	100
CAMK4	98
CAMKK1	87
CAMKK2	100
CASK	100
CDC2L1	100
CDC2L2	91
CDC2L5	100
CDK11	100
CDK2	82
CDK3	94
CDK4-cyclinD1	100
CDK4-cyclinD3	100
CDK5	100
CDK7	26
CDK8	100
CDK9	77
CDKL1	100
CDKL2	30
CDKL3	18
CDKL5	100
CHEK1	100
CHEK2	93
CIT	89
CLK1	1.8
CLK2	4.8
CLK3	20
CLK4	2.5
CSF1R	67
CSF1R-autoinhibited	100
CSK	91
CSNK1A1	42
CSNK1A1L	5.6
CSNK1D	2.2
CSNK1E	0.05
CSNK1G1	87
CSNK1G2	19
CSNK1G3	45

Target	IGS-2.37	Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM
CSNK2A1	95	ERK2	97
CSNK2A2	87	ERK3	48
CTK	80	ERK4	93
DAPK1	93	ERK5	83
DAPK2	93	ERK8	48
DAPK3	95	ERN1	100
DCAMKL1	74	FAK	93
DCAMKL2	90	FER	100
DCAMKL3	90	FES	96
DDR1	100	FGFR1	77
DDR2	100	FGFR2	94
DLK	92	FGFR3	85
DMPK	100	FGFR3(G697C)	100
DMPK2	95	FGFR4	95
DRAK1	100	FGR	94
DRAK2	100	FLT1	27
DYRK1A	16	FLT3	71
DYRK1B	3.6	FLT3(D835H)	76
DYRK2	31	FLT3(D835Y)	68
EGFR	94	FLT3(ITD)	84
EGFR(E746-A750del)	100	FLT3(K663Q)	72
EGFR(G719C)	86	FLT3(N841I)	88
EGFR(G719S)	93	FLT3(R834Q)	100
EGFR(L747-E749del, A750P)	93	FLT3-autoinhibited	100
EGFR(L747-S752del, P753S)	89	FLT4	84
EGFR(L747-T751del,Sins)	76	FRK	99
EGFR(L858R)	100	FYN	95
EGFR(L858R,T790M)	100	GAK	100
EGFR(L861Q)	100	GCN2(Kin.Dom.2,S808G)	100
EGFR(S752-I759del)	100	GRK1	100
EGFR(T790M)	100	GRK4	100
EIF2AK1	100	GRK7	100
EPHA1	99	GSK3A	86
EPHA2	94	GSK3B	79
EPHA3	100	HASPIN	100
EPHA4	98	HCK	100
EPHA5	90	HIPK1	90
EPHA6	96	HIPK2	68
EPHA7	92	HIPK3	96
EPHA8	94	HIPK4	38
EPHB1	100	HPK1	79
EPHB2	95	HUNK	97
EPHB3	99	ICK	100
EPHB4	99	IGF1R	98
EPHB6	100	IKK-alpha	100
ERBB2	100	IKK-beta	100
ERBB3	100	IKK-epsilon	100
ERBB4	89	INSR	100
ERK1	93	INSRR	100

Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM
IRAK1	100
IRAK3	65
IRAK4	100
ITK	100
JAK1(JH1domain-catalytic)	100
JAK1(JH2domain-pseudokinase)	100
JAK2(JH1domain-catalytic)	97
JAK3(JH1domain-catalytic)	92
JNK1	100
JNK2	90
JNK3	99
KIT	40
KIT(A829P)	100
KIT(D816H)	97
KIT(D816V)	100
KIT(L576P)	44
KIT(V559D)	30
KIT(V559D,T670I)	37
KIT(V559D,V654A)	75
KIT-autoinhibited	100
LATS1	92
LATS2	100
LCK	100
LIMK1	100
LIMK2	100
LKB1	84
LOK	99
LRRK2	93
LRRK2(G2019S)	98
LTK	100
LYN	100
LZK	95
MAK	46
MAP3K1	92
MAP3K15	69
MAP3K2	100
MAP3K3	98
MAP3K4	86
MAP4K2	100
MAP4K3	91
MAP4K4	100
MAP4K5	96
MAPKAPK2	90
MAPKAPK5	100
MARK1	88
MARK2	100
MARK3	100
MARK4	82
MAST1	100

Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM
MEK1	100
MEK2	80
MEK3	96
MEK4	100
MEK5	100
MEK6	91
MELK	84
MERTK	100
MET	69
MET(M1250T)	58
MET(Y1235D)	99
MINK	98
MKK7	96
MKNK1	99
MKNK2	92
MLCK	5.4
MLK1	97
MLK2	84
MLK3	99
MRCKA	94
MRCKB	100
MST1	100
MST1R	62
MST2	89
MST3	100
MST4	100
MTOR	92
MUSK	69
MYLK	100
MYLK2	61
MYLK4	64
MYO3A	99
MYO3B	91
NDR1	100
NDR2	88
NEK1	100
NEK10	94
NEK11	100
NEK2	100
NEK3	92
NEK4	100
NEK5	100
NEK6	95
NEK7	100
NEK9	99
NIK	99
NIM1	100
NLK	89
OSR1	100

Target	IGS-2.37	Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM	Gene Symbol	%Ctrl @ 10000nM
p38-alpha	97	PKN2	98
p38-beta	92	PKNB(M.tuberculosis)	100
p38-delta	72	PLK1	94
p38-gamma	85	PLK2	68
PAK1	93	PLK3	85
PAK2	97	PLK4	92
PAK3	100	PRKCD	85
PAK4	100	PRKCE	84
PAK6	100	PRKCH	100
PAK7	89	PRKCI	97
PCTK1	100	PRKCQ	91
PCTK2	92	PRKD1	99
PCTK3	72	PRKD2	100
PDGFRA	100	PRKD3	100
PDGFRB	17	PRKG1	100
PDPK1	77	PRKG2	100
PFCDPK1(P.falciparum)	100	PRKR	87
PFPK5(P.falciparum)	100	PRKX	100
PFTAIRE2	39	PRP4	94
PFTK1	66	PYK2	99
PHKG1	100	QSK	100
PHKG2	95	RAF1	95
PIK3C2B	84	RET	100
PIK3C2G	100	RET(M918T)	99
PIK3CA	86	RET(V804L)	100
PIK3CA(C420R)	100	RET(V804M)	98
PIK3CA(E542K)	100	RIOK1	68
PIK3CA(E545A)	97	RIOK2	89
PIK3CA(E545K)	97	RIOK3	90
PIK3CA(H1047L)	100	RIPK1	60
PIK3CA(H1047Y)	81	RIPK2	85
PIK3CA(I800L)	80	RIPK4	100
PIK3CA(M1043I)	100	RIPK5	100
PIK3CA(Q546K)	100	ROCK1	100
PIK3CB	100	ROCK2	100
PIK3CD	100	ROS1	100
PIK3CG	86	RPS6KA4(Kin.Dom.1-N-terminal)	91
PIK4CB	97	RPS6KA4(Kin.Dom.2-C-terminal)	94
PIM1	99	RPS6KA5(Kin.Dom.1-N-terminal)	92
PIM2	90	RPS6KA5(Kin.Dom.2-C-terminal)	100
PIM3	100	RSK1(Kin.Dom.1-N-terminal)	92
PIP5K1A	74	RSK1(Kin.Dom.2-C-terminal)	98
PIP5K1C	100	RSK2(Kin.Dom.1-N-terminal)	100
PIP5K2B	100	RSK2(Kin.Dom.2-C-terminal)	82
PIP5K2C	100	RSK3(Kin.Dom.1-N-terminal)	99
PKAC-alpha	80	RSK3(Kin.Dom.2-C-terminal)	89
PKAC-beta	94	RSK4(Kin.Dom.1-N-terminal)	91
PKMYT1	100	RSK4(Kin.Dom.2-C-terminal)	93
PKN1	75	S6K1	100

Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM
SBK1	100
SGK	89
SgK110	94
SGK2	99
SGK3	100
SIK	100
SIK2	100
SLK	93
SNARK	98
SNRK	100
SRC	90
SRMS	100
SRPK1	99
SRPK2	100
SRPK3	94
STK16	54
STK33	67
STK35	78
STK36	85
STK39	100
SYK	100
TAK1	88
TAOK1	100
TAOK2	95
TAOK3	99
TBK1	98
TEC	100
TESK1	100
TGFBR1	97
TGFBR2	94
TIE1	96
TIE2	86
TLK1	99
TLK2	100
TNIK	93
TNK1	89
TNK2	100
TNNI3K	100
TRKA	100
TRKB	100
TRKC	100
TRPM6	84
TSSK1B	81
TTK	83
TXK	83
TYK2(JH1domain-catalytic)	80
TYK2(JH2domain-pseudokinase)	100
TYRO3	100
ULK1	97

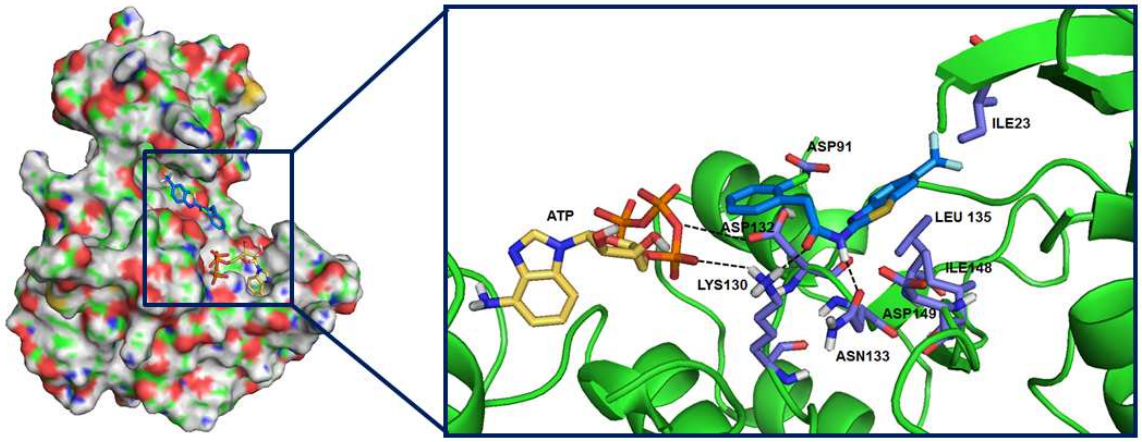
Target	IGS-2.37
Gene Symbol	%Ctrl @ 10000nM
ULK2	80
ULK3	89
VEGFR2	95
VRK2	100
WEE1	99
WEE2	100
WNK1	100
WNK3	100
YANK1	100
YANK2	84
YANK3	100
YES	100
YSK1	97
YSK4	100
ZAK	100
ZAP70	100

%Ctrl Legend

0≤x<.1	.1≤x<1	1≤x<10	10≤x<35	x≥35

Figura S1.- Docking studies with CK-1δ (PDB Code: 3UYS) of compound **24** (A) and **34** (B)

A)



B)

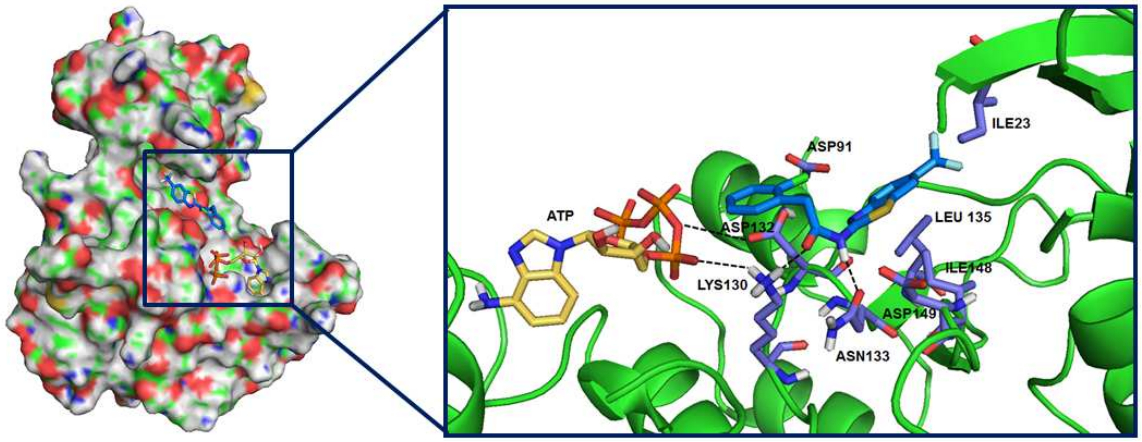


Figure S2.- Linear correlation between experimental and reported permeability of commercial drugs using the PAMPA-BBB assay.