Virtual screening (VS) based in the common binding site for negatively charged activators in K^+ channels. A comparison with a pharmacophore-based VS.

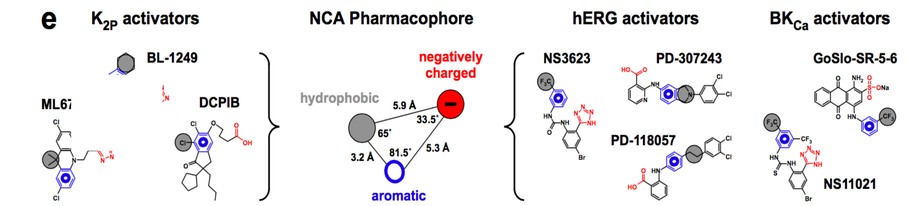
Wendy González [1], Marcelo Araneda[1], Estanislao Márquez[1], Fernando Vergara[1], Han Sun[2], Niels Decher[3]

[1]Center for Bioinformatics, Simulation and Modelling, University of Talca, Chile.[2] Leibniz Institute for Molecular Pharmacology, Berlin, Germany. [3] Philipps University Marburg, Germany. Correspondence to: **wgonzalez@utalca.cl**

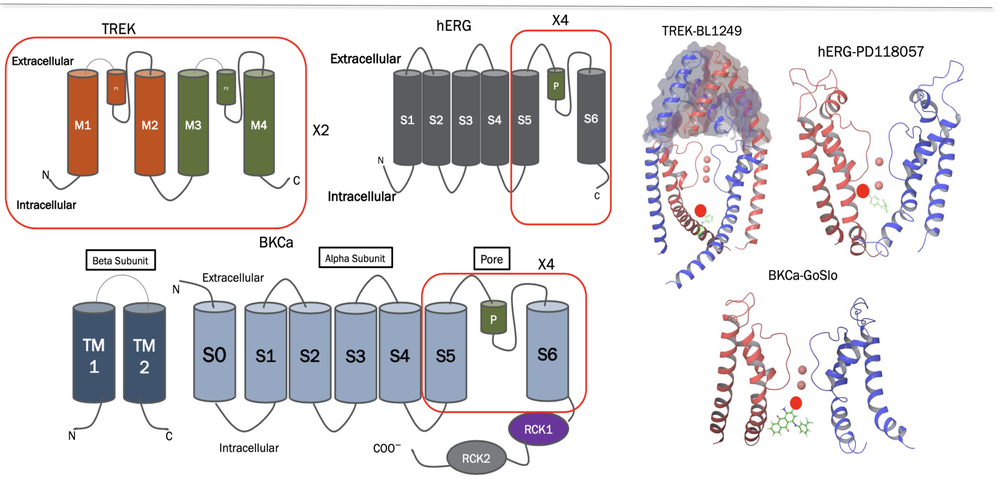
Abstract

A master key mechanism related to the pharmacophore of negatively charged activators (NCAs) to modulate TREK, BK_{Ca} and hERG potassium (K^+) channels was recently described. A polypharmacological behavior of NCAs was assessed, because all NCA found could activate these three type of K^+ channels. However, the role of the binding sites (BS) in the polypharmacological nature of NCAs remains unknown. In this context, the presence of structural common patterns at the BS appears to be a valid hypothesis. **Methods**: Residues determined experimentally as having a significant role on K^+ channel-NCAs interaction were retrieved. Structural common patterns at the NCAs BS were found between TREK, BKca and hERG K^+ channels using our program Geomfinder comparing by pairs. These common BS (named "receptophore") were used for a structure-based virtual screening (VS). In parallel, a pharmacophore-based VS was carried out based in the common features of the NCAs. The VS results were organized using MMGBSA. **Results**: Seven compounds target *in silico* the three types of K^+ channels studied. They also accomplish two features: 1) they were found simultaneously by structure-based VS and pharmacophore-based VS 2) All of them point their negative charge to the pore, a feature that it is mandatory for the activation of TREK, BK_{Ca} and hERG K^+ channels by NCAs. These seven compounds will be proposed to test by means of two-electrode voltage clamp technique in the three types of K^+ channels studied.

Introduction



Schewe *et al.*, Science. 2019; 363: 875–880



Methods

ZINC Database search

ZINCPharmer search based on NCAs pharmacophore (2D) → 349696 compounds

PHASE filter

Compounds with the NCAs pharmacophore (3D) → 219875 compounds

Sorting by RMSD using KNIME

To select the best 5000 compounds calculating the RMSD with the Pharmacophore

Ligprep

To prepare the compounds with Maestro

HTVS Docking (grid centered in the NCAs dockings, Schewe *et al.*, 2019)

To obtain the best 500 compounds

HTVS Docking (grid centered in BL1249 in TREK, crystal structure. BL1249 in BK_{Ca} and hERG was docked using the receptophore)

To obtain the best 500 compounds

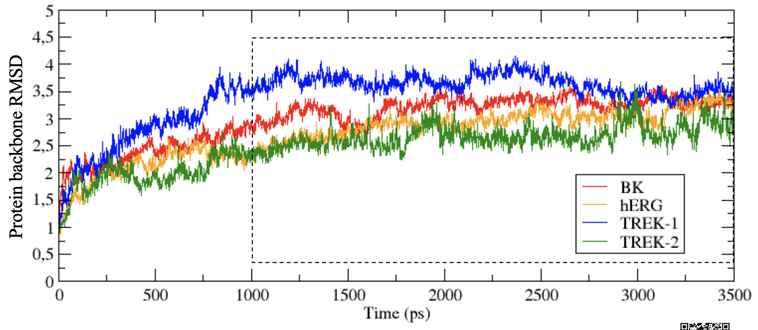
XP Docking

To obtain the best 100 compounds

MMGBSA

To calculate the free energy of the complexes

MD Simulation (MDs) Results



Geomfinder Results (BS similarities) Legend here

prot1	prot2	Gscore	SDist	SNbE	SSc	STsp	resP1	resP2	resid_report1	resid_report2
bk-frame2501	herg-frame2901	60,38	21,11	97,08	90	33,33	10	10	5	3
bk-frame2501	trek1-frame2501	60,90	24,44	96,94	100	22,22	10	10	5	3
bk-frame2501	trek2-frame2201	60,49	31,11	98,66	90	22,22	10	10	5	3
herg-frame2901	trek1-frame2501	61,63	34,44	99,86	90	22,22	10	10	3	3
herg-frame2901	trek2-frame2201	61,54	34,44	98,39	80	33,33	10	10	3	3
trek1-frame2501	trek2-frame2201	64,00	47,61	86,99	71,42	50	7	6	4	3

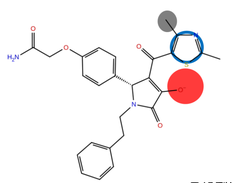
Geomfinder Results (Pattern residues) Legend here

	bk-frame2501	herg-frame2901	trek1-frame2501	trek2-frame2201
bk-frame2501		PHE300-A, **ILE301-A**, PHE304-A, **ALA305-A**, SER306-A, **ILE308-A**, **PRO309-A**, PHE304-D, **ILE308-D**, ILE311-D	PHE300-A, **ILE301-A**, PHE304-A, **ALA305-A**, SER306-A, **ILE308-A**, **PRO309-A**, PHE304-D, **ILE308-D**, ILE311-D	PHE300-A, **ILE301-A**, PHE304-A, **ALA305-A**, SER306-A, **ILE308-A**, **PRO309-A**, PHE304-D, **ILE308-D**, ILE311-D
herg-frame2901	PHE557-D, ILE560-D, LEU622-D, **THR623-D**, ILE647-D, **GLY648-D**, MET651-D, **TYR652-D**, ILE655-D, **PHE656-D**		PHE557-D, ILE560-D, LEU622-D, **THR623-D**, ILE647-D, **GLY648-D**, MET651-D, **TYR652-D**, ILE655-D, **PHE656-D**	PHE557-D, ILE560-D, LEU622-D, **THR623-D**, ILE647-D, **GLY648-D**, MET651-D, **TYR652-D**, ILE655-D, **PHE656-D**
trek1-frame2501	**ILE292-A**, **GLY293-A**, TRP295-A, LEU296-A, ILE299-A, SER300-A, PHE306-A, **PRO168-B**, LEU169-B, PHE172-B	**ILE292-A**, **GLY293-A**, TRP295-A, LEU296-A, ILE299-A, SER300-A, PHE306-A, **PRO168-B**, LEU169-B, PHE172-B		***LEU289-A***, ***ILE292-A***, ***GLY293-A***, *LEU296-A*, LEU165-B, ILE167-B, **PRO168-B**
trek2-frame2201	**PRO198-A**, ILE242-B, PHE244-B, ILE245-B, LEU246-B, TYR315-B, PHE316-B, VAL319-B, **LEU320-B**, **ILE323-B**	**PRO198-A**, ILE242-B, PHE244-B, ILE245-B, LEU246-B, TYR315-B, PHE316-B, VAL319-B, **LEU320-B**, **ILE323-B**	LEU199-A, PHE202-A, ***LEU320-B***, ***ILE323-B***, ***GLY324-B***, *LEU327-B*	

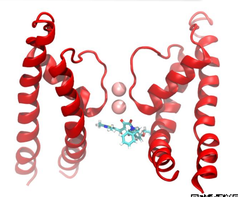
VS Results

Zinc Compound	BK (GoSlo)	hERG(PD118057)	TREK1 (BL1249)	TREK2 (BL1249)	BK (BL1249)	hERG (BL1249)
	Pharmacophore-based VS				Receptophore-based VS	
ZINC04188432			X	X	X	
ZINC09109211			X	X		X
ZINC21302097	X		X	X	X	
ZINC35520544		X	X	X	X	
ZINC35568098	X		X	X	X	X
ZINC72314542			X	X	X	
ZINC21302092	X			X		X

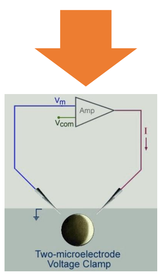
Compound ZINC35568098



Other compounds here



ZINC35568098 in BK_{Ca}.
Other representations here



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