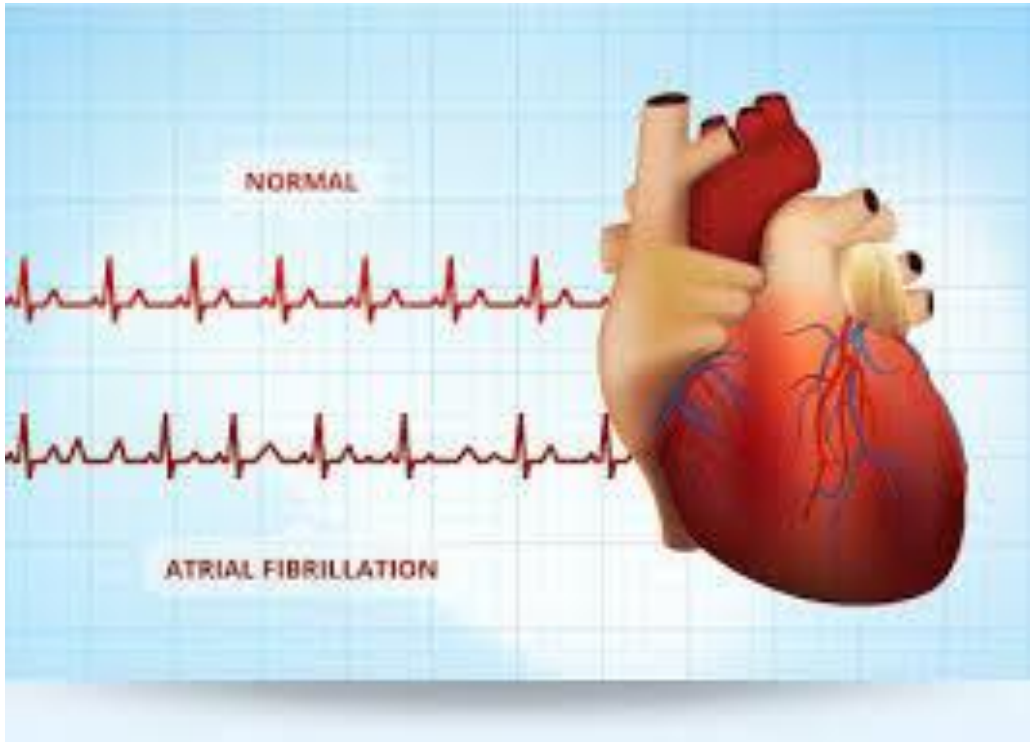
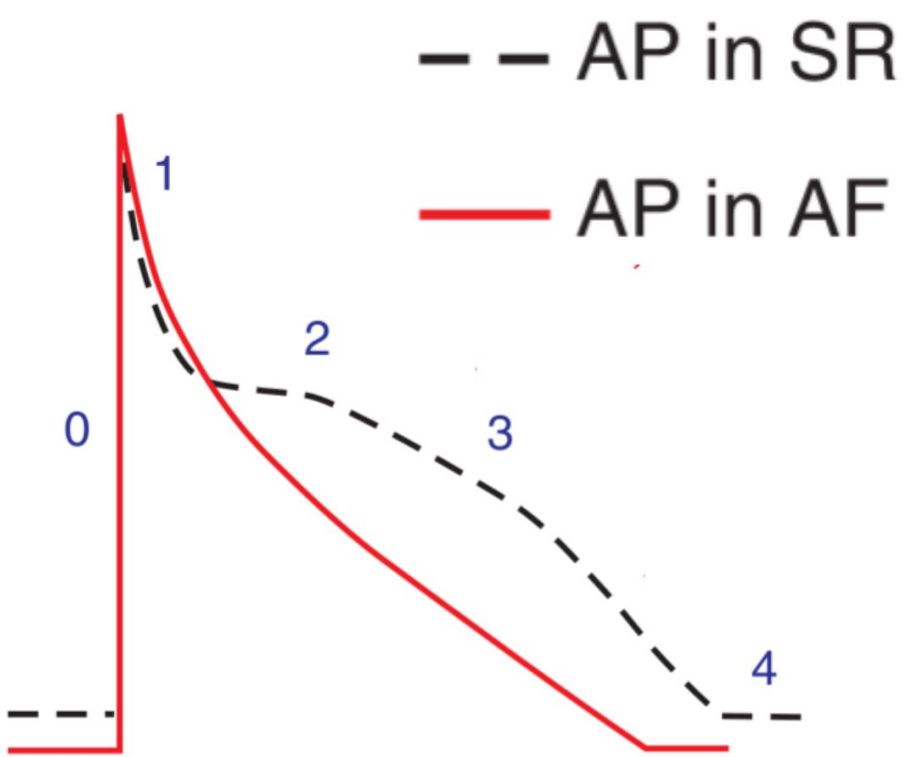
Rational design, synthesis, and in-silico evaluation homologous local anesthetic compounds as TASK-1 channel blockers

Lorena Camargo-Ayala[1], Luis Prent-Peñaloza[2], Mauricio Bedoya[3], Margarita Gutiérrez[2]*, Wendy González[3,4]*.

[1] Doctorate in Sciences Mention in Research and Development of Bioactive Products, Institute of Chemistry of Natural Resources, Organic Synthesis Laboratory and Biological Activity (LSO-Act-Bio), University of Talca, Casilla 747, Talca 3460000, Chile; ana.camargo@utalca.cl.
[2] Organic Synthesis Laboratory and Biological Activity (LSO-Act-Bio), Institute of Chemistry of Natural Resources, University of Talca, Casilla 747, Talca 3460000, Chile; luisprent@gmail.com, mgutierrez@utalca.cl.
[3] Center for Bioinformatics and Molecular Simulations (CBSM), Universidad de Talca, Casilla 747, Talca 3460000, Chile; maurobedoyat@gmail.com, wgonzalez@utalca.cl
[4] Millennium Nucleus of Ion Channels-Associated Diseases (MiNICAD). Universidad de Talca, Casilla 747, Talca 3460000, Chile; wgonzalez@utalca.cl
* Correspondence: MG, mgutierrez@utalca.cl; WG, wgonzalez@utalca.cl.

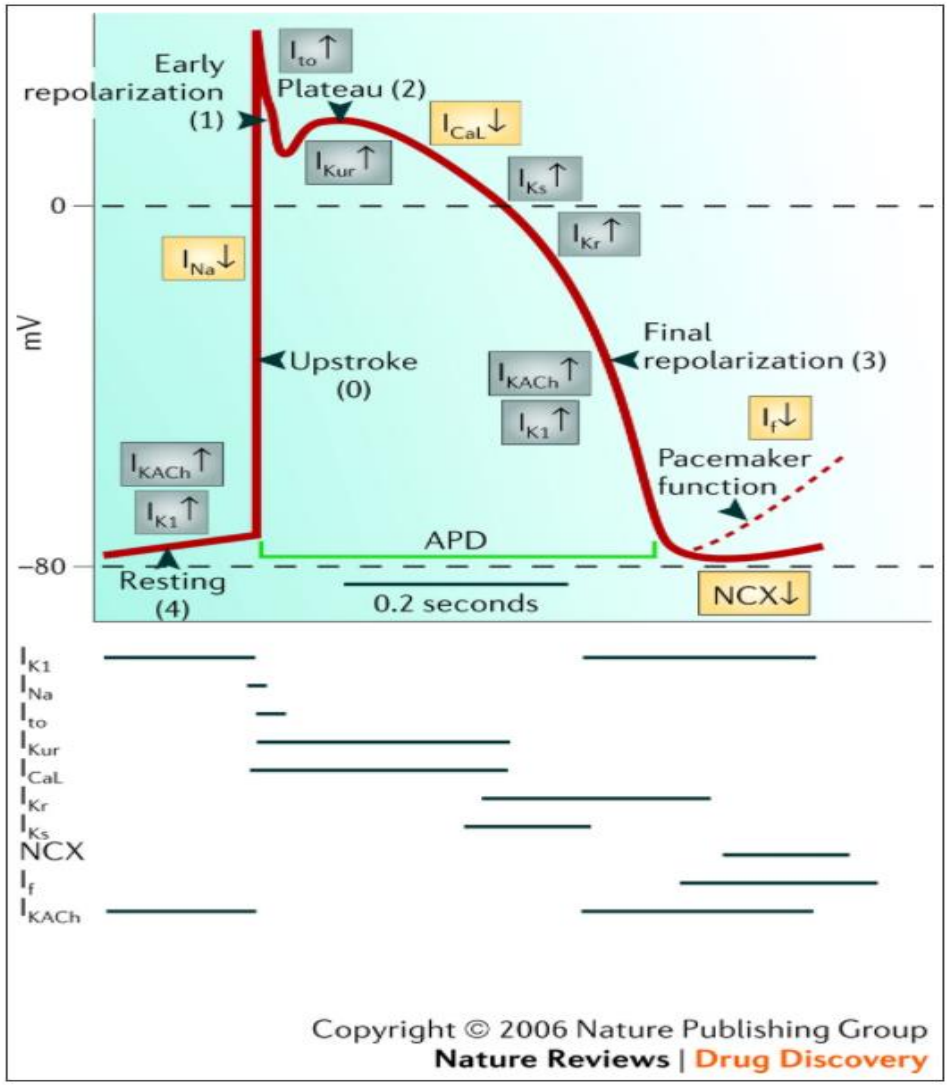
Introduction

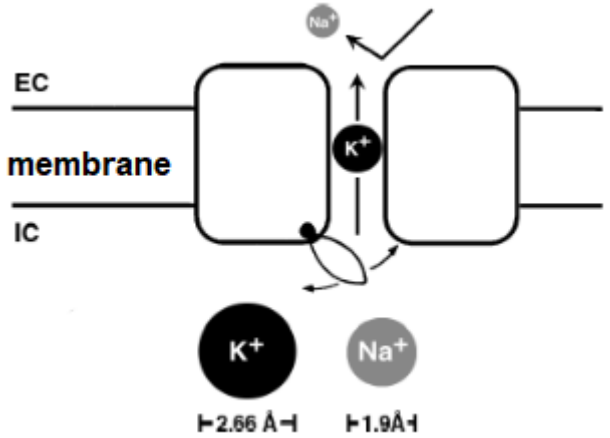




(Issa, Ziple, & Miller, 2018)

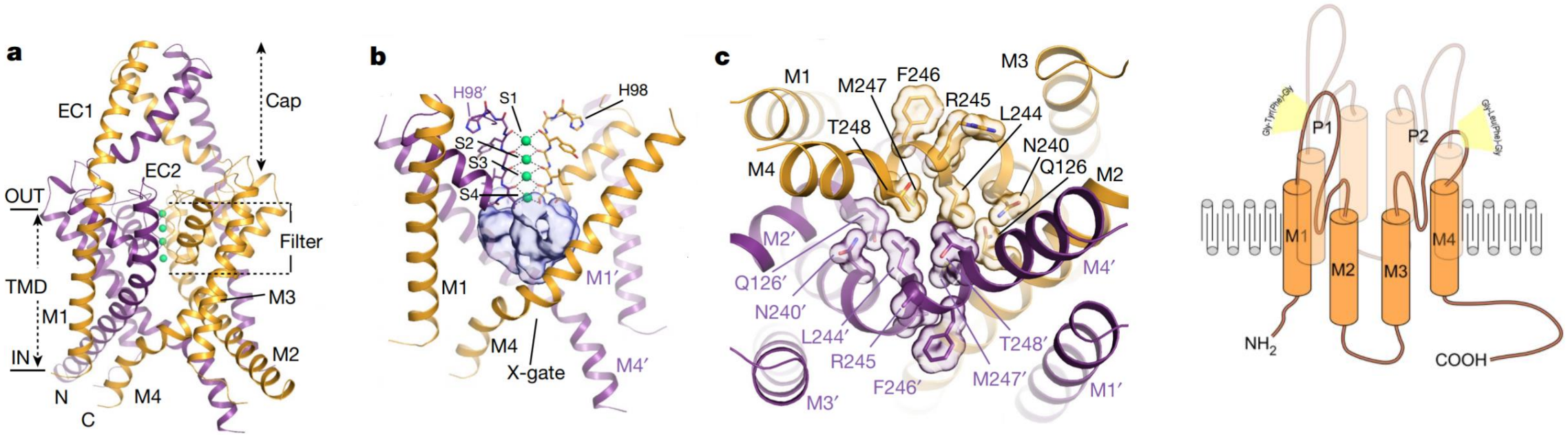
Introduction





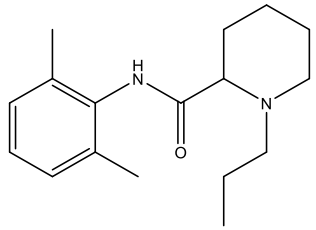
(Grant, 2009; MacKinnon, 2004; Marzian et al., 2013)

TASK-1 Channel

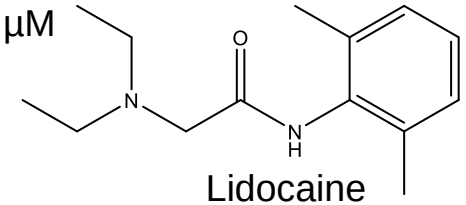


(Du et al., 2011; Kindler, Yost, & Gray, 1999; Rödström et al., 2020, Rinné et al., 2019)

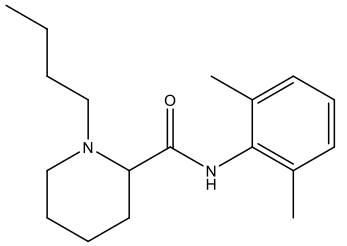
Introduction



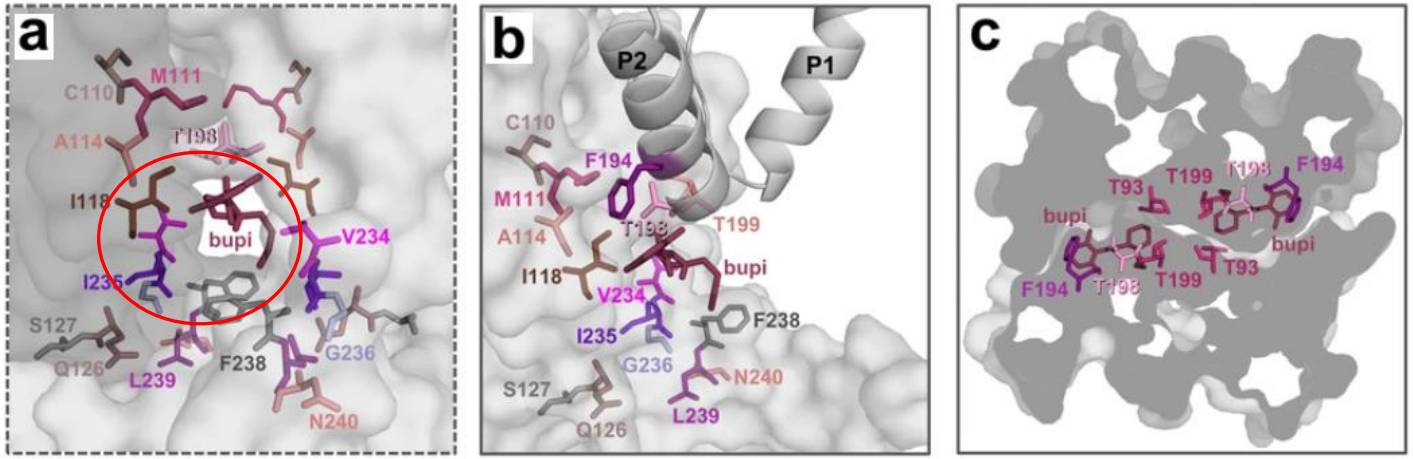
Ropivacaine
IC_{50} 17.6 µM



Lidocaine
IC_{50} 53.8 µM



Bupivacaine
IC_{50} 12.1 µM

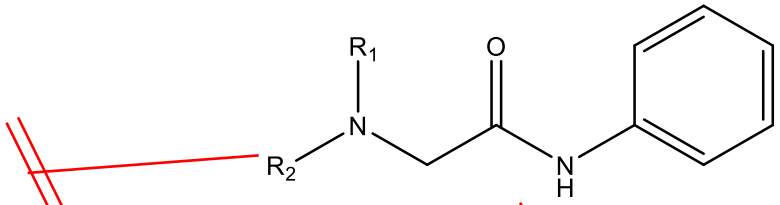


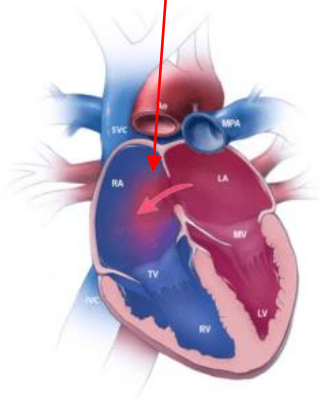
Homology model of the TASK-1 channel based on the TWIK-1 crystal (PDB: 3UKM). (a) Residues of the bupivacaine binding site in the M2 and M4 segments aligned with the lateral fenestrations. (b) Enlargement of bupivacaine interacting residues (c) Bupivacaine located below the second pore helix along with the binding residues at M2 and M4. Modified from Rinné, 2019 (19).

(Du et al., 2011; Kindler, Yost, & Gray, 1999; Rödström et al., 2020, Rinné et al., 2019)

Introduction

TASK-1

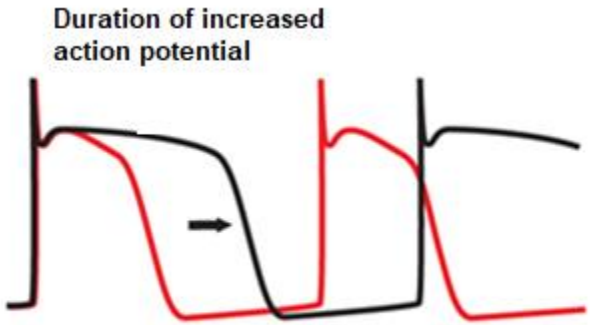




RA. Right Atrium
RV. Right Ventricle
LA. Left Atrium
LV. Left Ventricle

SVC. Superior Vena Cava
IVC. Inferior Vena Cava
MPA. Main Pulmonary Artery
Ao. Aorta

TV. Tricuspid Valve
MV. Mitral Valve



Fuente: Randa Hilal-Dandan, Laurence L. Brunton: *Goodman farmacología y terapéutica*, 2e: www.accessmedicina.com
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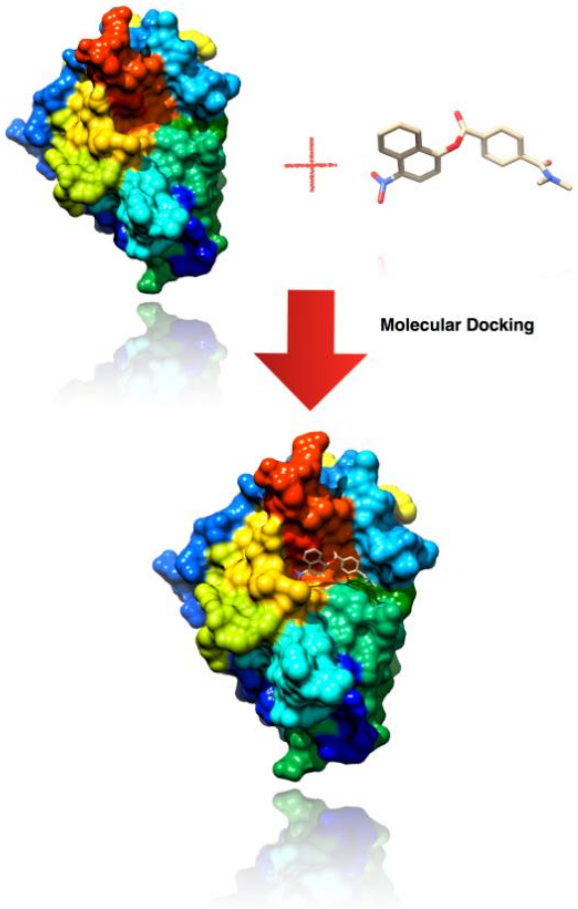
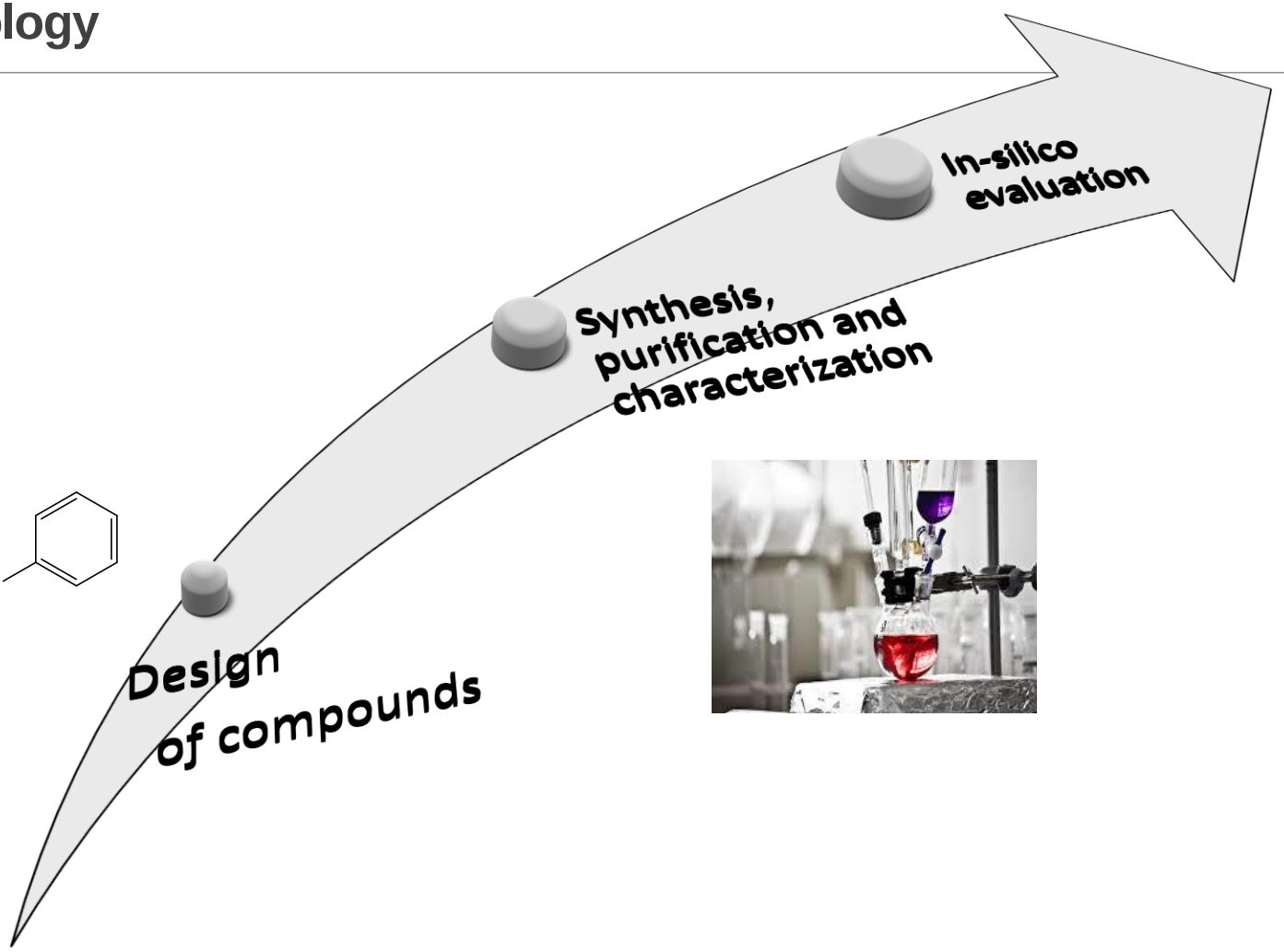
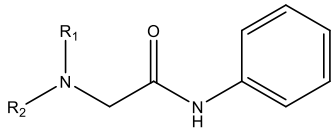
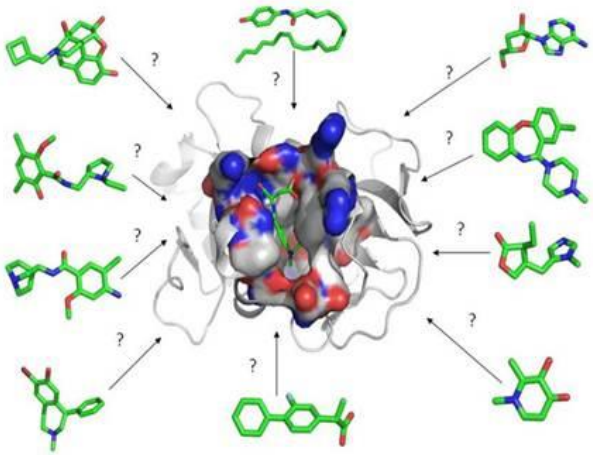


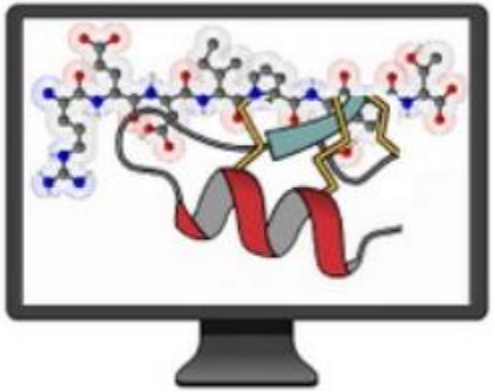
(Saldívar-González, Prieto-Martínez, & Medina-Franco, 2017; González, 2019)

Metodology

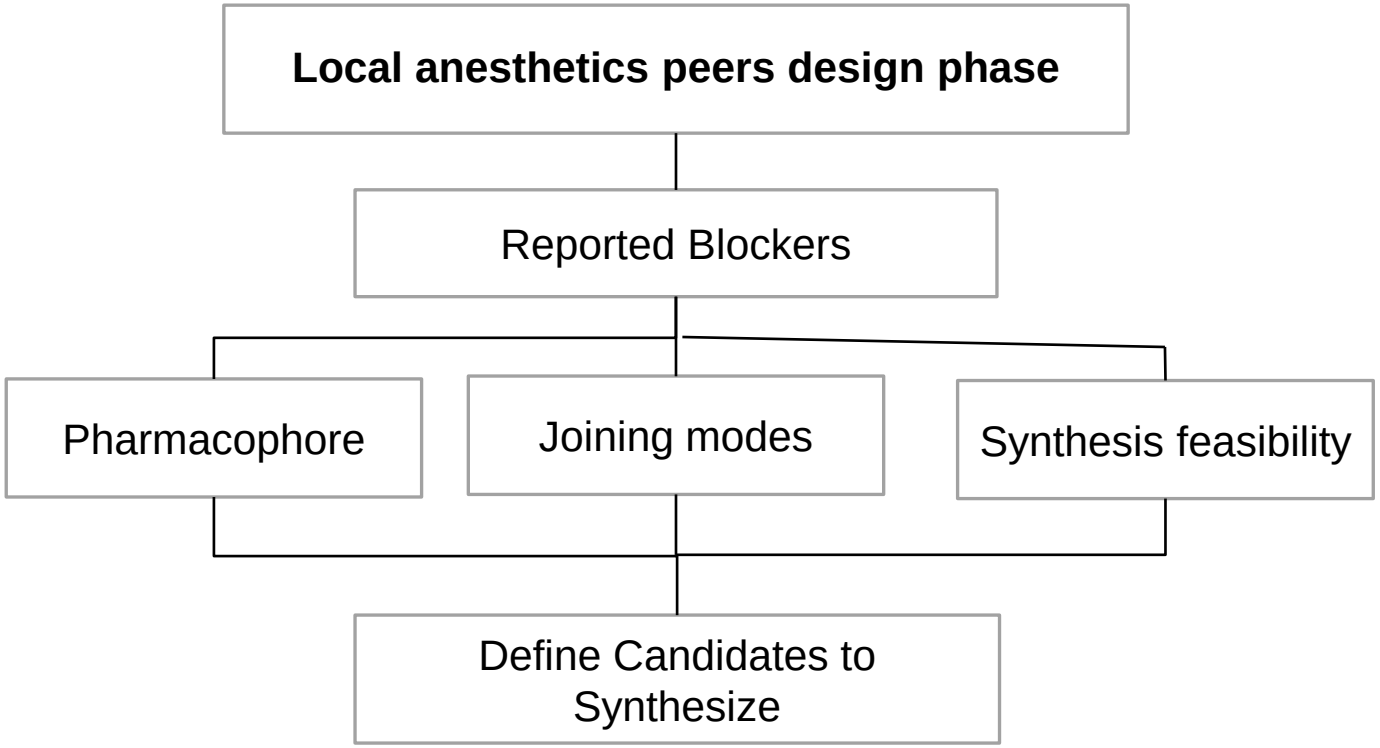

In-silico evaluation
Synthesis, purification and characterization
Design of compounds


R1
O
N
R2
N
H

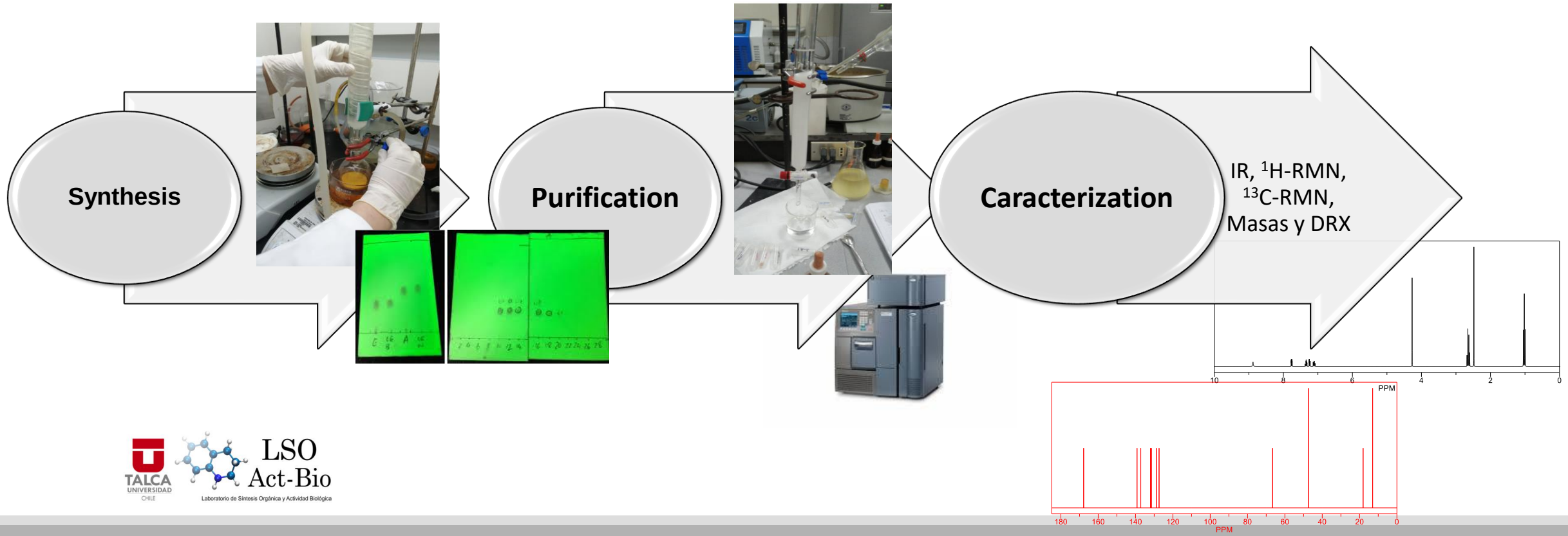




Local anesthetics peers design phase



Synthesis and Characterization Phase



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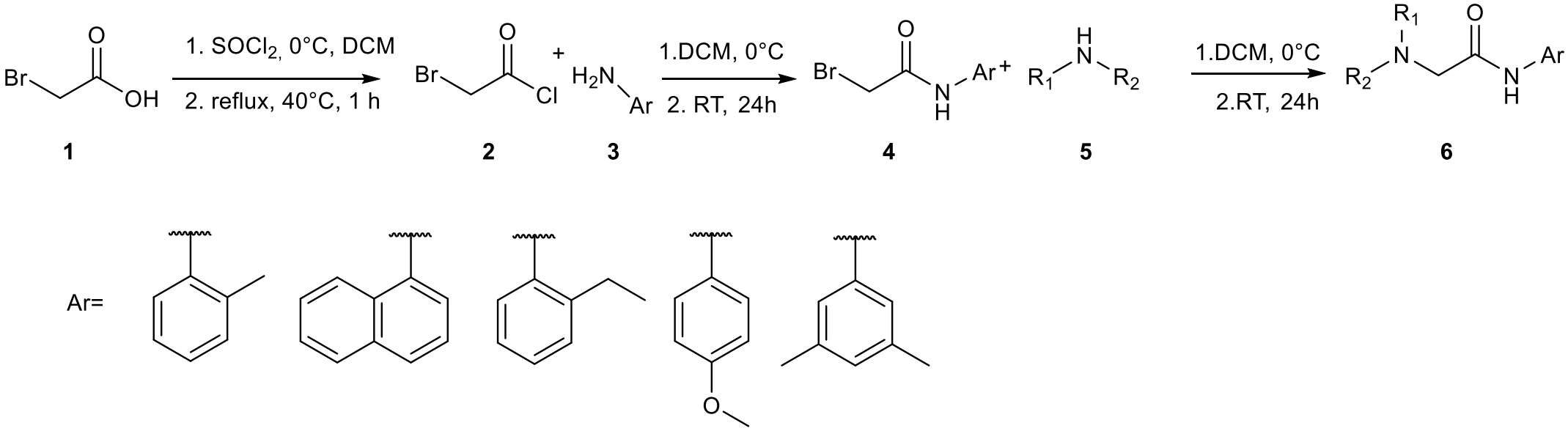
Synthesis and Characterization Phase

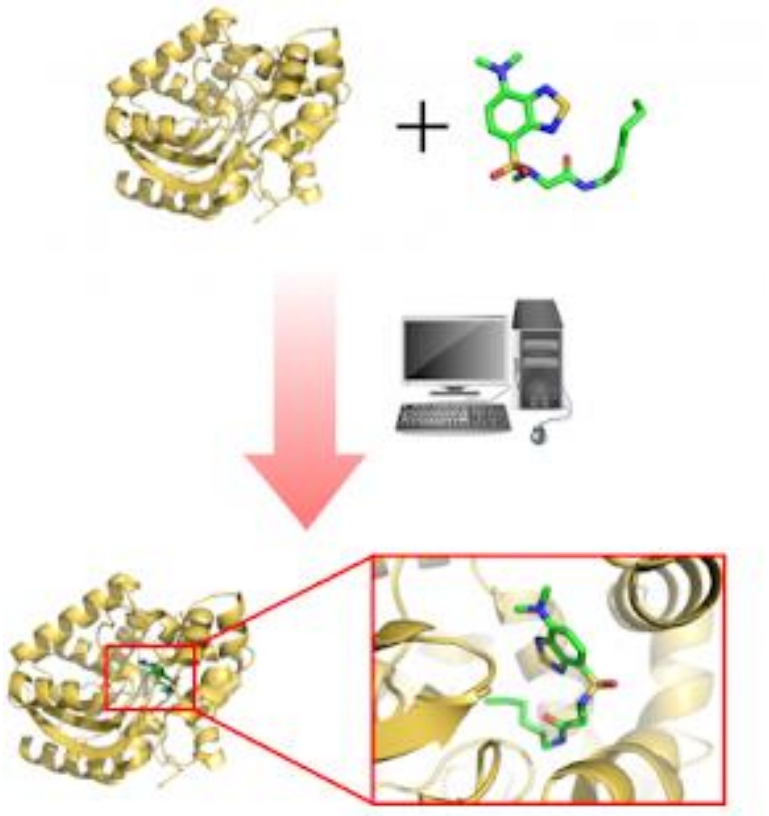


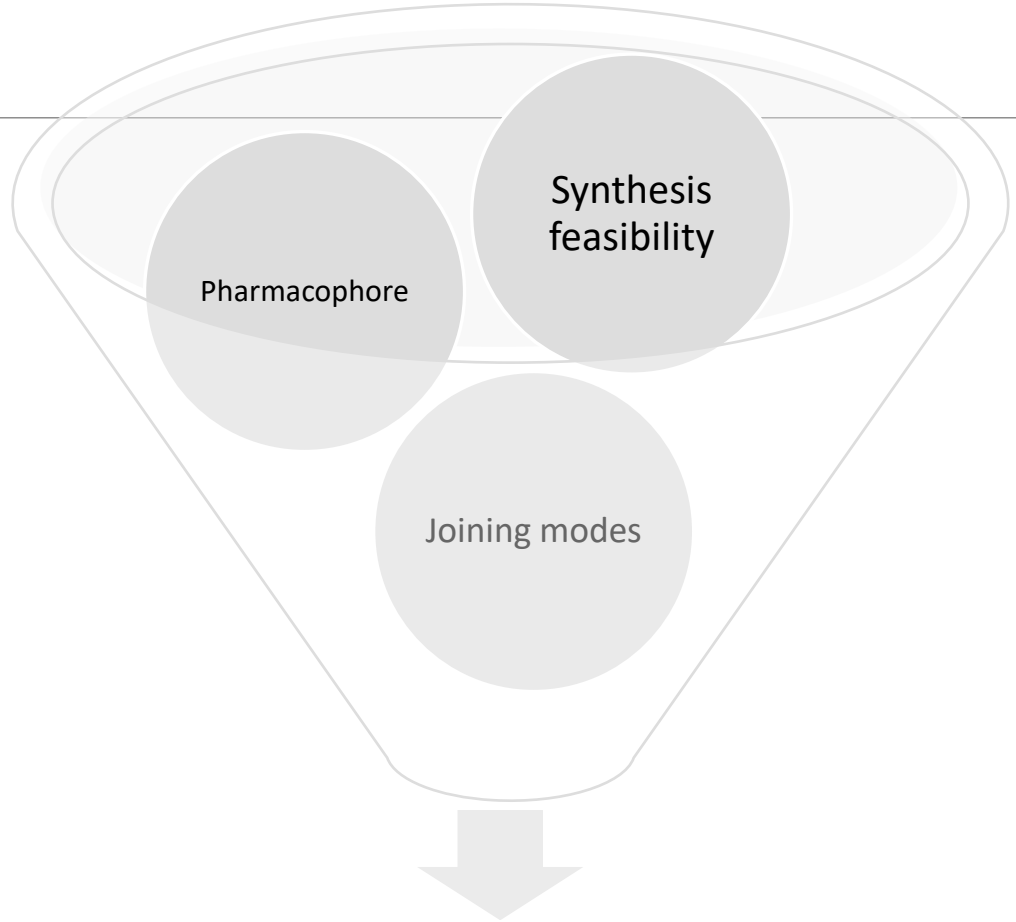
R_1= R_2= Et, Bu, isopropyl, pyrrolidine

Scheme 1. Synthesis of LA homologous compounds

(Wang et al., 2019)

In-silico evaluation phase



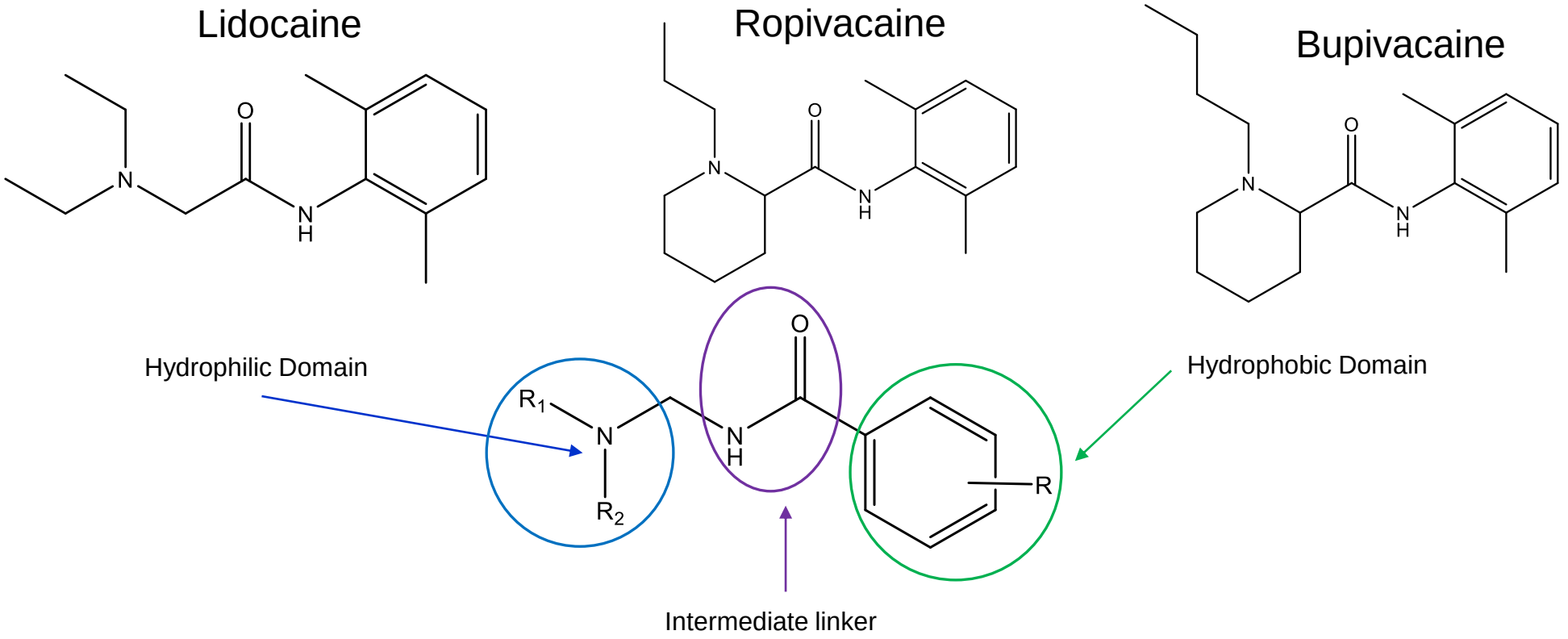


Best ESI score

Junction key residues

(Maulid, 2018)

Common structural features of local anesthetics



(Li, Galue, Meadows, & Ragsdale, 1999; Ragsdale, McPhee, Scheuer, & Catterall, 1994; Kindler et al., 1999; Ragsdale et al., 1994; Longobardo et al., 1998; Fozzard et al., 2011; L. Liu, Wendt, & Grant, 1994)

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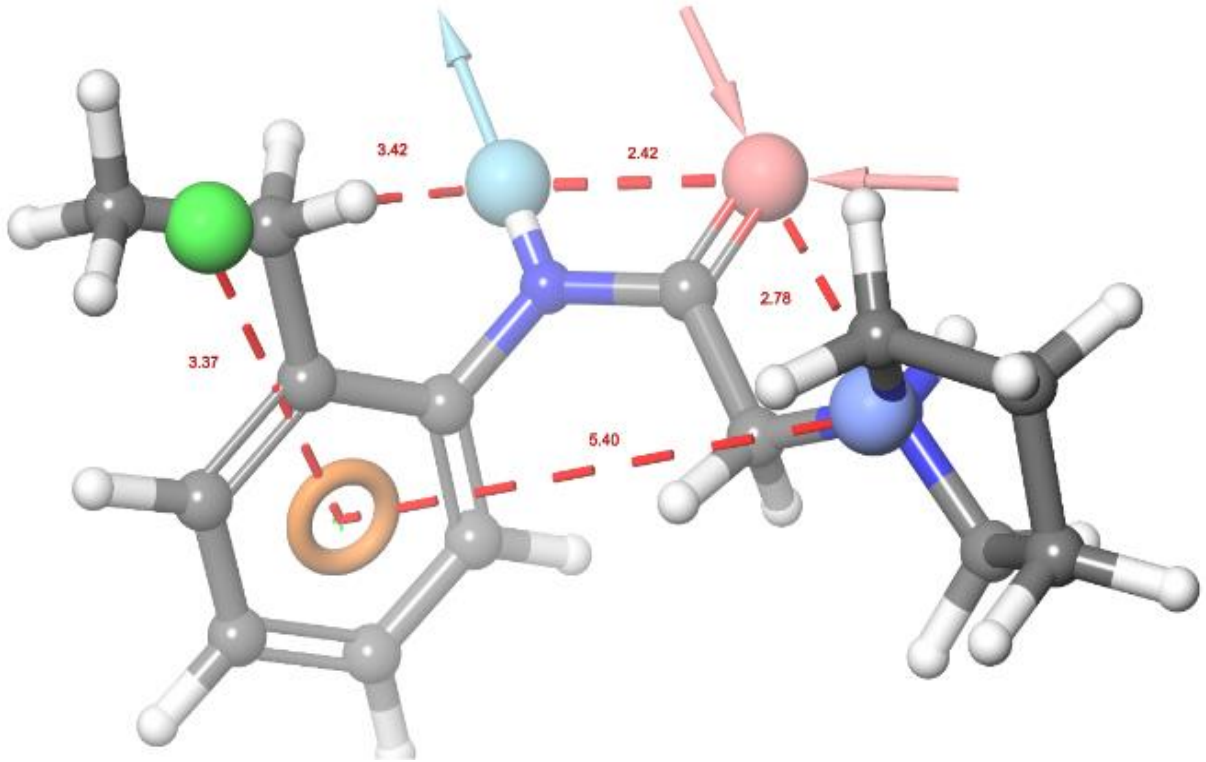
Pharmacophore



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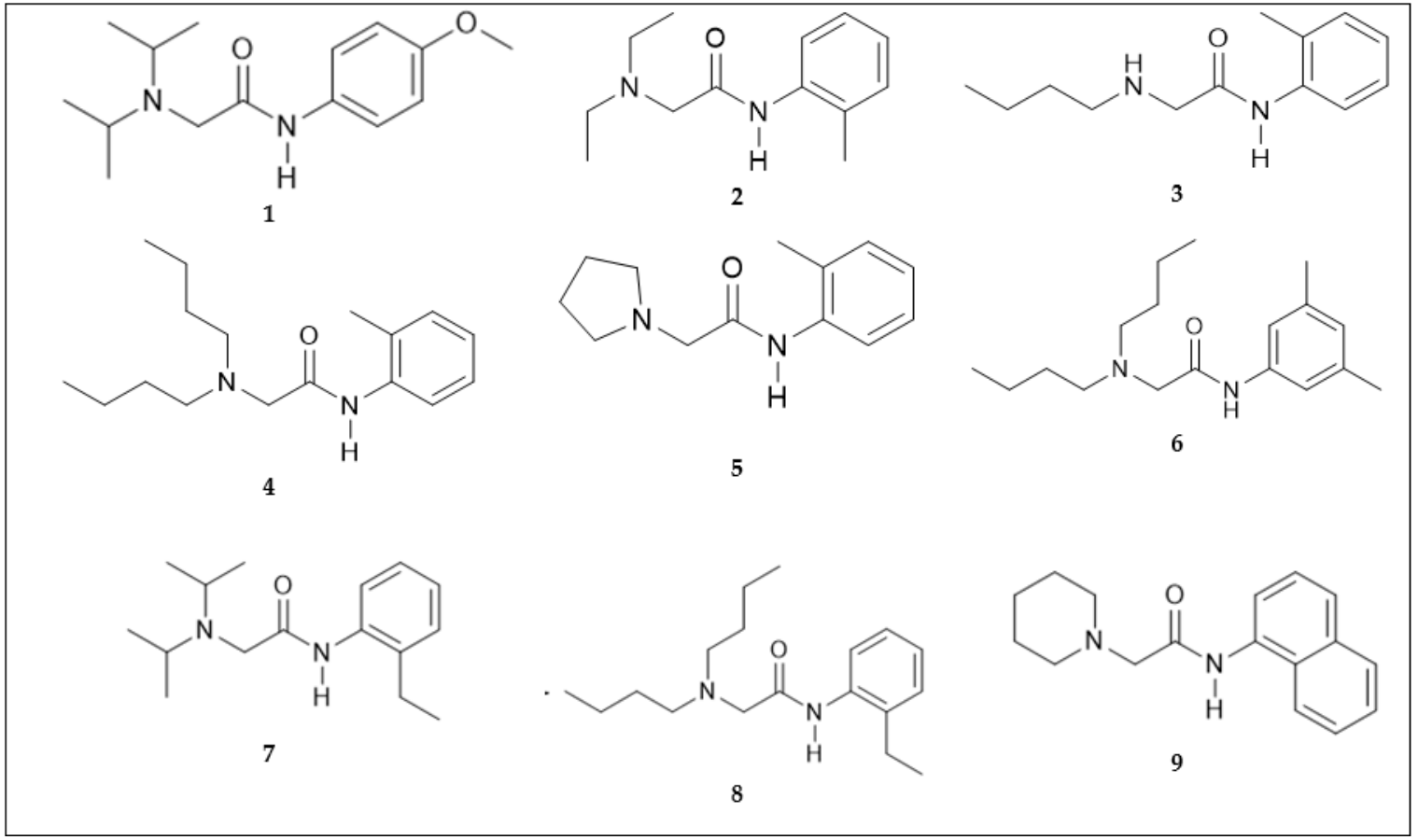
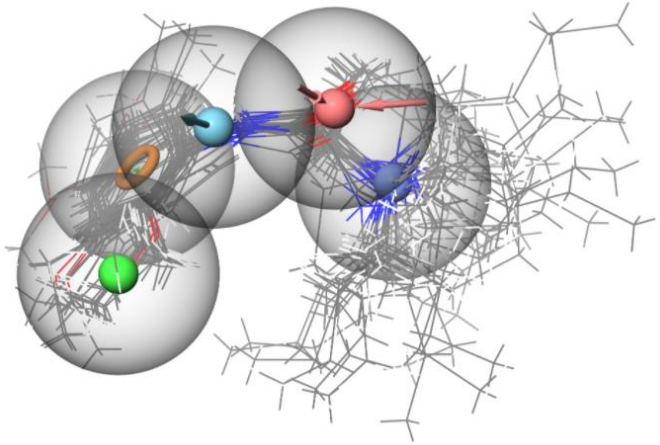
Synthesized compounds





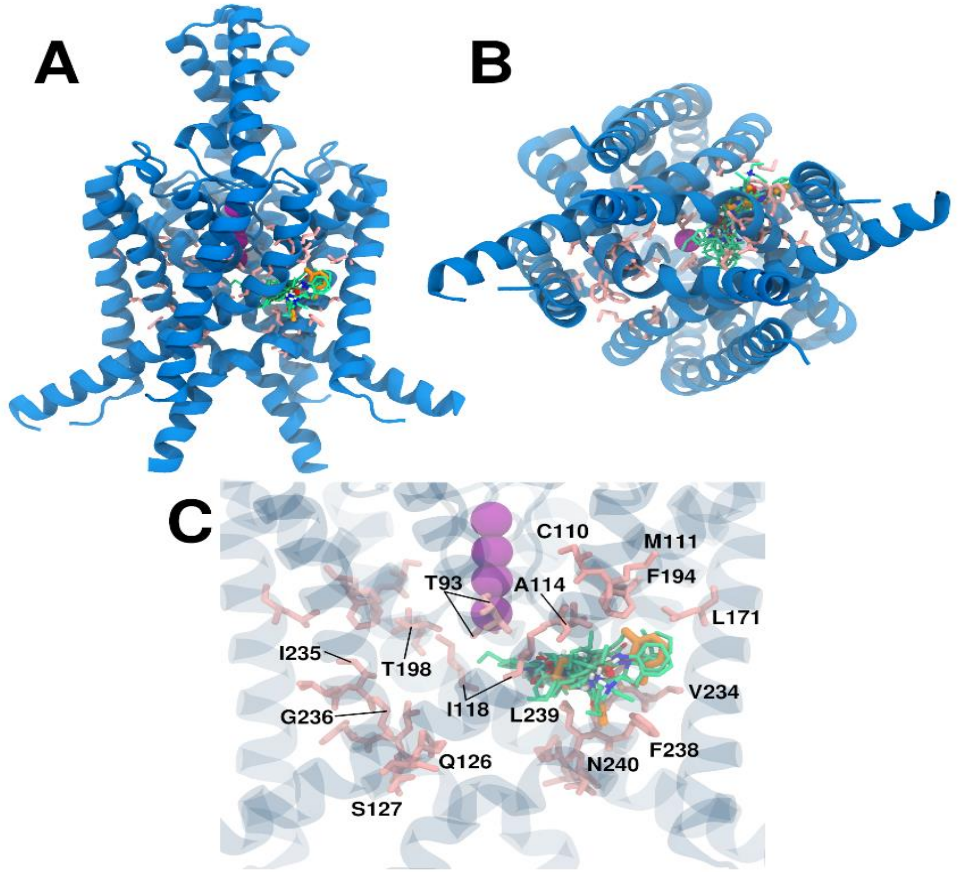
Results

Compound	IFD Score	Pose	Interactions	Total interactions	Total EIS
6_prot	-1052.16	7	A93, B93, B114, A118, B118, A126, A171, A194, A198, B198, A199, B199, A235, A236, A238, A239	16	91.85
6_neut	-1051.13	5	A93, B93, B111, B114, A118, B118, A126, A171, A194, A198, A199, B199, A235, A236, A238, A239	16	90.45
9_neut	-1052.34	8	A93, B93, B114, A118, B118, A126, A194, A198, A199, B199, A235, A236, A238, A239	14	85.42
8_neut	-1050.38	9	A93, B93, B111, B114, B118, A194, A198, A199, B199, A235, A236, A238, A239	13	82.14
5_prot	-1048.26	9	A93, B93, B114, B118, A194, A198, A199, B199, A235, A236, A238, A239	12	80.17
1_prot	-1051.92	3	A93, B93, B114, A118, B118, A126, A171, A194, A198, A199, A235, A236, A238, A239	14	78.26
3_prot	-1049.29	7	A93, B93, B114, A118, B118, A126, A171, A194, A198, A199, A235, A236, A238, A239	14	78.26
4_neut	-1051.27	1	A93, B93, B114, B118, A171, A194, A198, A199, A235, A236, A238, A239	12	73.01
3_neut	-1046.00	8	A93, B93, B114, B118, A126, A194, A198, A199, A235, A236, A238, A239	12	72.98
5_neut	-1050.12	7	A93, B93, B114, B118, A126, A194, A198, A199, A235, A236, A238, A239	12	72.98
7_prot	-1052.30	2	B93, B114, B118, A171, A194, A198, A199, A234, A235, A236, A238, A239	12	70.60
2_neut	-1049.67	10	A93, B93, B114, B118, A194, A198, A199, A235, A236, A238, A239	11	69.94
9_prot	-1053.36	6	A93, B93, B114, B118, A194, A198, A199, A235, A236, A238, A239	11	69.94
Bupivacaine	-1051.66	1	B93, B114, B118, A171, A194, A198, B198, A235, A236, A238, A239	11	62.78
2_prot	-1050.13	9	B93, B114, B118, A194, A198, A199, A235, A236, A238, A239	10	59.71
8_prot	-1051.78	4	B93, B111, B114, B118, A171, A194, A198, A199, A235, A238, A239	11	59.57
4_prot	-1050.99	1	B93, B114, B118, A171, A194, A198, A199, A235, A238, A239	10	57.61

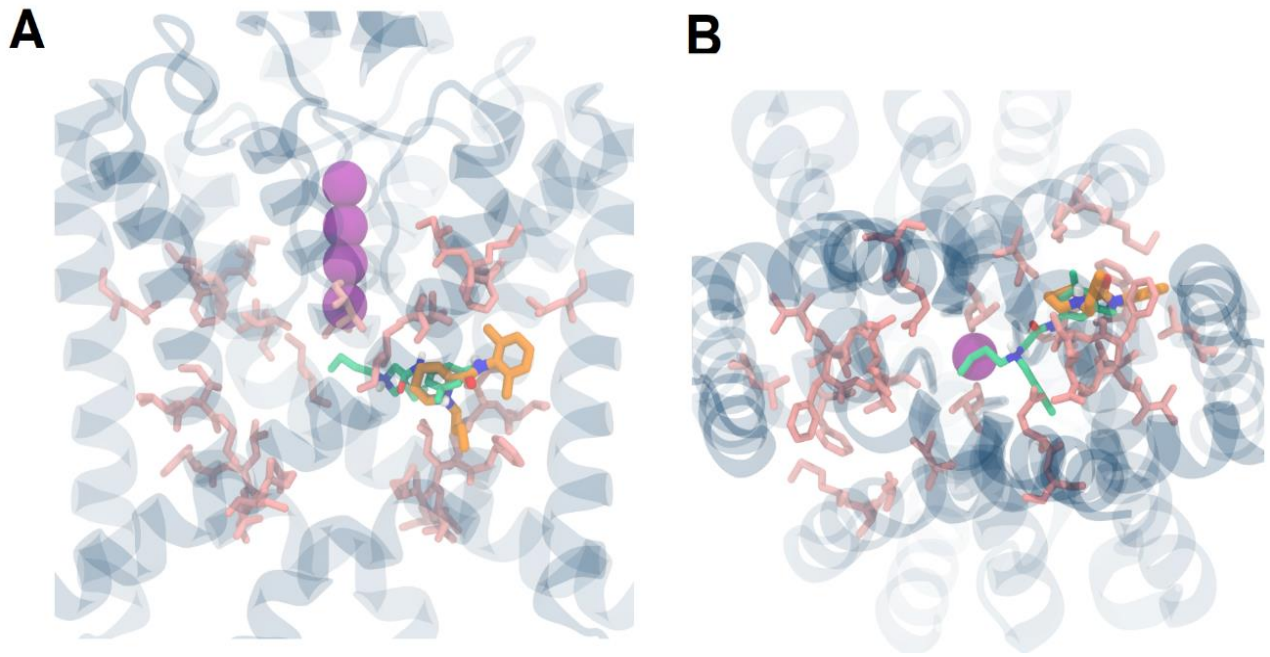
Molecular coupling results for each of the synthesized LA homologous compounds and their possible interactions with key bupivacaine blocking binding residues in the TASK-1 channel.

Results

TASK-1 model of the 6RV3 crystal. (a) Canal model with LA homologues aligned with lateral fenestrations. (b) Top view of the canal. (c) Enlargement of LA interaction residues with those reported for bupivacaine located below the second helix of the pore along with the binding residues in M2 and M4.



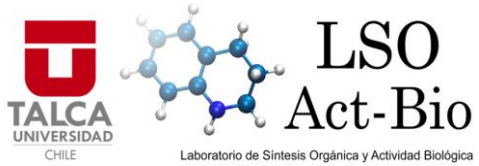
Comparison of the interaction of compound 6 (green) with bupivacaine (orange) in TASK-1 (a) View from the plane of the membrane (b) Top view



Conclusions

A rational design of LAs homologous compounds was carried out, based on the common structural chemical characteristics of LA, the identified pharmacophore, the reported binding site for bupivacaine in TASK-1 channel, and it was possible to establish that the binding site of these new compounds has similarities with bupivacaine BS. Such new compounds could be used in the treatment of AF through the modulation of the action potential.

Through molecular docking analysis it was possible to establish the most stable poses for each ligand with the channel, and by comparative analysis with the bupivacaine binding residues it was possible to calculate the EIS values obtaining higher values for the LAs homologues than for bupivacaine, which converted into interesting compounds as potential TASK-1 channel blockers.



Acknowledgments

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