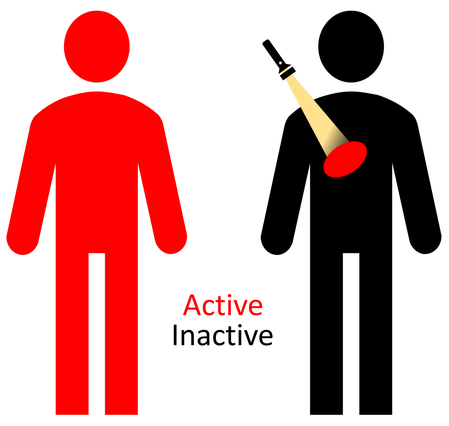
Photophysics and binding pockets of the DAD photoswitch in the $Na_V1.5$ channel: a theoretical study.

Lucía López-Pacios[1], Vito F. Palmisano[1,2], Lara Martínez-Fernández[1,3] and Juan J. Nogueira[1,3]

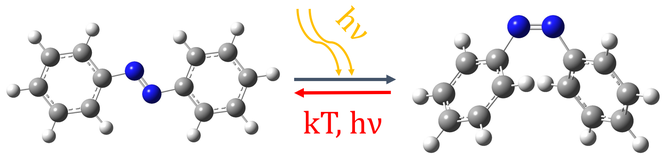
[1]Department of Chemistry, Universidad Autónoma de Madrid, 28049, Madrid, Spain
[2]Theoretical Chemistry Group, Zernike Institute for Advanced Materials, University of Groningen, 9747 AG, Groningen, The Netherlands
[3]Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049, Madrid, Spain

Motivation

Photopharmacology

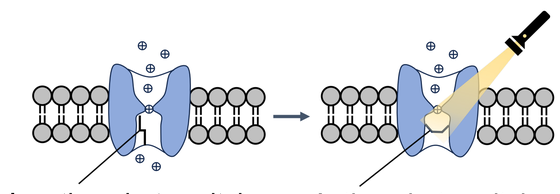


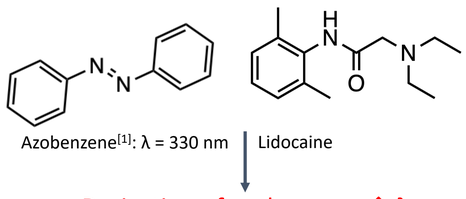
Conventional drugs Photoswitches



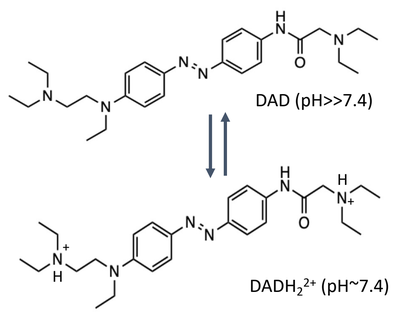
Conformation in the dark
- Biologically inactive
- Non-toxic everywhere

Conformation upon irradiation
- Biologically active only in the desired target



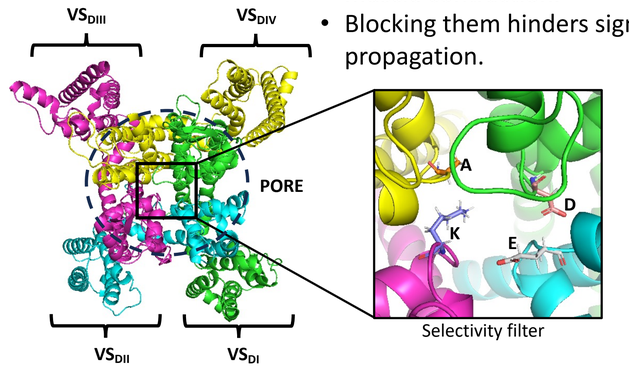


Derivation of azobenzene ↑ λ
DAD[2]: λ = 454 nm



Ion channels

- Transmembrane proteins that control ion transport.
- Key in neuronal transmission and muscle contraction.
- Blocking them hinders signal propagation.



Top view of the $Na_V1.5$ channel[3]

D: Aspartate
E: Glutamate
K: Lysine
A: Alanine

Computational details

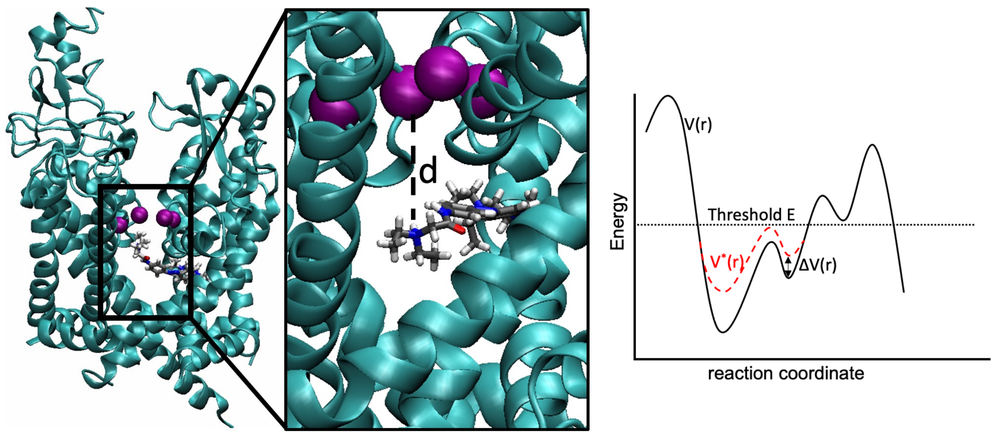
- Binding Pocket search ($DADH_2^{2+}$)

Docking → GaMD → cMD → MMGBSA
Docking: Preliminar pockets
GaMD: More accurate pockets
cMD: Stabilization of pockets
MMGBSA: ΔG of pockets

- Absorption spectra
  - Static (vacuum (TDDFT, CASSCF, CASPT2) and solvent (LR-PCM-TDDFT)) → DAD, $DADH_2^{2+}$, azobenzene
  - Dynamic (solvent (LR-PCM-TDDFT, QM/MM) and pockets (QM/MM)) → QM region = $DADH_2^{2+}$

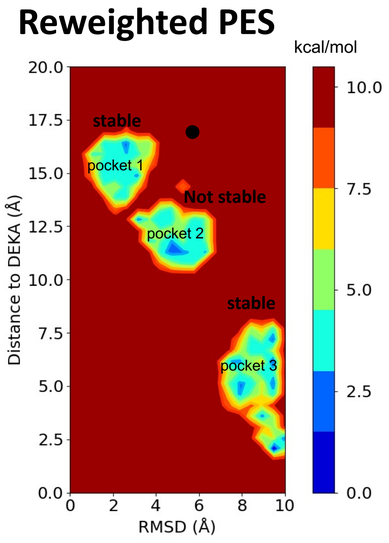
- Photoisomerization (DAD, $DADH_2^{2+}$, azobenzene): vacuum (TDDFT) and solvent (LR-PCM-TDDFT)

Reweighting reaction coordinate

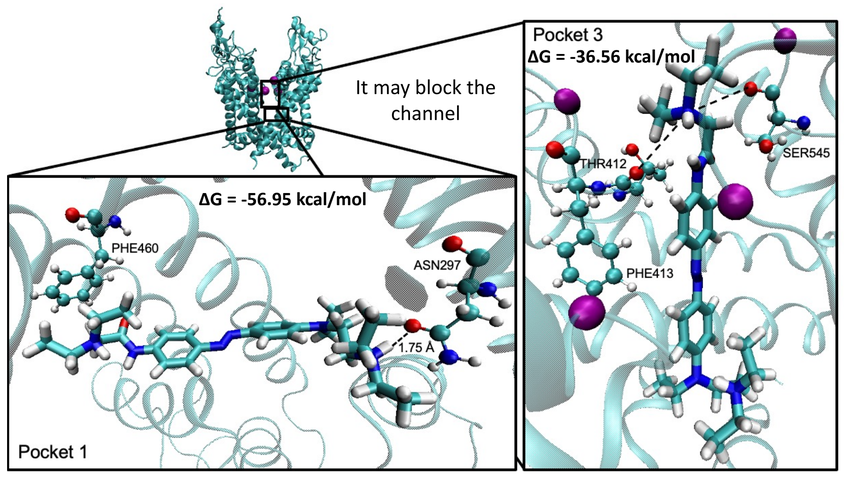


Binding pocket search

Reweighted PES



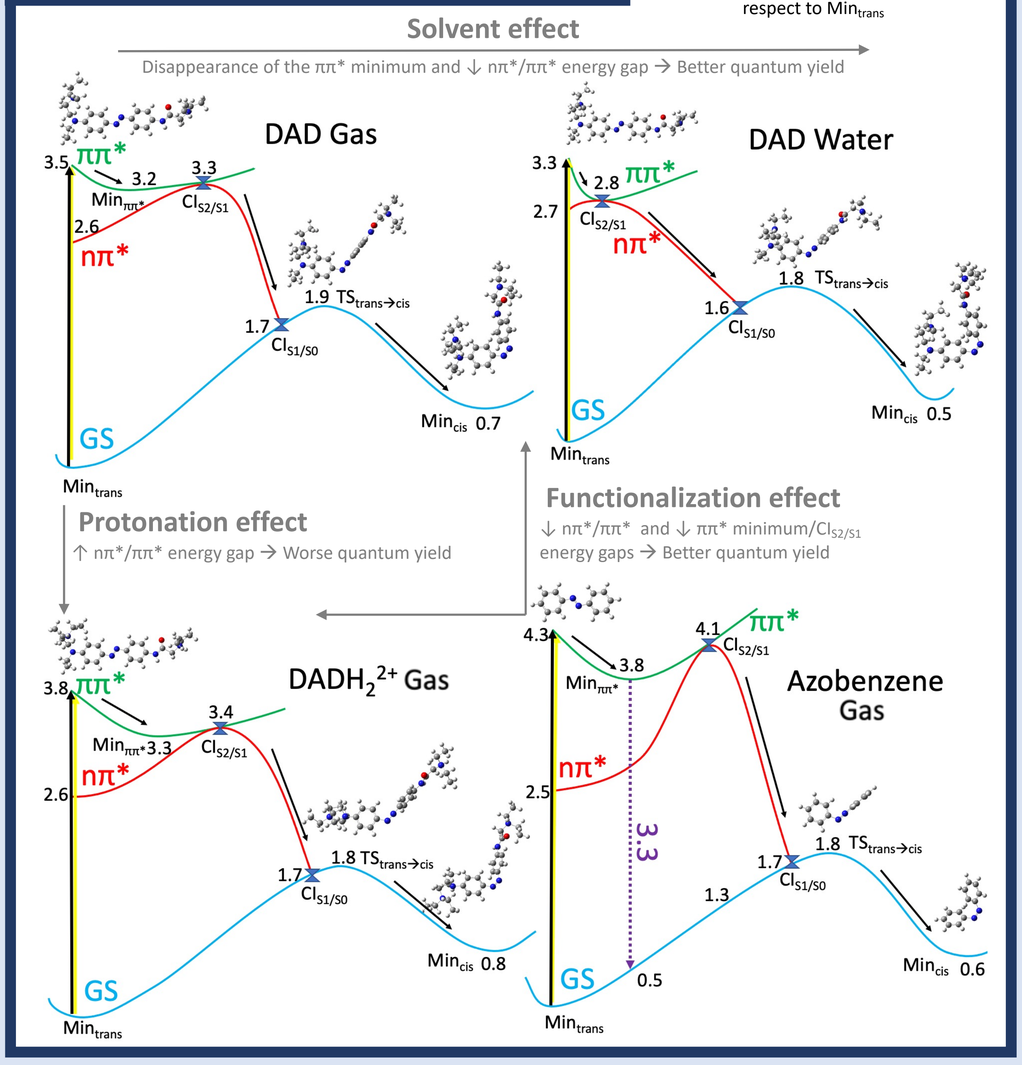
MMGBSA Analysis



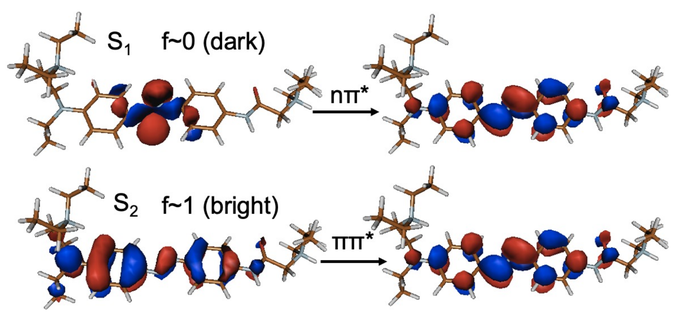
Most important contribution to stabilisation: electrostatic

Photoisomerisation

Energies in eV at M06-2X/cc-pVDZ with respect to Min_{trans}



Absorption spectra

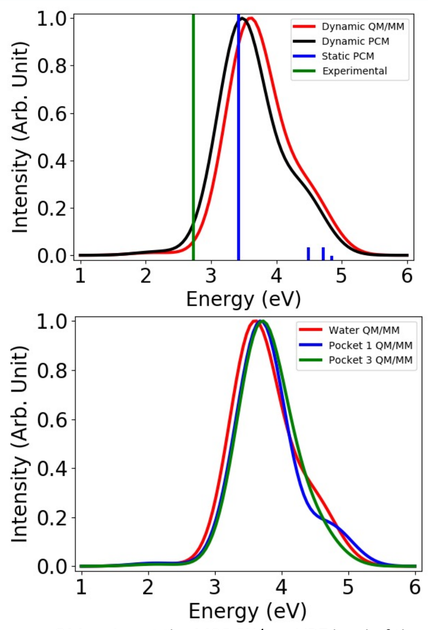


Solvent effect and functionalization
- ππ* (S_2) ↓
- nπ* (S_1) ↑

} S_2-S_1 gap ↓

Protonation effect
- ππ* (S_2) ↑
- nπ* (S_1) ↓

} S_2-S_1 gap ↑



QM region at the M06-2X/cc-pVDZ level of theory

Conclusions

- Pocket 1 is the most favourable pocket for *trans*-$DADH_2^{2+}$.
- The nπ*/ππ* gap
  - ↓ Polar solvents, Derivation of azobenzene
  - ↑ DAD protonation
- Among the considered systems, the most favourable photoisomerization occurs for DAD in water.
- The QM region will be increased to describe the protein environment more accurately.

References

1. Jianqiang Zhao *et. al*., *J. Theor. Comput. Chem.*, **2021**, 1200, 113244.
2. Laura Laprell *et. al*., *J. Clin. Investig.*, **2017**, 127(7), 2598-2611.
3. Daohua Jiang *et. al*., *Cell*, **2021**, 184(20), 5151-5162.e11.
4. Juan J. Nogueira *et. al*. *The Oxford Handbook of Neuronal Ion Channels*, **2019**.