Caractérisation de la toxicité des insecticides néonicotinoïdes à l'échelle microscopique : que peut-on apprendre de la modélisation moléculaire ?

Jean-Yves Le Questel, CEISAM UMR 6230

Equipe ModES

https://ceisam.univ-nantes.fr/activites-de-recherche/equipe-modes/

Introduction

- Limited ressources
- Growing demography
- Need to feed earthlings and protect the cultures
- Various politics for agriculture around the world
- Global warming (expansion of exotic species (asian hornet, tiger mosquito…)
- Vector-borne diseases
- Threats on biodiversity
- Pollution by chemicals

Introduction

Some (very brief) chronology

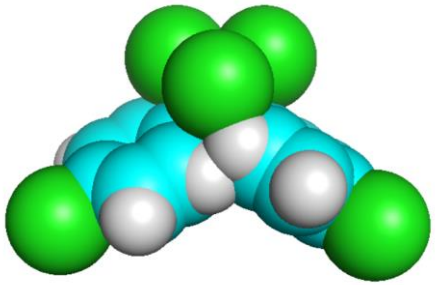
- Homer (*The Iliad and The Odyssey*) : the "divine cleansing" ritual using sulfur which helped to get rid of lice…

- Till the mid 1940s : inorganic and botanical preparations (eg : tobacco extracts…)

- The « era » of DDT : Nobel prize in 1948… forbidden in 1958

- Second half of the 20th century:
  - Organophosphates
  - Carbamates (among which carbaryl, Bhopal 1984)
  - Pyrethrins /pyrethroids (permethrin, cypermethrin, and deltamethrin)

- Then ? Neonicotinoids !



Dichloro-Diphenyl-Trichloroethane (DDT)

Introduction

The gold period of neonicotinoids

- Considered as the most improved and selective insecticides
- Much more selective than the other insecticides for insects over mammals
- Lower toxicity
- Mode of action very different from other insecticides: *systemic*: absorbed by the plant and move around in its tissues (not used by spray but by seed coating)

Pest Management Science *Pest Manag Sci* **64**:1084–1098 (2008)

Review

Neonicotinoids – from zero to hero in insecticide chemistry

Peter Jeschke[1]* and Ralf Nauen[2]

[1]*Bayer CropScience AG, Research Insecticides Chemistry Insecticides, Building 6240, Alfred-Nobel Str. 50, D-40789 Monheim am Rhein, Germany*

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Introduction

- Adverse effects
  - Involved in the bees colony collapse disorder
  - Accute and chronic poisoning for several species

  (not only non targeted insect species like bees, bird species, fishes…)

- Extensive use: frequent occurrence of corresponding metabolites in humans

- Raising concerns on potential health effects on non-targeted mammals

Environ Sci Pollut Res (2015) 22:68–102
DOI 10.1007/s11356-014-3471-x

WORLDWIDE INTEGRATED ASSESSMENT OF THE IMPACT OF SYSTEMIC PESTICIDES ON BIODIVERSITY AND ECOSYSTEMS

Effects of neonicotinoids and fipronil on non-target invertebrates

L. W. Pisa · V. Amaral-Rogers · L. P. Belzunces · J. M. Bonmatin · C. A. Downs · D. Goulson · D. P. Kreutzweiser · C. Krupke · M. Liess · M. McField · C. A. Morrissey · D. A. Noome · J. Settele · N. Simon-Delso · J. D. Stark · J. P. Van der Sluijs · H. Van Dyck · M. Wiemers

Environment International 163 (2022) 107201

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/envint

Review article

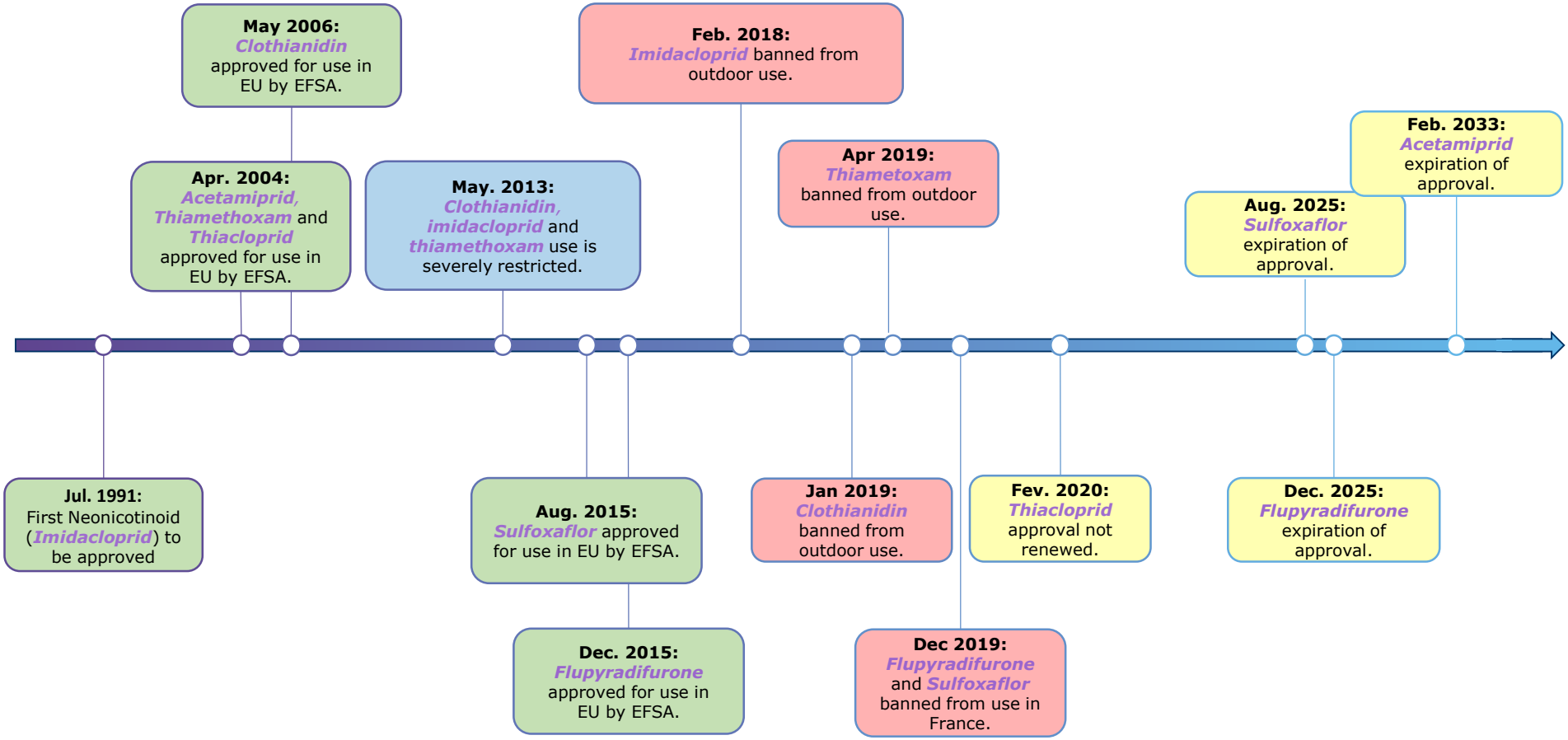
Human exposure to neonicotinoids and the associated health risks: A review

Duo Zhang, Shaoyou Lu *

School of Public Health (Shenzhen), Sun Yat-sen University, Guangzhou 510275, China

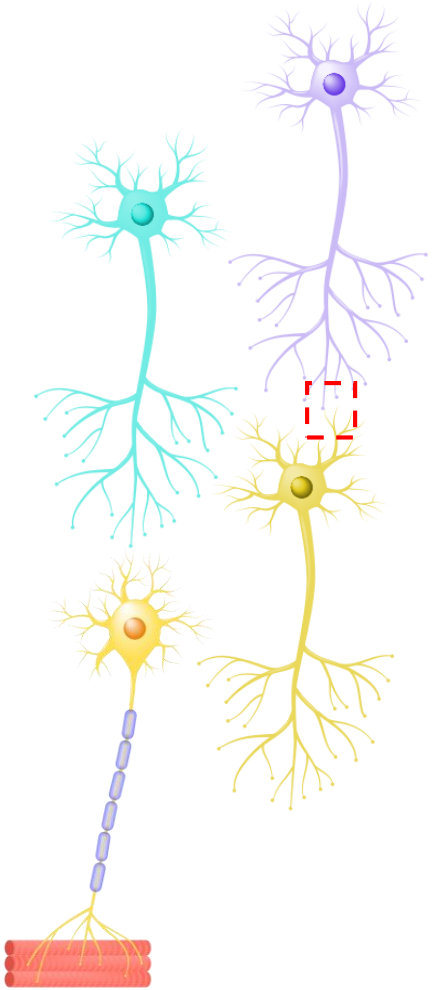
Introduction

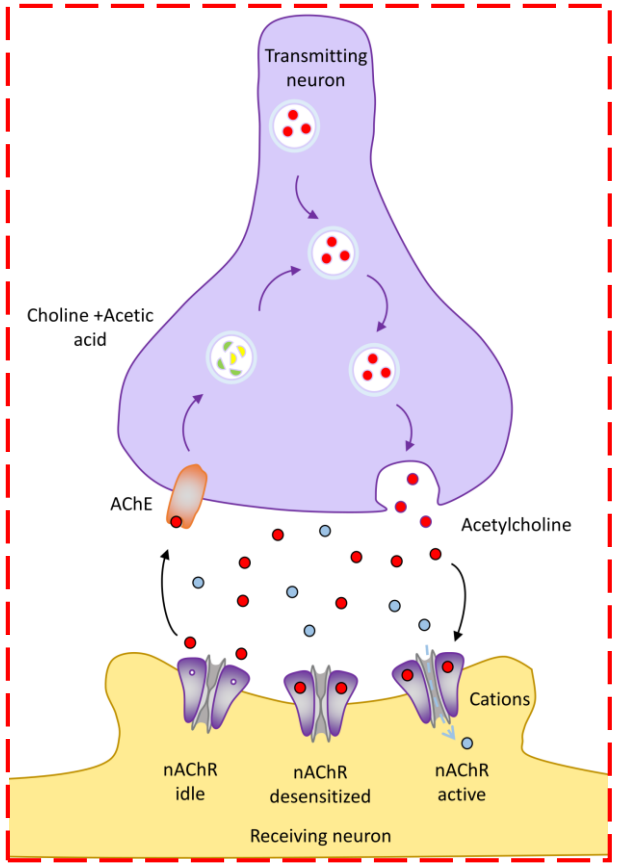
Neonicotinoids legal timeline in European Union

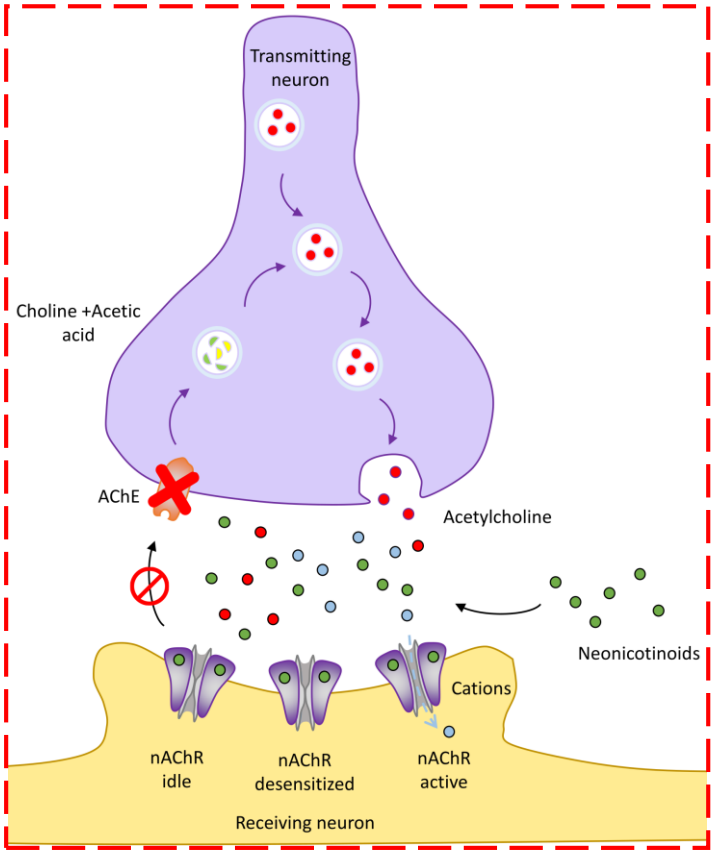


How do neonicotinoids work ?

- Nervous system :
- Normal Neurotransmission :
- Neonicotinoids' effect:

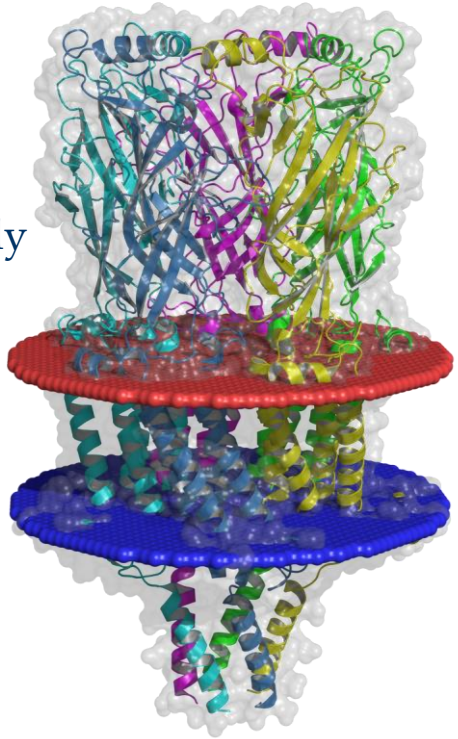


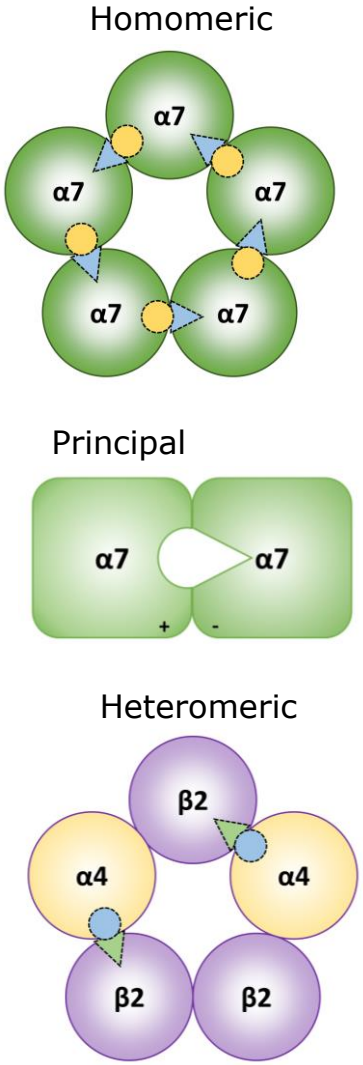




Neonicotinoids target

- Nicotinic Acetylcholine reptors (nAChRs)
- Ligand-gated ion channels (**LGIC**)
- Belong to the **Cys-loop receptors** superfamily
- **Pentameric** organisation: α, β, δ, γ and ε subunits
- Structural information:
  heteromeric human α4β2, *Nature* (2016)
  homomeric human α7, *Cell* (2021)
- Limited informations on insects nAChRs
- No structural information…



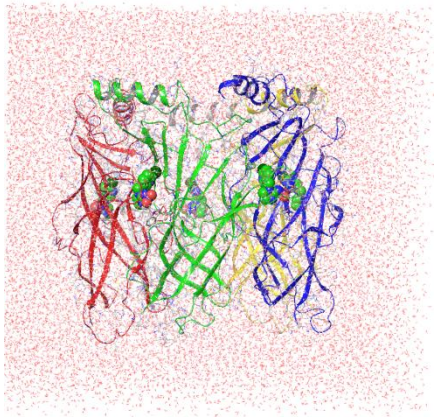


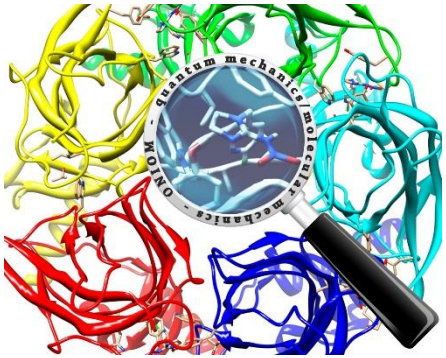
Our approach

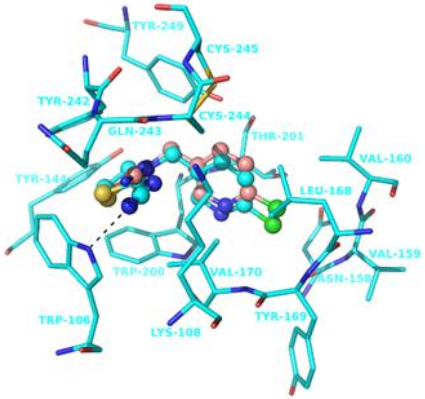
Molecular Modeling

Quantum physics

Classical physics

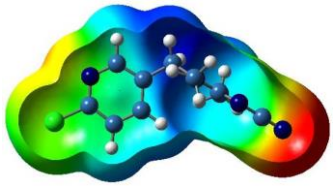






Hybrid methodologies
(QM/QM')
Refinement (geometry, energy)

Molecular Dynamics simulations
Average geometry over the simulation period



Docking (best orientation, interaction geometry …)
ranking, scoring…

Quantum chemistry
(conformations, interaction sites…)
of the **ligands**)

3D Experimental structures
(ligand, nAChR) ?

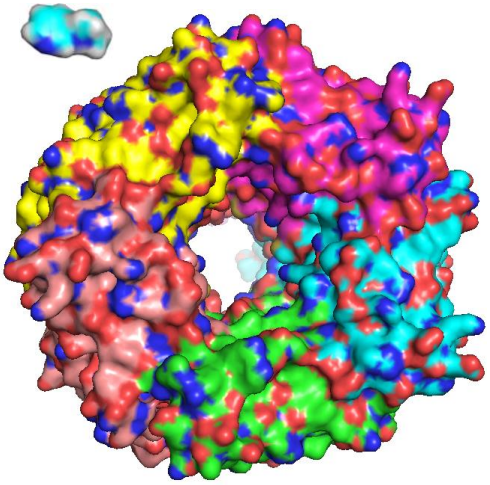
Homology modeling

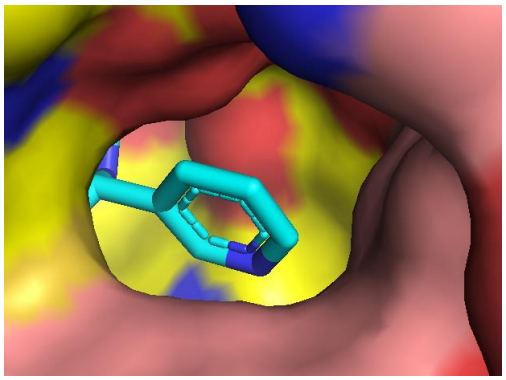
Some key points about molecular molecular modeling

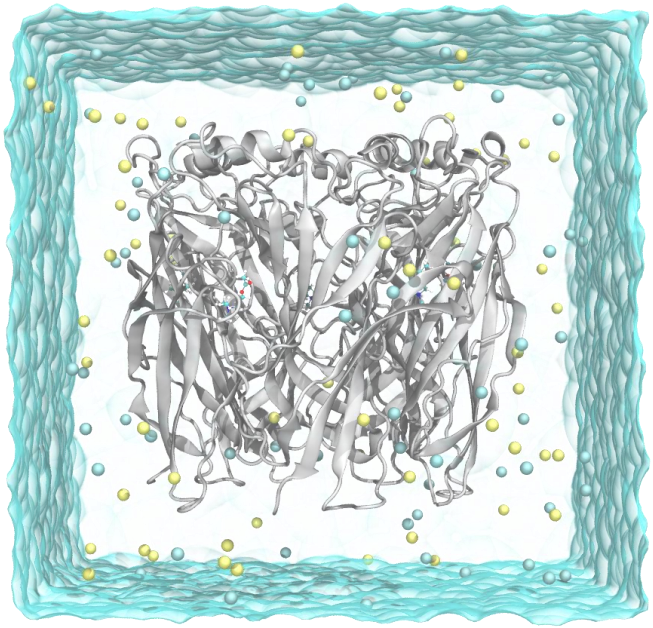
- Are **experimental** structures available ?
- For classical physics methods, are the **required parameters** available in the tools used ?

  tailored predominantly for pharmaceutical research
- **Dynamic effects** might be important

  challenging simulations (size of the system? time length ?)







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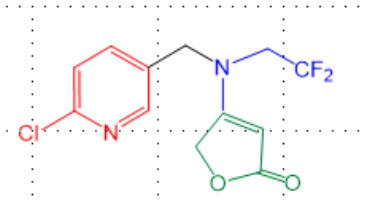
Some results Molecular docking of flupyradifurone to human α7 nAChRs



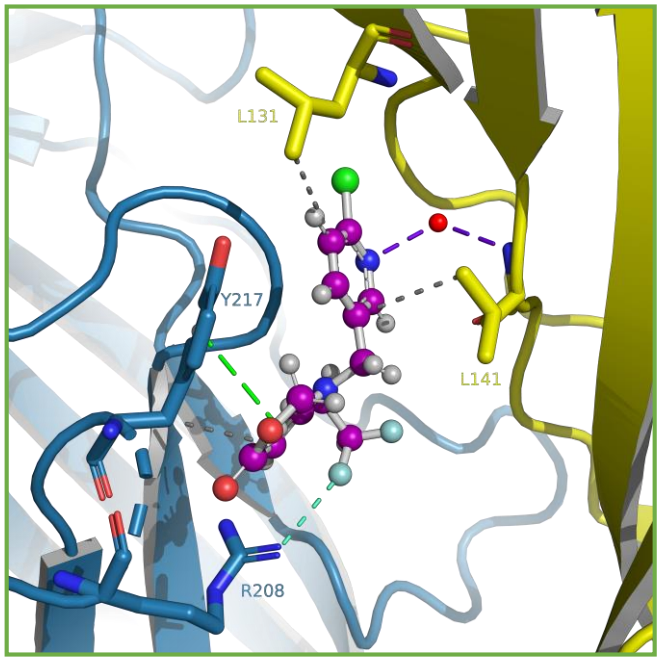
- 2 possible **binding modes** identified

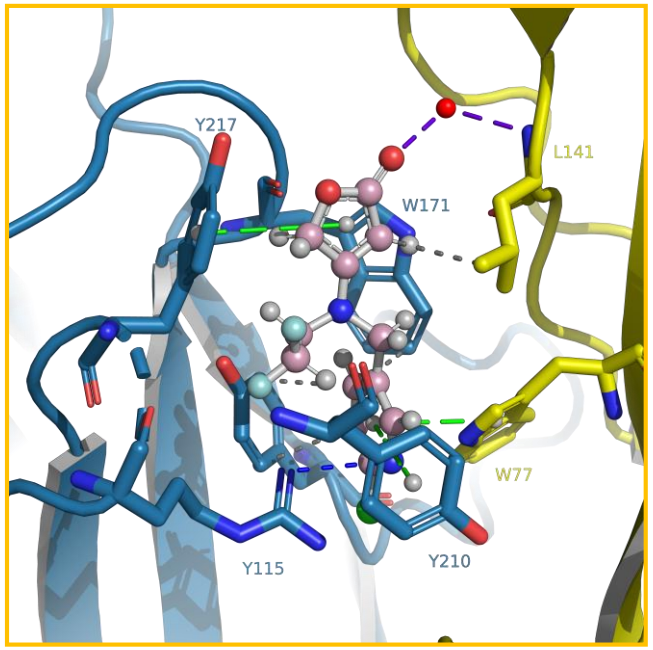
Journal of Medicinal Chemistry
pubs.acs.org/jmc
Article

Structural Biology-Guided Design, Synthesis, and Biological Evaluation of Novel Insect Nicotinic Acetylcholine Receptor Orthosteric Modulators

Mark Montgomery, Stefano Rendine, Christoph T. Zimmer, Jan Elias, Jürgen Schaetzer, Thomas Pitterna, Fides Benfatti, Marisa Skaljac, and Aurélien Bigot*

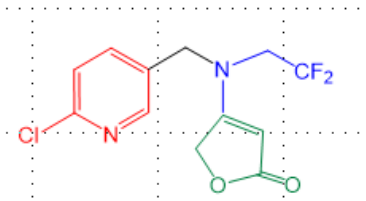
Cite This: J. Med. Chem. 2022, 65, 2297−2312 Read Online

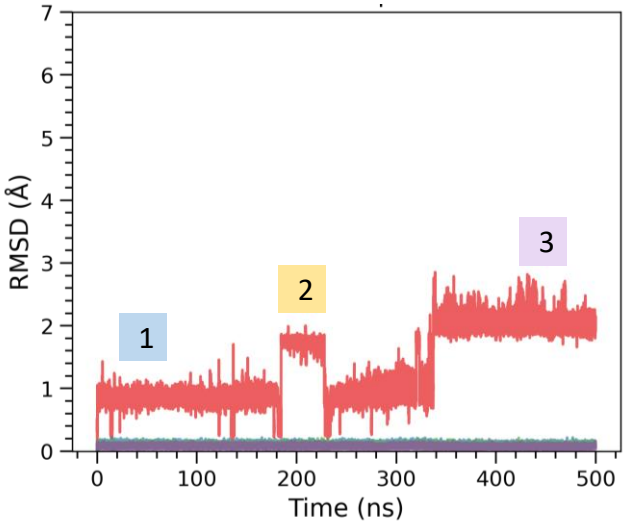


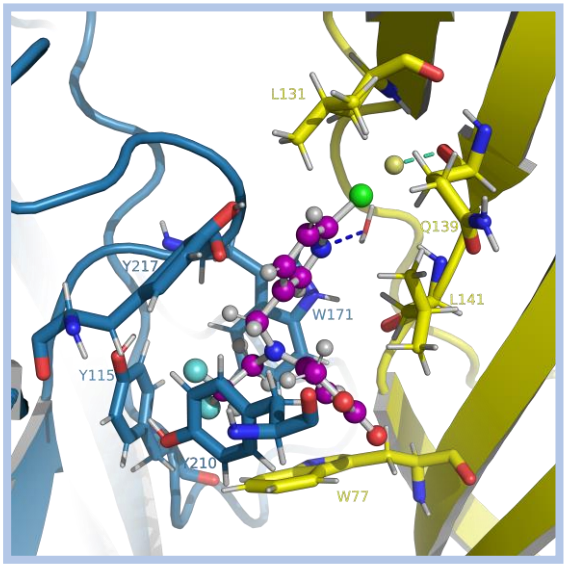


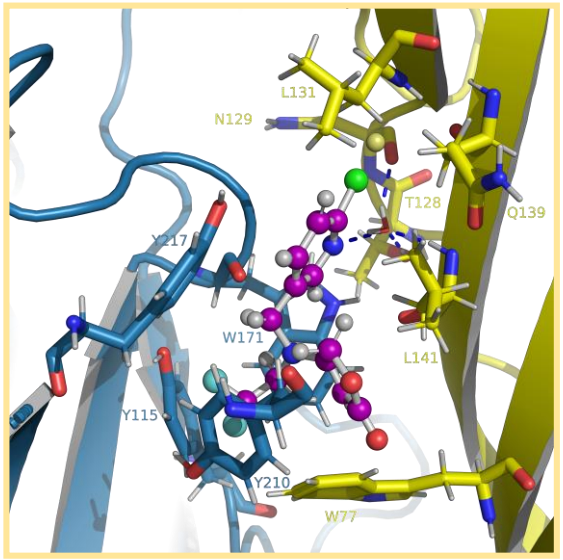
Flupyradifurone /human α7 nAChRs

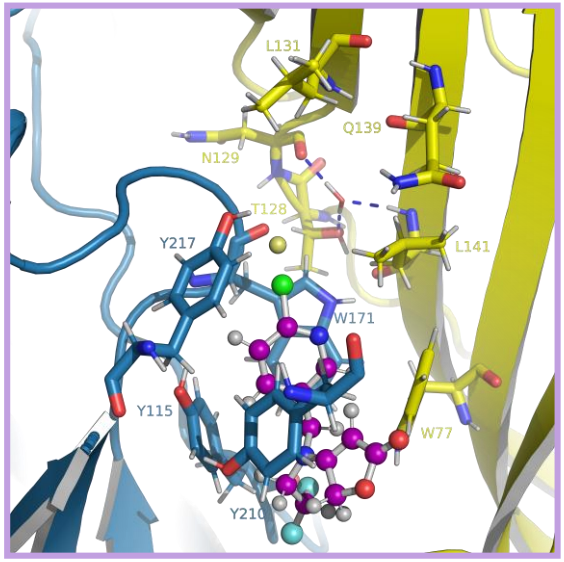
- **Five replicas of 500 ns**
  - Only **one** stable !...











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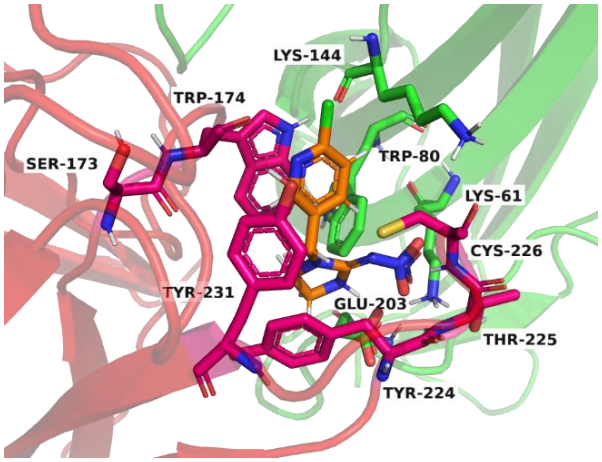
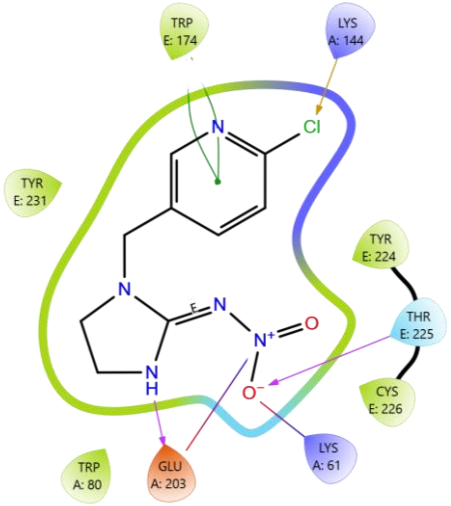
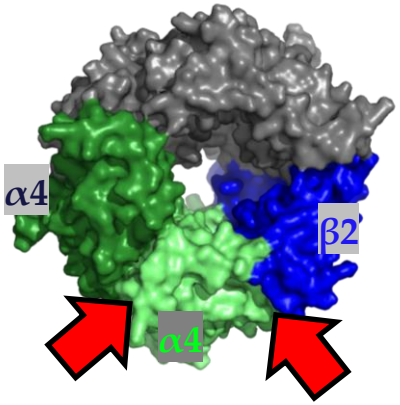
Some results

Bees nAChRs : heteromeric α4β2

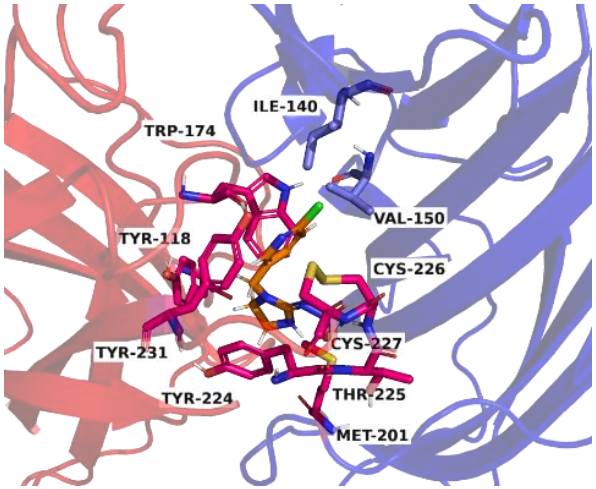
α4/α4 interface

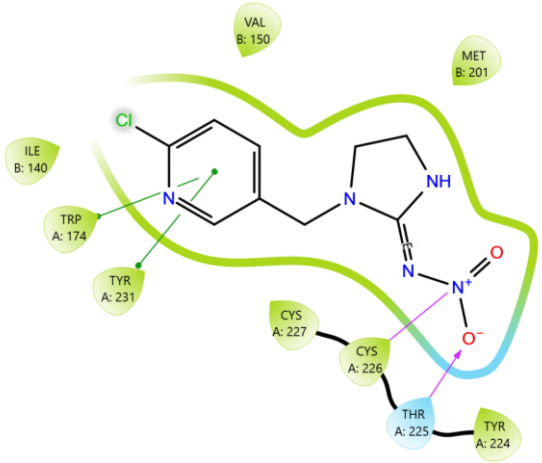






α4/β2 interface





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Conclusions

- A challenging target
- The need of **experimental** collaborations and data
- Important gap between the various scales of study
- The « unique » position of Molecular Modeling…
- « **Validation** » of the theoretical results required…
- Insights into key features (physicochemical, binding) of neonicotinoids
- Rationalisation of their behavior / mode of action

Aknowledgements

PhD students

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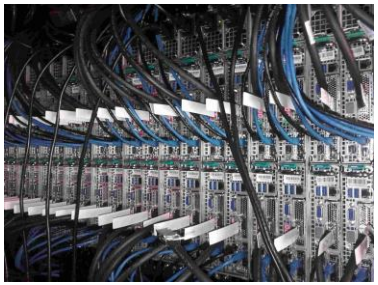
Steeve Thany

Nicolas Galland

Funding

Computing resources:



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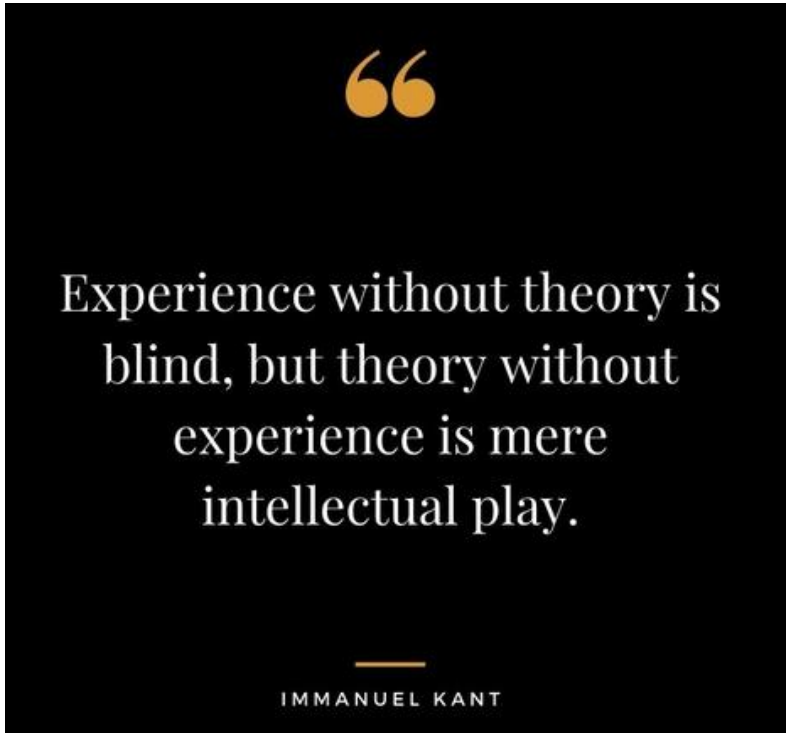

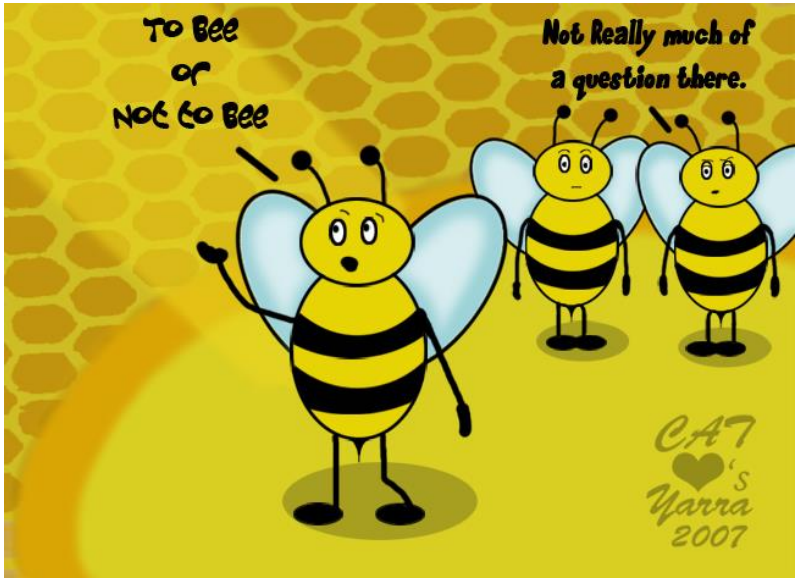

Questions ??…

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