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Diversity in the binding interactions of nicotinic ligands to the nAChRs and associated conformational fluctuations: Insights into the core motif dictating antagonism (JMC 2019, Poster)

Yves Bourne, Gerlind Sulzenbacher, Zoran Radić, Laurent Chabaud, Rómulo Aráoz, Evelyne Benoit, Armen Zakarian, Denis Servent, Catherine Guillou, Palmer Taylor, et al.

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Yves Bourne, Gerlind Sulzenbacher, Zoran Radić, Laurent Chabaud, Rómulo Aráoz, et al.. Diversity in the binding interactions of nicotinic ligands to the nAChRs and associated conformational fluctuations: Insights into the core motif dictating antagonism (JMC 2019, Poster). Canaux ioniques activés par les ligands: de la structure atomique à la transmission synaptique / Ligand-gated ion channels: from atomic structure to synaptic transmission, May 2019, Roscoff, France. , 2024. hal-04771646

HAL Id: hal-04771646

<https://hal.science/hal-04771646v1>

Submitted on 8 Nov 2024

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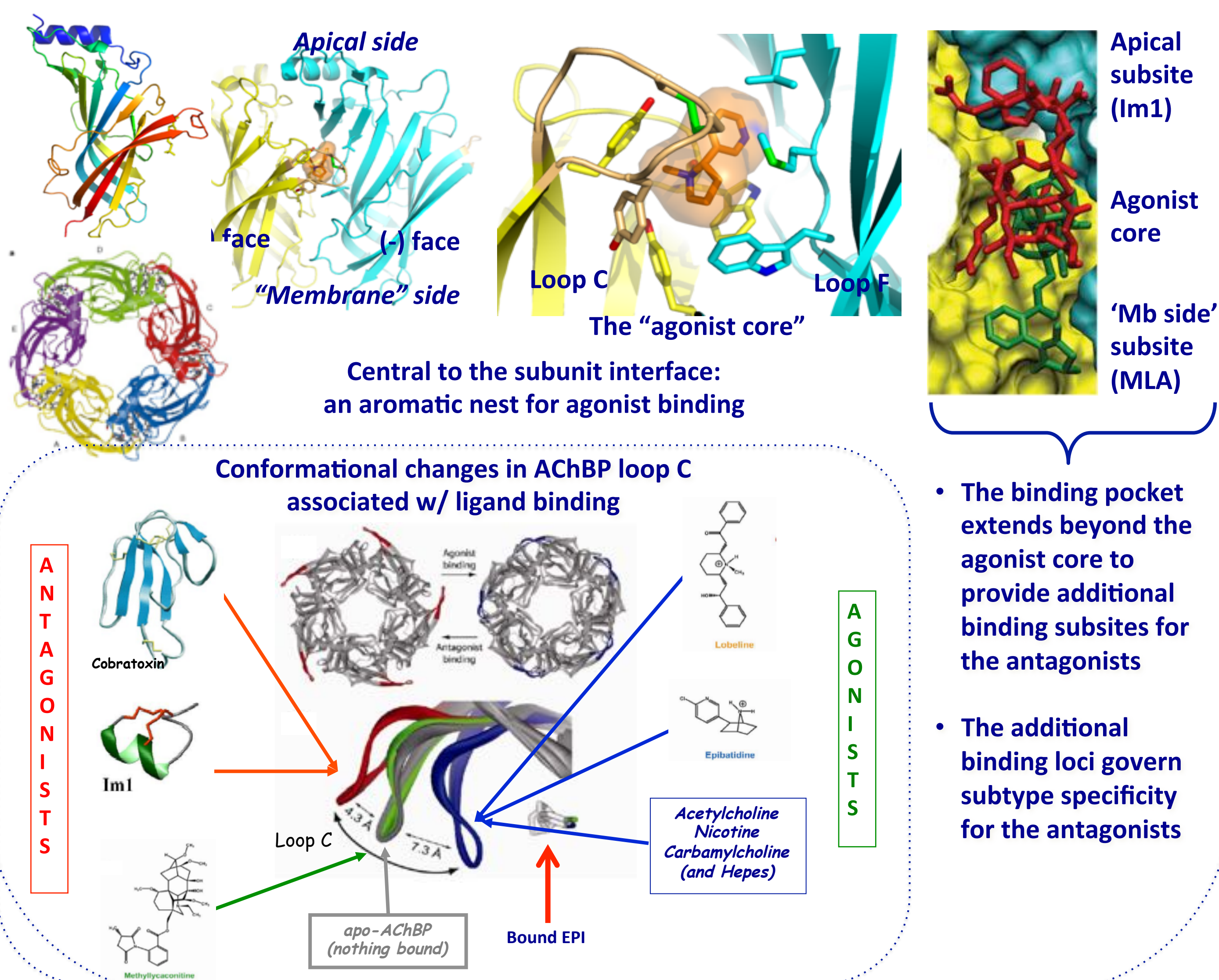
Diversity in the binding interactions of nicotinic ligands to the nAChRs and associated conformational fluctuations: Insights into the core motif dictating antagonism

Bourne Y¹, Sulzenbacher G¹, Radić Z², Chabaud L³, Aráoz R⁴, Benoit E⁴, Zakarian A⁵, Servent D⁴, Guillou C³, Taylor P², Molgo J⁴, & Marchot P¹



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1- Binding of nicotinic antagonists and agonists to the soluble, homopentameric nAChR surrogate, AChBP



2- Marine phycotoxins from dinoflagellate organisms

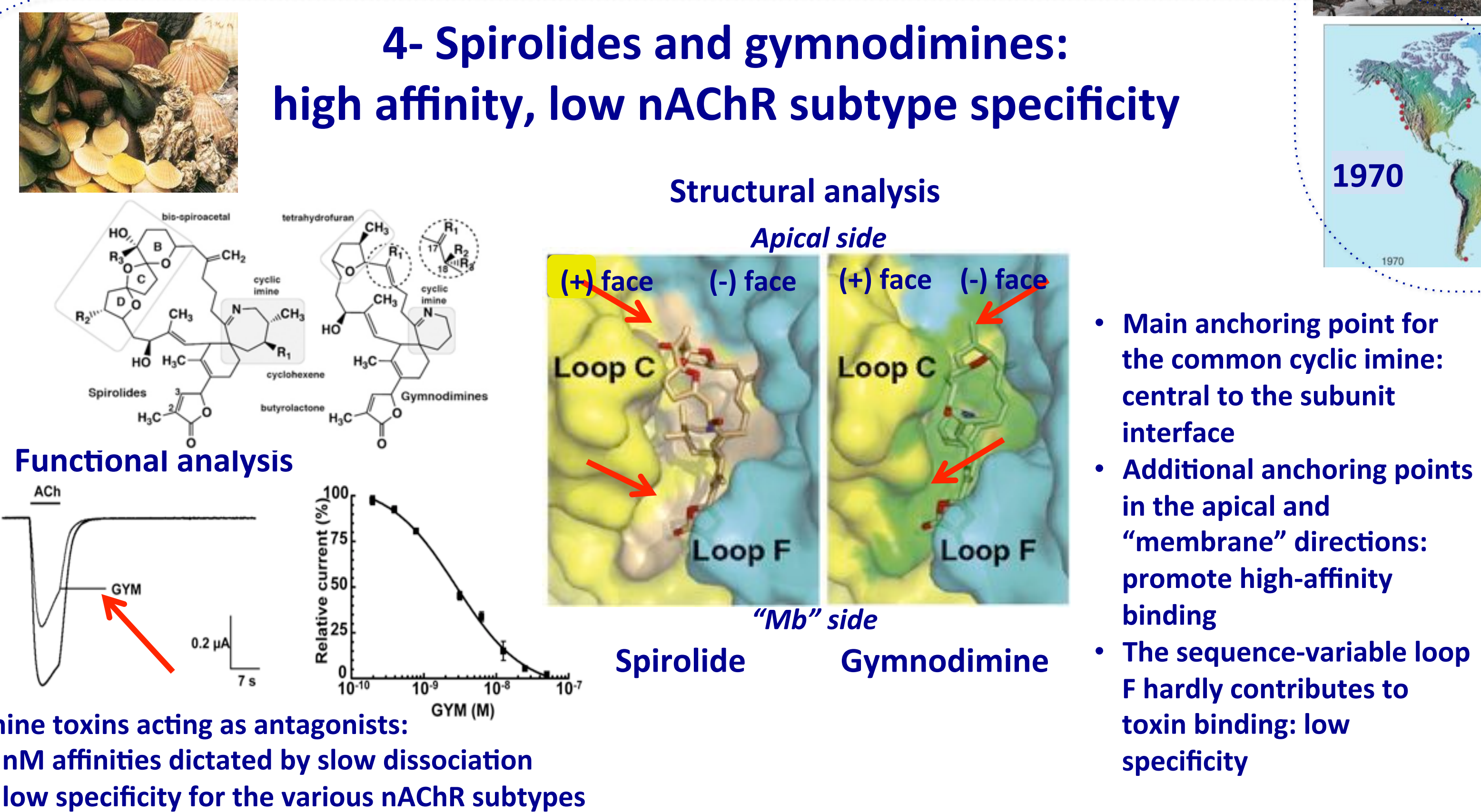


3- A combination of experimental approaches

- Synthesize toxins and analogs with controlled (+/-) and (R/S) properties
- Define mode of action, affinity, and subtype specificity for nAChR subtypes* in the membrane state (transfected oocytes), using voltage-clamp electrophysiology
- Record affinity and subtype specificity by competition binding at equilibrium to nAChR subtypes* in the membrane state (transfected HEK cells)
- Record kinetics and affinities for binding to soluble AChBP subtypes and mutants
- Crystallize (by hand!) the preformed AChBP complexes and solve their crystal structures

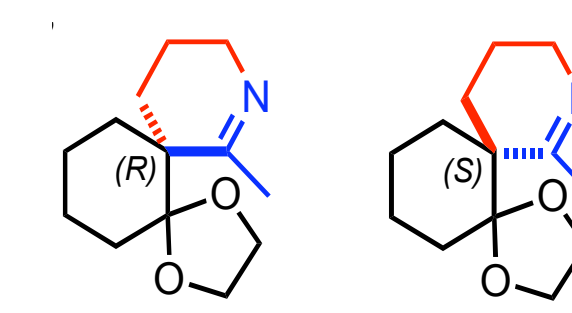
*muscle-type $\alpha_1\beta\gamma\delta$ and neuronal α_7 , $\alpha_4\beta_2$, $\alpha_3\beta_4$

4- Spirolides and gymnodimines: high affinity, low nAChR subtype specificity

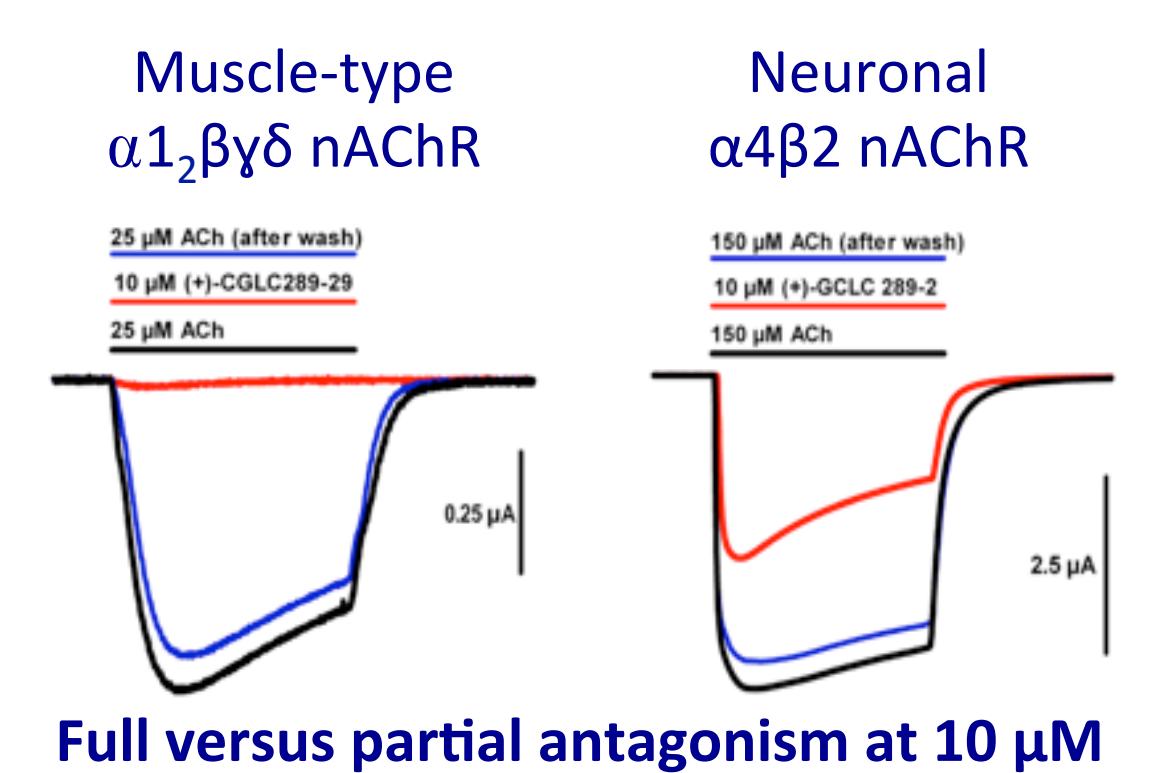


6- Is the imine core found in the macrocyclic toxins sufficient for dictating nicotinic antagonism?

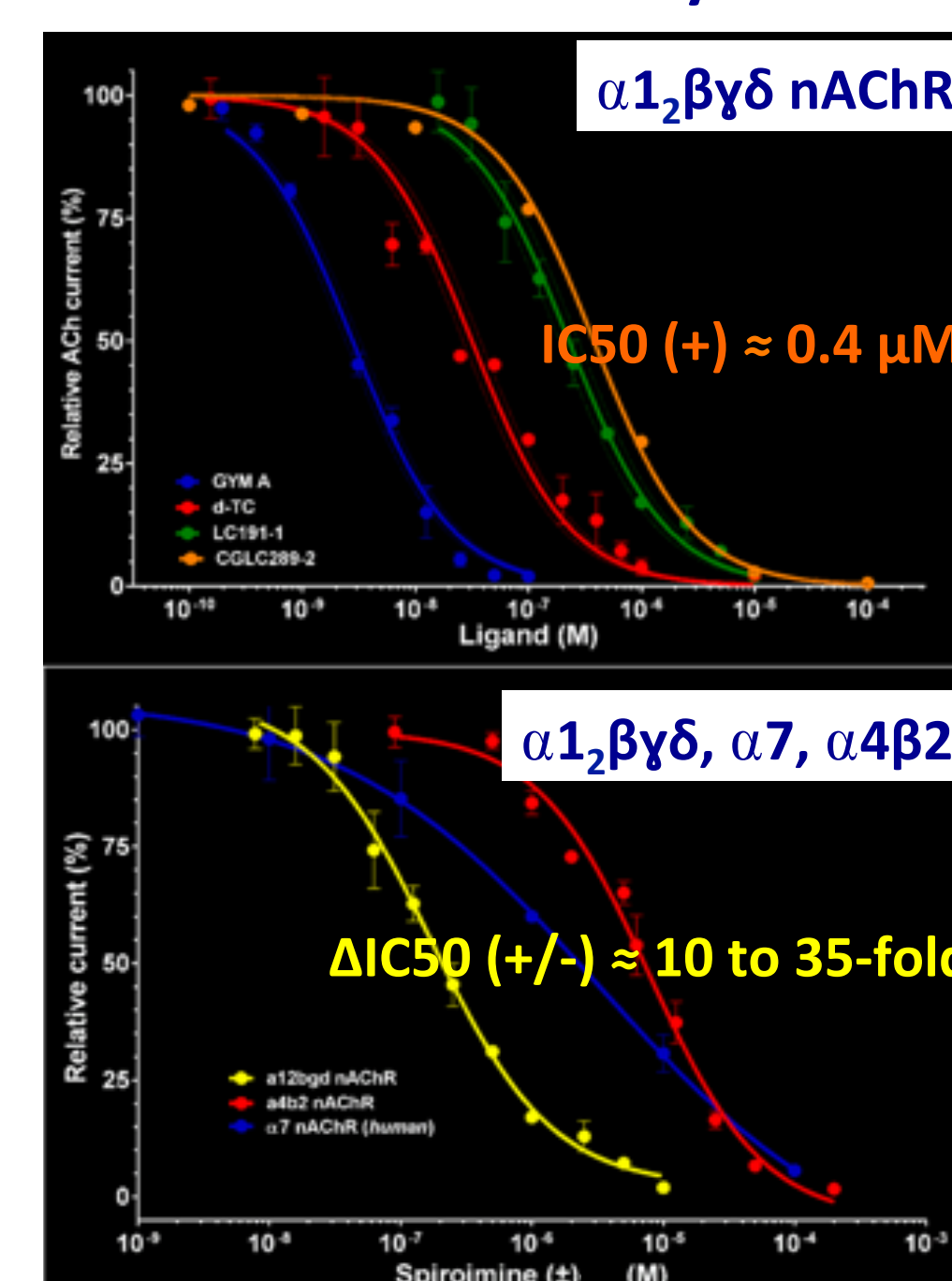
(R)-(+)- and (S)-(-) spiroimine



Inhibition of ACh-evoked currents

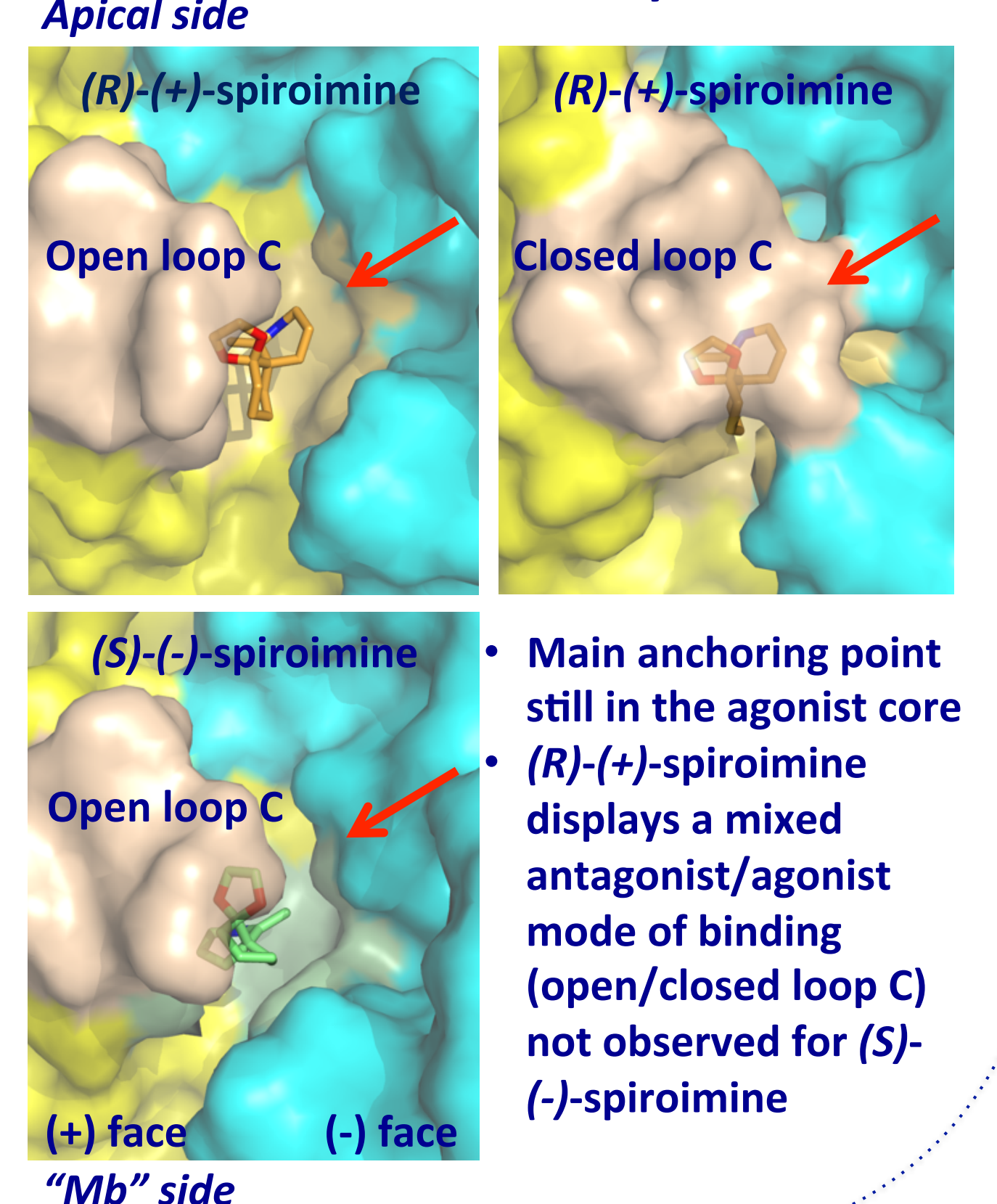


Functional analysis



- Compared with the macrocyclic imines:
- much lower affinity for the nAChRs and AChBPs, associated with limited interaction networks
 - moderate nAChR subtype specificity
 - longer term antagonistic properties

Structural analysis



5- Pinnatoxins: high affinity, high nAChR subtype specificity

