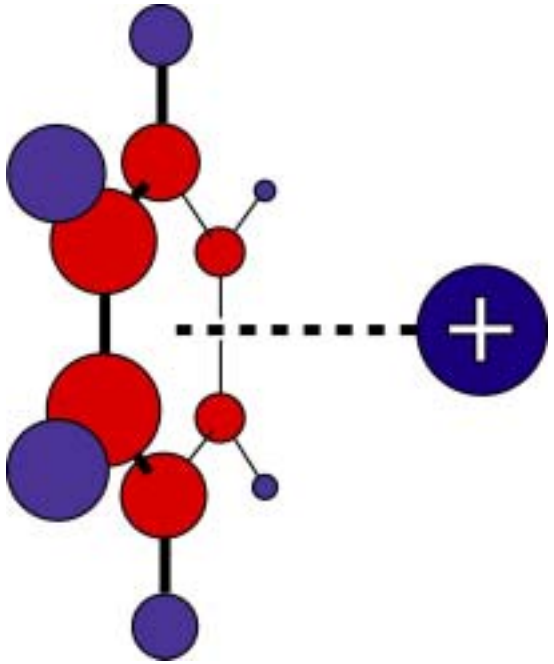
Case Study 1: Determining Key Binding Interactions Between the Neurotransmitter and the Receptor

- Neurotransmitters generally carry a positive charge
- We have established that in several systems, that positive charge is recognized by a tryptophan or tyrosine residue of the receptor, making a cation-π interaction

The Cation-π Interaction



Stabilizing Interaction Between a Cation and the Face of a Simple Aromatic

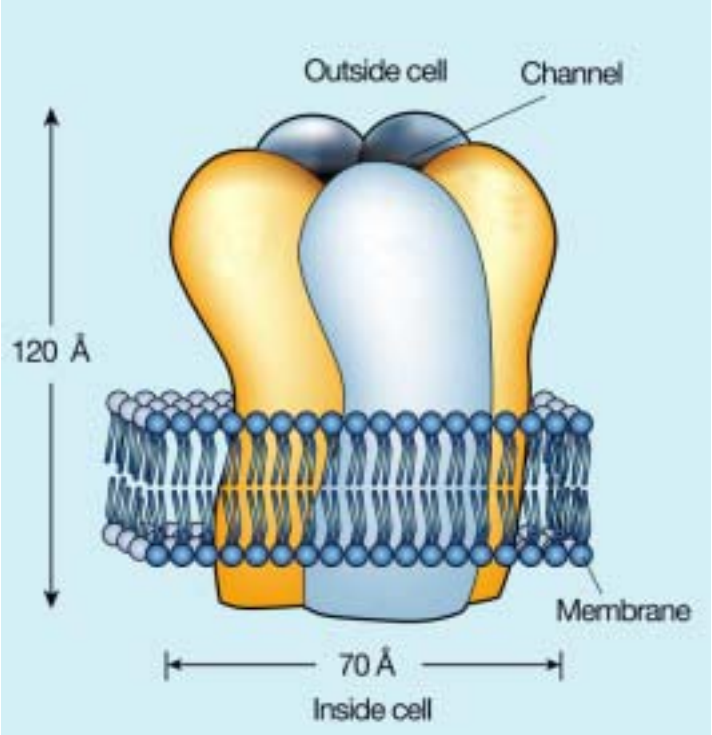
Broadly Utilized in Stabilizing Both Protein Secondary Structure & Receptor-Ligand Binding Interactions

Comparable to Hydrogen bond or Ion Pair in Strength

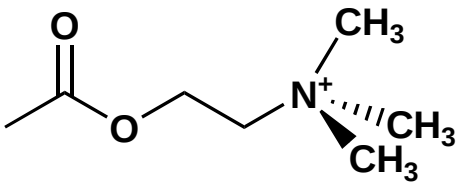
For more on the cation-π interaction, go to: [link]

DA Dougherty, DA Stauffer, *Science*, **250**, 1558 (1990)
JC Ma, DA Dougherty, *Chem. Rev.*, **97**, 1303 (1997)
DA Dougherty, *Science*, **271**, 163 (1996)
N Zacharias, DA Dougherty *TiPS*, **23**, *281 (2002)*

The Nicotinic Acetylcholine Receptor (nAChR)

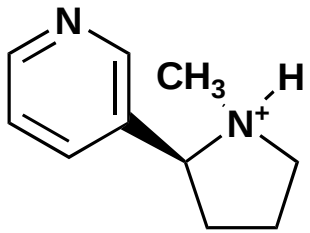


The natural ligand - the neurotransmitter - is ACh



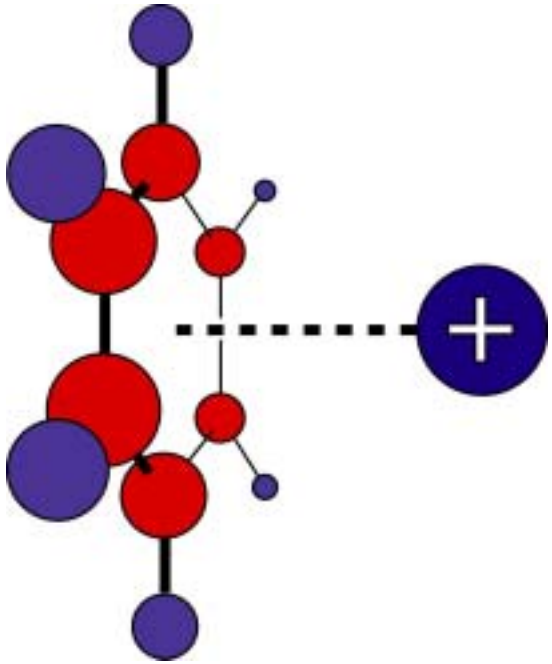
Acetylcholine (ACh)

The nAChR also responds to nicotine, and the initial chemical event in nicotine addiction is nicotine binding the the nAChR in the brain



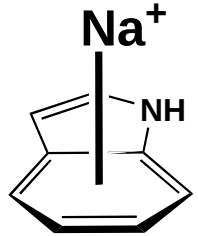
Nicotine

The Cation-π Interaction

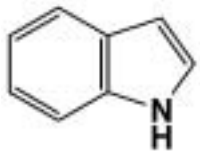


- Early biochemical studies identified 9 different aromatics residues (Tyr and Trp) that might contribute to ACh binding in the nAChR
- Trp is generally preferred in the cation-π interaction

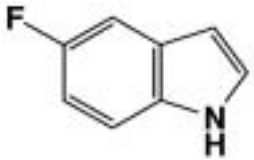
For the Cation-π Interaction, Fluorination is Very Informative



6-31G**; gas phase



32.6



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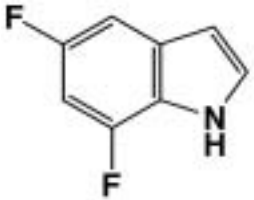
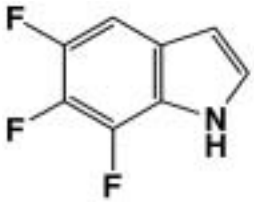


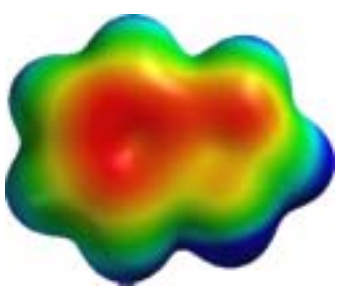
23.2

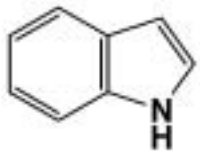
18.9



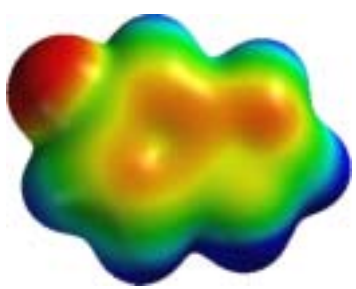
14.4

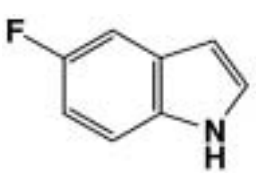
For the Cation-π Interaction, Fluorination is Very Informative



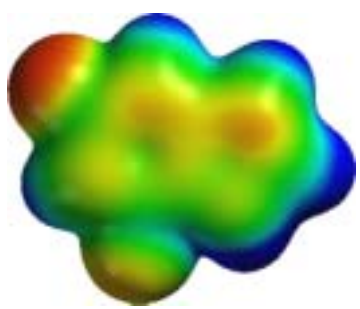


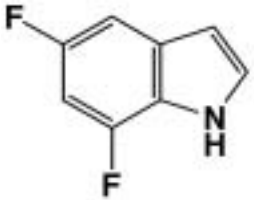
32.6



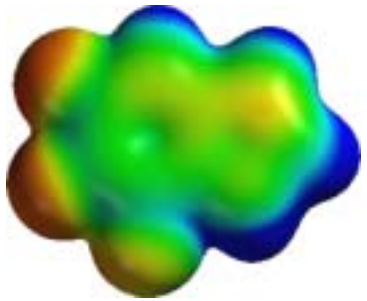


27.5

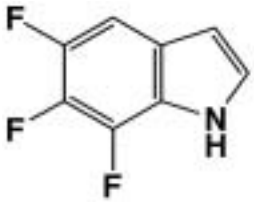


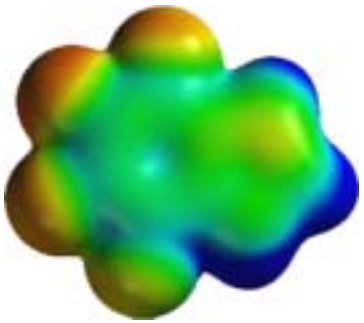


23.2



18.9



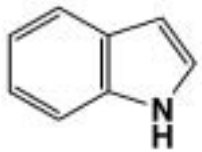
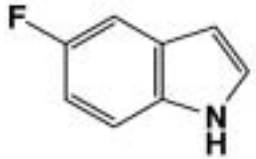
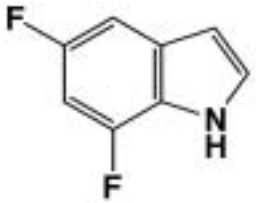
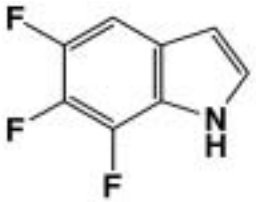


14.4

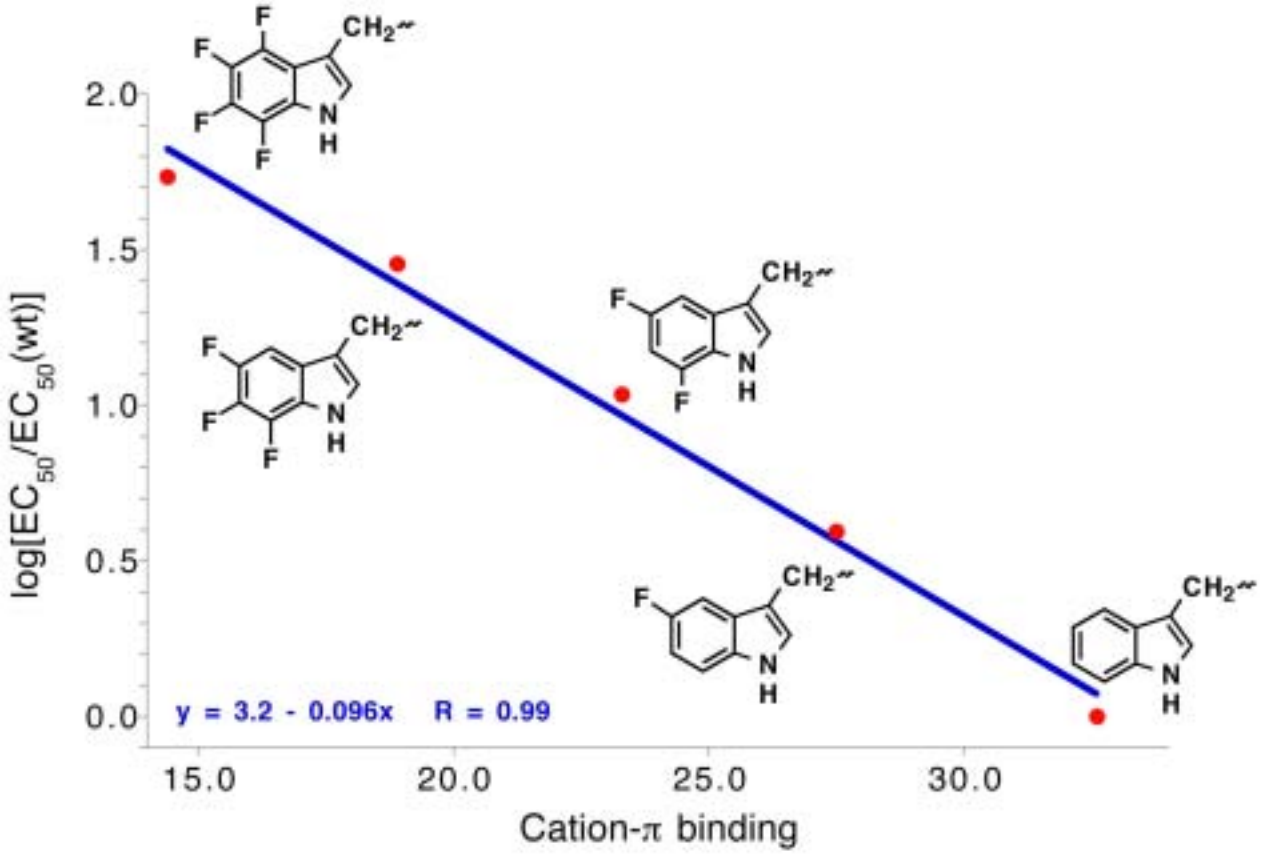
Electrostatic potential surfaces; red is negative, blue is positive.

One Trp - αW149 - shows a remarkable response to fluorination

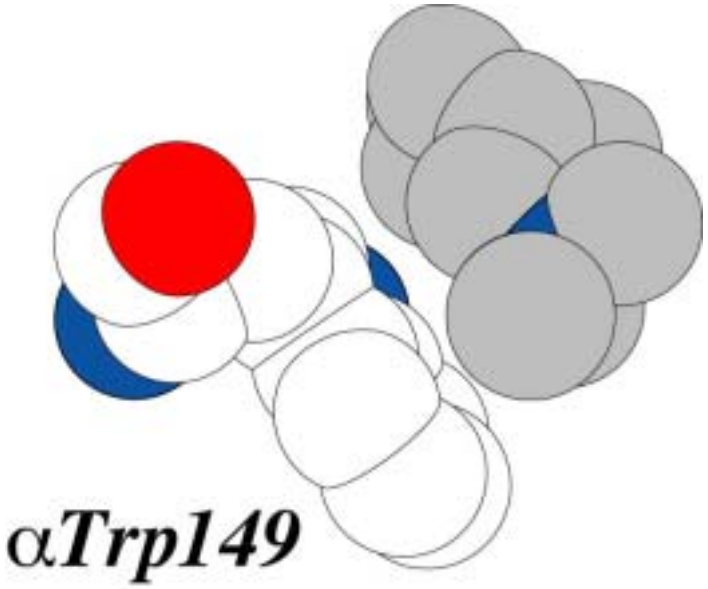
EC_{50} (mM) vs. 6-31G** Binding Energy for Na^+(kcal/mol)

	EC_{50}	Cation-π
	50	32.6
	200	27.5
	552	23.2
	1470	18.9
	2800	14.4

The Plot


2.0
1.5
1.0
0.5
0.0
log[EC50/EC50(wt)]
y = 3.2 - 0.096x
R = 0.99
15.0
20.0
25.0
30.0
Cation-π binding

The Quat of ACh Binds to Trp α149



W. Zhong, J. P. Gallivan, Y. Zhang, L. Li, H. A. Lester, and D. A. Dougherty,

Proc. Natl. Acad. Sci. (USA), **95**, 12088-12093 (1998).

In 2001, a soluble ACh-binding protein was crystallized, and the derived structure fully supports this conclusion.

Ongoing studies have probed other binding sites have revealed the unusual binding properties of nicotine:

Cation-π Interactions in Ligand Recognition at Serotonergic (5-HT_{3A}) and Nicotinic Acetylcholine Receptors. The Anomalous Binding Properties of Nicotine. D. L. Beene, G. S. Brandt, W. Zhong, N. M. Zacharias, H. A. Lester, and D. A. Dougherty, *Biochemistry*, **41**, 10262-10269 (2002).

Different Binding Orientations for the Same Agonist at Homologous Receptors: A Lock and Key or a Simple Wedge? T-W. Mu, H. A. Lester, and D. A. Dougherty, *J. Am. Chem. Soc.*, **125**, 6850-6851 (2003).

Using Physical Chemistry to Differentiate Nicotinic from Cholinergic Agonists at the Nicotinic Acetylcholine Receptor, Amanda L. Cashin, E. James Petersson, Henry A. Lester, and Dennis A. Dougherty *J. Am. Chem. Soc.*, **127**, 350-356 (2005).

A Cation-π Binding Interaction with a Tyrosine in the Binding Site of the $GABA_C$ Receptor. Sarah CR Lummis; Darren L Beene, Neil J Harrison; Henry A Lester and Dennis A Dougherty*, *Chem. Biol.*, **12**, 993-997 (2005).