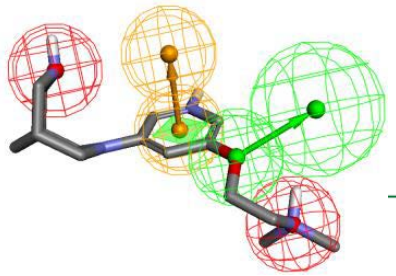
The Hybrid Approach for Nicotinic Acetylcholine Receptor (nAChR) Ligands

Background:

- Nicotinic acetylcholine receptors play key roles in a wide range of cognitive processes, including attention, reward, learning, and memory.
- In addition, they are notably involved in several neurodegenerative diseases, such as Alzheimer's disease, and of course, nicotine addiction.
- As a means to develop therapeutics with compound but selective targeting for these highly complex diseases, expansion of chemical ligands from natural sources is an important avenue.



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Semisynthetic Analogues of Toxiferine I and Their Pharmacological Properties at α7 nAChRs, Muscle-Type nAChRs, and the Allosteric Binding Site of Muscarinic M_2 Receptors

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Advance:

- Toxiferine is a curare alkaloid muscle relaxant, a naturally occurring "twin drug" or bisindole hybrid.
- Semisynthetic analogues derived from toxiferine were found to have differential activity not only at muscle---type nicotinic receptors, but also at the alpha7 nAChR which is one of the major nicotinic receptors in brain, and at M2 muscarinic receptors which are present in the brain and the heart.
- In addition, azacyclic scaffolds attached to N,N---dimethyl---2---(pyridine---3---yloxy)ethan---1---amine provided hybrids ("twin drugs") with high affinity and subtype selectivity for alpha4beta2* nAChRs.
- Structure---activity studies using these new analogues will inform further development of highly selective nicotinic receptor drugs, potential therapeutics for Alzheimer's, addiction and mood disorders.