Discovery of novel insect repellent candidates with predictive pharmacophores identified with Accelrys' Catalyst software environment.

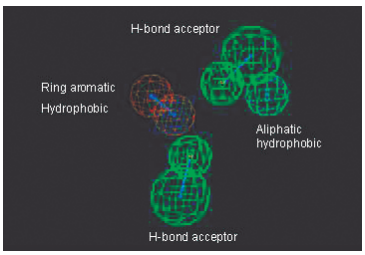
Study summarized by Samuel Toba and Shikha Varma-O'Brien

The spread of disease by mosquitoes continues to cause epidemics in both rural and urban settings. Efforts to find long-lasting, safe, and cosmetically-acceptable agents that repel multiple species of biting arthropods continue to be a challenge.

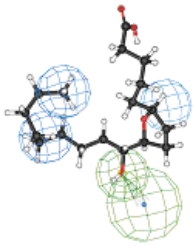
In this study, Bhattacharjee et al., from the Walter Reed Army Institute of Research (Silver Spring, MD), used Accelrys' Catalyst® software environment to develop a pharmacophore model based on the known features of eleven structurally-diverse insect repellent compounds (including DEET). The resulting pharmacophore model contains two aliphatic hydrophobes, one aromatic hydrophobe, and one hydrogen-bond acceptor. For lead identification, the model was used to screen an in-house (WRAIR-CIS) database of 290,000 compounds. The screening resulted in 138 compounds that were predicted to have repellent activity due to their structural similarity to the pharmacophore model compound. The 138 compounds were subsequently screened by shape-based filters (using Catalyst) and for ADME/Tox properties (using Accelrys' Cerius^2 and TOPKAT). This second screening resulted in the identification of four novel compounds. Upon further testing, these four compounds were found to exhibit remarkable repellent activity.

The selected pharmacophore model was further validated by comparing it to previously discovered insect repellent compounds. One such compound—a novel, 18-carbon acid that deters mosquitoes (which is isolated from the hairs of Indian wild buffalo, gaur)—maps extremely well to the identified pharmacophore model. This validation illustrates the pharmacophore model's ability to provide insight into the minimal chemical features required for a molecule to be active as a repellent.

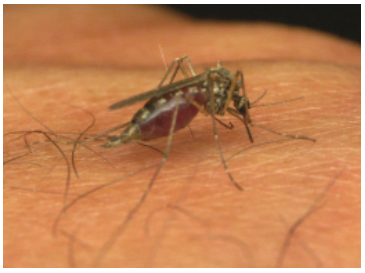
This study is a powerful illustration of the role computational techniques and filters can play in lead generation. Pharmacophore modeling of diverse structures and three-dimensional database mining with Catalyst, in combination with predictive ADME/Tox screening, allows scientists to explore and rationalize structure-activity data and rapidly identify novel lead compounds.



Accelrys' Catalyst software environment was used to develop a 3-D pharmacophore model containing structural features associated with insect repellent activity: hydrogen-bond acceptor (middle-bottom, green), hydrophobic aliphatic (top-left, blue), hydrophobic aromatic (top-right, blue).



5-[5-(1-Hydroxy-nonyl)-tetrahydro-furan-2-yl]-pentanoic acid (a compound isolated from the hairs of Indian wild buffalo, gaur)



Reference

1. Apurba K. Bhattacharjee, Watanaporn Dheranetra, Daniel A. Nichols, Raj K. Gupta., "3D Pharmacophore Model for Insect Repellent Activity and Discovery of New Repellent Candidates," *QSAR & Comb. Sci.*, **2005**, *24*, 593–602

Accelrys Corporate Headquarters
10188 Telesis Court, Suite 100
San Diego, CA 92121, USA
Tel: +1 858 799 5000

Accelrys European Headquarters
334 Cambridge Science Park
Cambridge, CB4 0WN, UK
Tel: +44 1223 228500

Accelrys Asia Headquarters
Nishi-Shinbashi TS Bldg.11F
3-3-1 Nishi-Shinbashi, Minato-Ku
Tokyo 105-0003 JAPAN
Tel: +81 3 3578 3860

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