Development of docking-based QSAR model for the identification of novel mosquito repellents

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INTRODUCTION

A mosquito repellent is applied to skin, clothing, or other surfaces to prevent insects from landing on the surface. They consist of synthetic or natural chemicals such as Deet, Permethrin, neem and citronella oil etc. The commonly used DEET suffers from skin irritation whereas other repellents are hazardous to the environment. As natural repellents are more expensive, need frequent re-application, may cause rashes on the skin, hence there is a need to design new synthetic mosquito repellents, devoid of skin irritation and safer to environment.

The state of art approaches to design novel chemicals are ligand or structure-based drug design (SBDD) where in the former Quantitative structure activity relationship (QSAR) and in the latter a target structure (protein) is used. This protein may be odorant binding protein 1 (AaegOBP1) from *Aedes aegypti* for mosquito repellent design. A novel approach[1-2] considering the number of docking interactions between the amino acid residues (AARs) of the receptor and the ligand as independent, and mosquito repellent activity as dependent parameter has been used to develop mathematical models using multi parameter linear regression analysis and may be termed as Quantitative structure interaction activity relationship (QSIAR). These predictive models may be useful in the design of novel molecules as mosquito repellents.

OBJECTIVES

To develop the predictive model using mosquito repellent activity data against *Aedes aegypti* from a class of novel carboxamides using the Quantitative structure interaction activity relationship (QSIAR) which may be useful for designing of novel mosquito repellents. .

MATERIALS AND METHODS

A) Dataset

- A dataset of 34 mosquito repellents comprising of novel carboxamides and DEET were taken from literature[3] (Fig 1).
- The dataset was arranged in the increasing order of activity and divided into an unbiased training and test set in the ratio of ~80:20. The most and the least active molecule formed the part of the training set. In the list of the remaining molecules every fifth molecule was included in the test set and the rest were included in the training set.

B) Docking studies

- The structures were drawn and minimized in Chemdraw and Chem3d respectively using the default settings.
- The crystal structure of odorant binding protein 1 (AaegOBP1) of *Aedes aegypti* with pdb id: 3K1E was downloaded from the protein data bank.
- The receptor and the ligand were prepared using the default settings in Autodock 4.2, while the docking studies were performed using Autodock Vina. The results in terms of number of interactions between the amino acid residues (AARs) and ligand along with activity [log(d)] are given in Table 1.
- The results in terms of number of interactions between the amino acid residues (AARs) and ligand are given in Table 1. The 3D and 2D images of the best poses of the most active molecules are given in Figure 2.

C) Model development

The data comprising of interactions and activity were imported to Minitab software for developing models using multi-parameter linear regression analysis.

D) Model validation

The developed model was validated by predicting the test set compounds.

RESULTS AND DISCUSSION

The regression analysis between independent (interactions with important amino acids) and dependent (protection time [log(d)] in days) parameters by gradual reduction in number of parameters using backward stepwise regression technique led to a statistically significant (>99%) model (Eq. 1) with correlation coefficient (R=0.755) explained variance (R^2=60.8%). The model well predicted the test set molecules with correlation coefficient of 0.754 (Fig.3).

Log(d) =0.3874 -0.584 (±0.194) LEU89A + 0.469 (±0.152) LEU96A + 0.695 (±0.232) HIS111B -0.348 (±0.116) MET91B + 0.418 (±0.145) PHE123B (Eq. 1)

N=26; S= 0.299746; R-sq= 57.05%; R-sq(adj)= 46.31%; F=5.31; R-sq(pred)= 31.81%

CONCLUSIONS

In an urgent need of human and environment safe mosquito repellents this study utilizing state of the art QSIAR approach integrating SBDD and QSAR resulted in a robust and validated predictive model. The model may be useful to design novel mosquito repellents which may be devoid of skin irritation and are safe for the environment.

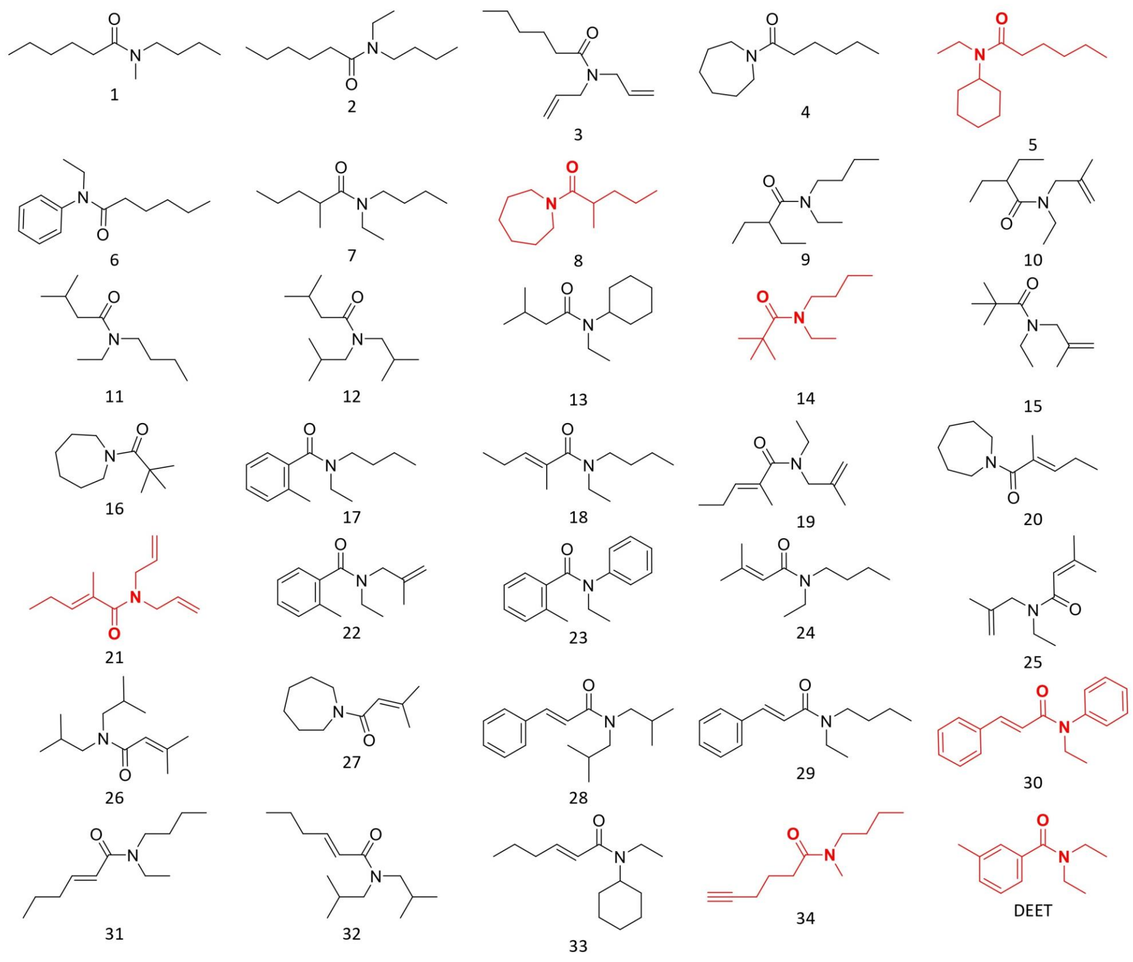

Fig. 1: Structures of data set compounds (red indicate test set and the rest comprise the training set)

Comp. No.	Protection time (d) [Log (d)]	Interacting amino acid residues				
		LEU89A	LEU96A	HIS111B	MET91B	PHE123B
1	0.17609	0	1	0	1	0
2	0.30103	0	0	0	2	1
3	0	1	1	0	1	0
4	0.84509	0	0	0	0	0
5	1.07918	0	1	0	0	0
6	0.87506	0	1	0	1	0
7	0	0	0	1	2	1
8	0.54406	0	1	0	1	0
9	0.47712	0	0	0	0	0
10	0	0	0	0	2	1
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	0.84509	0	0	0	0	0
14	0	0	0	0	2	1
15	0	1	1	0	0	0
16	0	0	0	0	0	0
17	1.17609	0	0	0	2	1
18	0.30103	0	0	0	1	0
19	0.30103	0	1	0	1	0
20	0.60205	0	1	0	1	0
21	0.30103	1	1	0	1	0
22	1.11394	0	1	0	0	0
23	0.54406	0	0	1	1	0
24	0	0	0	0	1	1
25	0	1	0	0	0	0
26	0.30103	0	0	0	0	0
27	0.47712	0	0	0	0	0
28	0.92941	0	0	0	0	1
29	0.30103	0	0	0	0	0
30	0	0	0	0	1	0
31	0.87506	0	1	0	0	0
32	0.90308	0	0	0	1	2
33	1.34242	0	0	1	1	1
34	0.84509	0	0	0	1	2
DEET	0.84509	0	0	2	2	2

Table 1: Important interactions between amino acid residues and ligand along with protection time of the compounds of the dataset

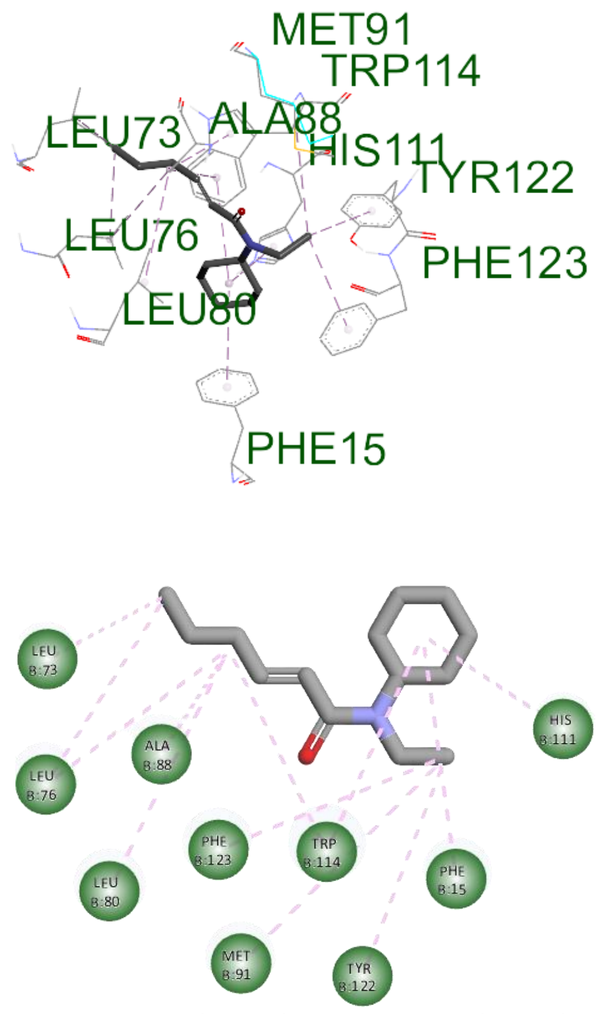

Fig 2: The 3D (above) and the 2D (below) images of the best poses of the most active molecule of the dataset.

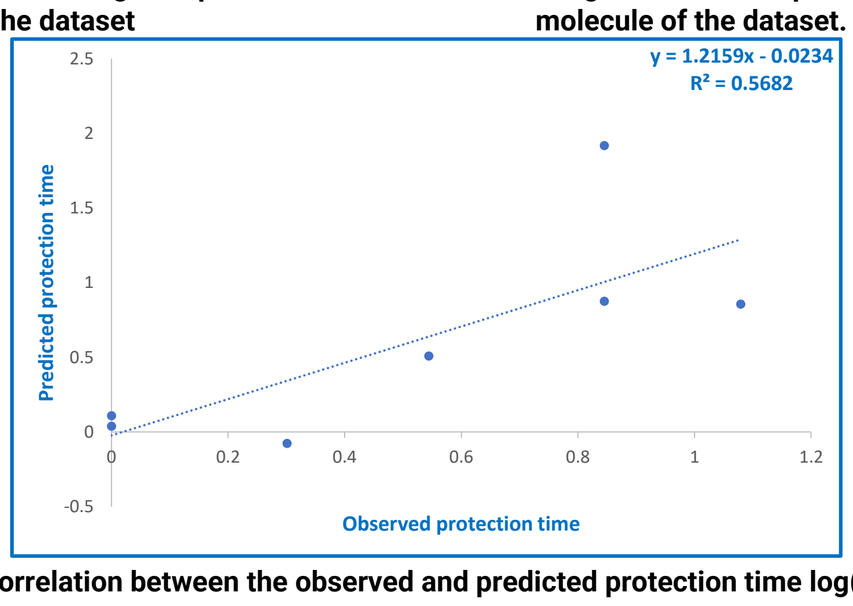

Fig 3: Correlation between the observed and predicted protection time log(d) of the test set.

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3. Katritzky, A. R. et al. (2010) "Novel carboxamides as potential mosquito repellents," Journal of medical entomology, 47(5), pp. 924–938. doi: 10.1093/jmedent/47.5.924.