

ponds at the Fish Breeding Centre, Malampuzha. They were introduced in glass bottles, 25 cm high and containing 1 litre water. When the insect reached the surface and just breathed, the bottle was closed without air bubbles and the time was recorded. The time taken for death which is determined by the lack of response to physical stimuli and also the inability to recover when placed in contact with air was also noted.

Analysis of the data showed that the difference in the average time taken for death by the small (9.56 min) and large (9.92 min) size groups of animals was not statistically significant. Two to three minutes after introduction, the insect showed frantic effort to obtain air by striking at the top of the bottle and then started sinking to the bottom. There were occasional efforts to reach the surface which also ceased in 7–8 min and the animals died due to asphyxiation.

In the field, synthetic velon netting (1/12" mesh) attached with sinkers and floats along strips was spread over the entire water surface of the nursery pond and allowed to remain for 11–12 min, killed all notonectids. The same technique was conveniently applied with success to kill and separate notonectids from fish fry, collected in containers for distribution. The physical method of eradication of notonectids has several advantages over the other conventional methods. In the chemical methods, the hydrocarbon component, particularly diesel used in emulsions is found to settle to the bottom and mix with soil, affecting soil fertility. Further, notonectids are found to repopulate the eradicated ponds from the neighbouring water bodies necessitating repeated applications of emulsions which are highly detrimental to pond productivity. However, the present method can be employed repeatedly even under adverse weather conditions and is devoid of any side effects. The technique is simple and can be effectively used in small nursery ponds without any recurring expenditure.

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## SYNTHESIS OF SUBSTITUTED AMIDES FOR REPELLENCY AGAINST MOSQUITOES

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REPELLENTS play an important role in reducing the man-vector contact and therefore could help in interrupting the vector-borne disease transmissions. The repellent compounds (like dimethyl phthalate) that are available in the market are found to give a protection only for one or two hours. The other well-known repellent compound DEET<sup>1,2</sup> (N,N-Diethyl-m-toluamide) though is very effective, its prohibitive cost curtails its usage in countries like India and cannot be afforded by economically weaker sections of the society. Earlier reports<sup>3-5</sup> on the synthesis of substituted amides as mosquito repellents exist. In this paper, the synthesis and testing of thirty five substituted amides for repellency against the man biter *Aedes aegypti* is reported.

The acid chlorides of seven carboxylic acids, viz phenyl propionic acid, 2-chloro benzoic acid, 2,4-dichloro phenoxy acetic acid, 2-ethyl hexanoic acid, 4-ethoxy benzoic acid and 4-methoxy benzoic acid were prepared in relatively good yields by reacting the acid with thionyl chloride under reflux condition followed by removal of unreacted thionyl chloride and vacuum distillation.

The acid chloride was then reacted with different secondary amines like diethyl amine, dimethyl amine, piperidine, N-methyl aniline and N-ethyl aniline in dry ether at 5–10°C. The compounds were purified by either vacuum distillation or by crystallization. The purity of each compound was tested based on single spot in TLC and by IR spectral analysis.

The compounds were tested for repellency on animal model and on human skin following the methods outlined below:

### *Testing on Animal Model*

Albino rabbits (30–40 day old) were used as experimental animals. The top surface (6.0 × 4.0 cm) on the animal skin was shaven and a solution of the test compound in alcohol was applied uniformly over that area at the rate of 1 mg/cm<sup>2</sup>. The test animal (100 in number) was then placed inside a small circular animal

cage (12.5 cm dia) and introduced into a mosquito cage (55 × 55 × 55 cm) containing 3–4 day old unfed *A. aegypti* mosquitoes. The time taken for the first bite was observed which would be the protection time for the compound. The experiment was repeated four times. Any side effect on the skin of the animal was also observed.

#### Testing on human skin

After initially ascertaining that the compound did not cause skin irritancy or any other allergic reaction on the human skin, a solution of the compound in the respective oil base (olive, coconut and palmolein) was applied on the forearm of a human subject at the rate of 1 mg/cm<sup>2</sup>. A control was set up with oil only. The treated surface was exposed in a mosquito cage containing three to four day unfed *A. aegypti* mosquitoes (100 in number) for 2 min to see any biting of mosquitoes on the treated surface. The treated surface was exposed repeatedly at every 30 min intervals and the time taken for the first bite was taken as the protection time of the compound. The experiment was repeated with four different men.

The amides were tested for repellency on rabbits and human skin. Two compounds, namely N-ethyl N-phenyl phenyl propionamide and N-methyl N-phenyl phenyl propionamide showed irritancy and therefore were not tested. Of the remaining 33 compounds, nine compounds were found to give protection for more than 3 hr (table 1). The compounds which gave protection for more than 5 hr were grouped as Class I repellents and those which gave protection time rang-

ing between 3 and 5 hr were classified as Class II repellents.

N,N-diethyl 2-chloro benzamide, N,N-dimethyl 2-chloro benzamide, N-methyl N-phenyl 2-chloro benzamide, piperidinyl 2-ethyl hexanamide and N,N-dimethyl 4-methoxy benzamide fell under Class I whereas N,N-diethyl 2,4-dichloro phenoxy acetamide, piperidinyl 2-chloro benzamide, piperidinyl 4-methoxy benzamide and N,N-dimethyl 4-ethoxy benzamide fell under Class II repellents.

The cost analysis of the effective compounds that fell under Class I was worked out depending on the percentage yield of the acid chloride and the amide and based on the cost of the laboratory reagent grade of the chemicals used for synthesis. The cost for producing one kilogram of the active material is given in table 2. All the three amides of 2-chloro benzoic acid were comparatively cheaper than the other two amides. It is noteworthy that the cost of the compounds can be reduced by a single step process by means of a high pressure – high temperature reactor. The cost of DEPA, N,N-diethyl phenyl acetamide a repellent compound reported earlier from this Centre<sup>4</sup> could be reduced from Rs.408/- to Rs.120/- per kg. by performing the reaction at 300 psi and 250°C in a high pressure reactor using phenylacetic acid and diethylamine with phosphoric acid catalyst.

It is found that DEPA is very much cheaper than DEET, N,N-diethyl-m-toluamide, a repellent used in European countries and DEPA is equally effective as a mosquito repellent as DEET. Moreover, the starting material of DEPA, phenylacetic acid is easily available whereas that for DEET, m-toluic acid needs to be

Table 1 Testing of amides for repellency against *Aedes aegypti*

Name of the compound	Protection time (Hours)			
	On rabbits	Olive base	Coconut base	on human forearm Palmolein base
<b>Class I</b>				
1. N,N-Diethyl 2-chloro benzamide	7	6	7	6
2. N,N-Dimethyl 2-chloro benzamide	6	6	6	5
3. N-methyl N-phenyl 2-chloro benzamide	7	7	7	7
4. Piperidinyl 2-ethyl hexanamide	5.5	6	5	5
5. N,N-Dimethyl 4-methoxy benzamide	6.5	7	7	7
<b>Class II</b>				
6. N,N-Diethyl 2,4-dichloro phenoxy acetamide	3	4	2	5
7. Piperidinyl 2-chloro benzamide	4	4	4	2
8. Piperidinyl 4-methoxy benzamide	4	5	4	4
9. N,N-Dimethyl-4-ethoxy benzamide	4	4	5	4

**Table 2** Cost analysis of the effective compounds

Name of the compound	Cost per kilogram (Rs.)
1. N,N-Diethyl 2-chloro benzamide	520
2. N,N-Dimethyl 2-chloro benzamide	550
3. N-methyl N-phenyl 2-chloro benzamide	640
4. Piperidiny 2-ethyl hexanamide	1750
5. N,N-Dimethyl 4-methoxy benzamide	2250
6. DEET	3000
7. DEPA	408

imported. From these studies, we found that DEPA is superior to the rest of the known repellents both on cost factor and efficacy followed by the substituted amides of 2-chloro benzoic acid.

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