Natural Products as Leads to Potential Mosquitocides

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Abstract

Mosquitoes are the crucial vectors for a number of mosquito-borne infectious diseases i.e. dengue, yellow fever, chikungunya, malaria, Rift Valley fever, elephantiasis, Japanese Encephalitis, and Murray Valley encephalitis etc. Besides, they also transmit numerous arboviruses (arthropod-borne viruses) for example West Nile virus (WNV), Saint Louis encephalitis virus, Eastern equine encephalomyelitis virus (EEE), Everglades virus (EVEV), Highlands J (HJ) virus, and La Crosse Encephalitis virus. The emergence of widespread insecticide resistance and the potential environmental issues associated with some synthetic insecticides (such as DDT) has indicated that additional approaches to control the proliferation of mosquito population would be an urgent priority research. The present review highlights some natural product mosquitocides that are target-specific, biodegradable, environmentally safe, and botanicals in origin.

Key words: Mosquitocides, Medicinal Plants, Natural Products

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INTRODUCTION

Mosquitoes, the flying insects of family Culicidae, are crucial vectors for a number of mosquito-borne infectious diseases that are maintained in nature through the biological transmission by blood feeding mosquitoes to susceptible vertebrate hosts causing dengue, yellow fever, malaria and filariasis in the American tropics; Rift Valley fever, elephantiasis, Japanese Encephalitis, chikungunya, malaria and filariasis in Africa and Asia; and Murray Valley encephalitis in Australia. They are also known to transmit numerous arboviruses (arthropod-borne viruses) for example West Nile virus (WNV), Saint Louis encephalitis virus, Eastern equine encephalomyelitis virus (EEE), Everglades virus (EVEV), Highlands J (HJ) virus, La Crosse Encephalitis virus in the United States etc.

Vector control is by far the most successful method for reducing incidences of mosquito born diseases. The discovery of DDT's and the subsequent development of organochlorines, organophosphates and pyrethroids suppressed natural product research, as the problem for insect control were thought be solved. However, high cost of synthetic pyrethroids, environment and food safety concerns, unacceptability and toxicity of many organophosphates and organochlorines, and a global increase in insecticidal resistance, have argued for stimulated research towards the development of potential insecticides of botanic origin (Severini et al. 1993).

The use of herbal products is one of the best alternatives for mosquito control. The search for herbal preparations and pure compounds that do not produce adverse effects in the non-targeted organisms, along with the benign environmental characteristics, remain a top priority research for scientists associated with the development of alternative vector control measures (Chowdhury et al. 2008). Many plant species are known to possess biological activity that is frequently assigned to the secondary metabolites. Among these, essential oils and their constituents have received considerable attention in the search for new biopesticides. Many of them have been found to possess an array of properties, including insecticidal activity, repellency, feeding deterrence, reproduction retardation, and insect growth regulation against various mosquito species (Rice and Coats 1994; Isman 2000; Cheng et al. 2004; Traboulsi et al. 2005; Yang et al. 2005). The present review covers the entire formal and constant research on mosquitocidal natural products reported in literature from the 1947 to late 2012 with a sufficient focus on structure activity relationship (SAR) and mechanism of action.

TRADITIONAL MOSQUITO REPELLENTS AND USAGE CUSTOM

The phytochemicals have received considerable renewed attention as potential bioactive agents for insect vector management. However, there is a little other than anecdotal, traditional, or cultural evidence on this topic (Grodner 1997). The Greek natural philosopher Pliny the Elder (1'st century AD) recorded all the known pest control methods in ‘‘Natural History’’. The use of powdered *chrysanthemum* as a significant insecticide was traced from Chinese record. Pyrethrum extracted from flowers was sprayed in houses as a short-term knockdown insecticide. The other natural products like derris, quassia, nicotine, hellebore, anabasine, azadirachtin, *d*-limonene, camphor, and turpentine were among some important phytochemical insecticides widely used in developed countries (Wood 2003).

There are several reports, particularly in Africa that describe the buring of plant materials to drive away mosquitoes. Thirteen percent of rural Zimbabweans use plants (Lukwa et al. 1999) while 39% of Malawians burn wood dung or leaves (Ziba et al. 1994). Up to 100% of Kenyans burn plants to repel mosquitoes (Seyoum et al. 2002), and in Guinea Bissau, about 55% of people burn plants or hang them in the home to repel mosquitoes (Palsson and Jaenson 1999). The local communities adapt various methods to repel mosquitoes. Application of smoke by burning the plant parts is one of the most common practices among the local inhabitants. Other types of applications are spraying the extracts by crushing and grinding the repellent plant parts, hanging and sprinkling the repellent plant leaves on the floor etc. The leaf of repellent plant is one of the commonly and extensively used plant parts to repel the insects and mosquitoes, followed by root, flower, and remaining parts of repellent plants. Various traditional repellent plants used by the local inhabitants to avoid mosquito bites have been listed in Table 1.

Table 1: Traditional plants as mosquito repellents (Karunamoorthi et al. 2009)

Traditional Names	**Scientific Names**	**Family**
Tinjut	*Ostostegia integrifolia*	Lamiaceae
Woira	*Olea europaea*	Oleaceae
Neem	*Azadirachta indica*	Meliaceae
Wogert	*Silene macroserene*	Caryophyllaceae
Kebercho	*Echinops* sp.	Asteraceae
Waginos	*Brucea antidysenterica*	Simaroubaceae
Eucalyptus	*Eucalyptus camaldulensis*	Myrtaceae
Ades	*Myrtus communis*	Myrtaceae
Gemmero	*Capparis tomentosa*	Capparidaceae
Tej-sar	*Cymbopogen citrates*	Rutaceae
Ats-faris	*Datura stramonium*	Solanaceae
Endode	*Phytolacca dodecandra*	Phytolaccaceae
Azo-hareg	*Clematis hirsuta*	Ranunculaceae
Berberra	*Millettia ferruginea*	Fabaceae
Gullo	*Ricinus communis*	Euphorbiaceae

PLANTS WITH POTENTIAL MOSQUITOSIDAL PROPERTIES

The search for natural and benign envornmental mosquiotsides is ongoing worldwide (Kuo et al. 2007; Balandrin et al. 1985; Ghosh and Chandra 2006). Insecticidal effects of plant extracts vary not only according to plant species, mosquito species and plant parts, but also to extraction methodology (Swain 1977). A brief delve into the literature reveals that many applied investigations (Perrucci et al. 1997; Lee et al. 2001; Nawamaki and Kuroyanagi 1996) sofar have been made towards biological screening of botanic extracts against a large number of pathogens and arthropods. However, the lack of reviews in concerned area is highly surprising since much of efforts have been invested in locating mosquitocidal phytochemicals from edible crops, ornamental plants, herbs, grasses, tropical and subtropical trees and marine angiosperms. A review by Roark (1947) estimates about 1200 plant species with a wide spectrum of bioactive insecticides. Similarly, a review by Sukumar et al. (1991) lists about 344 insecticides of botanical origin. Other reviews by Schmutterer (1990), Mulla and Su (1999), Ghosh et al. (2012) and Boulogne et al. (2012) could not cover significant topics such as mode & site of action and joint action of botanical extracts with other phytochemicals and synthetic insecticides. The botanical extracts with promicing mosquitosidal effects have been summarized in Table 2.

Table 2: Mosquitocidal activity of crude plant extracts

Plant Family	Plant Species	Plant Parts	Mosquitos species	References
Acanthaceae	*Rhinocanthus nasutus*	Leaf	*Ae. aegypti* *An. Stephensi* *Cx. quinquefasciatus*	Pushpalatha and Muthukrishnan (1999)
	Hygrophila auriculata	Shoot	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Justicia adhatoda	Leaf	*Cx. quinquefasciatus*	
Acoraceae	*Acorus calamus*	Rhizome	*Cx. quinquefasciatus* *Ae. aegypti* *Ae. albopictus* *An. tessellates* *An. subpictus* *Cx. fatigans*	Ranaweera (1996), Sharma et al. (1994)
Agavaceae	*Agave sisalana*	Fiber	*Cx. pipiens*	Pizarro et al. (1999)
Alliaceae	*Allium sativa*	Bulb	*Cx. pipiens*	Thomas and Callaghan (1999)
Anacardiaceae	*Mentha microcorphylla*	Leaf	*An. Stephensi*	Ghosh et al. (2008)

	Pistacia lentiscus	Leaf	*An. Stephensi*	
Annonaceae	*Annona squamosa*	Leaf	*Ae. aegypti* *Cx. quinquefasciatus*	Monzon et al. (1994)
	Annona squamosa	Bark	*Cx. quinquefasciatus* *An. stephensi*	Kamaraj et al. (2010)
	Annona glabra	Seed	*Ae. aegypti*	
	Annona muricata	Root	*Ae. aegypti*	
	Annona squamosa	Root	*Ae. aegypti*	Omena et al. (2007)
	Annona crassiflora	Root wood	*Ae. aegypti*	
	Mkilua fragrans	Aerial Part	*An. gambiae*	
	Xylopia caudata	Leaf	*Ae. aegypti*	Zaridah et al. (2006)
	Xylopia ferruginea	Leaf	*Ae. aegypti*	
Apiaceae	*Daucus carota*	Seeds	*Ae. Aegypti,* *Cx. fatigans*	Sharma et al. (1994)
Apocynaceae	*Calotropis procera*	Root	*An. labranchiae*	Markouk et al. (2000)
	Catharanthus roseus	Whole	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Rhazya Stricta	Leaf Acute	*Cx. pipens*	
	Solenostemma argel	Aerial parts	*Cx. pipens*	Al-Doghairi et al. (2004)
Araceae	*Homalomena propinqua*	Rhizome	*Ae. aegypti*	Al-Doghairi et al. (2004)
Aristolochiaceae	*Aristolochia saccata*	Root	*Cx. pipens*	Das et al. (2007)
Asclepiadaceae	*Pergularia extensa*	Leaf	*Cx. pipens*	Das et al. (2007)
	Hemidesmus indicus	Root	*Cx. quinquefasciatus*	Khanna and Kannabiran (2007)
	Gymnema sylvestre	Leaf	*Cx. quinquefasciatus*	
Asphodelaceae	*Aloe ngongensis*	Leaf	*An. gambie*	Matasyoh et al. (2008)
	Aloe turkanensis	Leaf	*An. gambiae*	Matasyoh et al. 2008
Asteraceae	*Anthemis nobilis*	Flower	*Cx. pipiens*	Soliman and El-Sherif (1995)
	Baccharis spartioides	Aerial Part	*Ae. aegypti*	Gillij et al. (2008)

	Cotula cinerea	Whole Plant	*An. labranchiae*	Markouk et al. (2008)
	Sassurea lappa	Leaf	*Ae. Aegypti*	Sharma et al. (1994)
			Cx. fatigans	
	Artemisia annua	Leaf	*An. Stephensi*	Sharma et al. (2006)
			Cx. quinquefasciatus	
	Ageratina adenophora	Twigs	*Ae. aegypti*	
			Cx. quinquefasciatus	Raj Mohan and Ramaswamy (2007)
	Chrysanthemum Indicum	Leaf	*Cx. tritaeniorhynchus*	
	Tridax procumbens	Leaf	*An. subpictus*	Kamaraj et al. (2011)
	Tagetes minuta	Whole Plant	*Ae. aegypti*	Perich et al. (1995)
			An. stephensi	
Betulaceae	*Alnus glutinosa*	Old Litter	*Cx. pipiens*	David et al. (2000)
			Ae. rusticus	
			Ae. albopictus	
			Ae. aegypti	
			Ae. coquillettidia	
			Cx. coquillettidia	
Bignoniaceae	*Cybistax antisyphilitica*	Stem, wood	*Ae. aegypti*	Rodrigues et al. (2005)
	Millingtonia hortensis	Leaf	*An. stephensi*	Kaushik and Saini (2008)
			Ae. aegypti	
			Cx. quinquefasciatus	
Caesalpinaceae	*Cassia tora*	Seed	*Ae. aegypti*	Jang et al. (2002)
			Cx. pipiens pallens	
Cannabaceae	*Cannabis sativa*	Leaf	*An. Stephensi*	Jalees et al. (1993)
			Cx. quinquefasciatus	
			Ae. aegypti	
Capparidaceae	*Cleome viscosa*	Whole Plant	*Cx. quinquefasciatus*	Kalyanasundaram and Babu (1982)

Caricaceae	*Carica papaya*	Seed	*Cx. quinquefasciatus*	Rawani et al. (2009)
Caryophyllaceae	*Dictyota caryophyllum*	Flower	*Ae. aegypti*	Tunon et al. (2006)
Caulerpaceae	*Caulerpa scalpelliformis*	Whole Plant	*Ae. aegypti*	Thangam and Kathiresan (1991)
Clusiaceae	*Calophyllum inophyllum*	Leaf and Seeds	*Cx. quinquefasciatus* *An. Stephensi* *Ae. aegypti*	Pushpalatha and Muthukrishnan (1999)
Cucurbitaceae	*Bryonopsis laciniosa*	Whole Plant	*Cx. quinquefasciatus*	Kabir et al. (2003)
	Momordica charantia	Fruit	*An. stephensi* *Cx. quinquefasciatus* *Ae. aegypti*	Singh et al. (2006)
	Momordica charantia *Trichosanthes anguina* *Luffa acutangula* *Benincasa cerifera* *Citrullus vulgaris*	Leaf	*Cx. quinquefasciatus*	Prabhakar and Jebanesa (2004)
	Coccinia indica *Cucumus sativus*	Leaf	*Cx. quinquefasciatus* *Ae. aegypti*	Rahuman and Venkatesan (2008)
	Coccinia indica *Cucumis sativus* *Momordica charantia*	Leaf	*Ae. albopictus*	
	Gymnopetelum cochinchinensis	Fruit & Pericarp	*Ae. albopictus*	
	Citrullus vulgaris	Leaf	*Ae. stephensi*	Mullai et al. (2008)
	Citrullus vulgaris	Leaf	*Ae. aegypti*	Mullai & Jebanesan (2007)
Cupressaceae	*Callitris glaucophylla*	Wood	*Ae. aegypti* *Cx. annulirostris*	Shaalan et al. (2003)
Dictyotaceae	*Dictyota dichotoma*	Whole Plant	*Ae. aegypti*	Kalyanasundaram and Babu (1982)
Euphorbiaceae	*Codiaeum variegatum*	Leaf	*Ae. Aegypti*	Monzon et al. (1994)

			Cx. quinquefasciatus	
	Jatropha curcus	Leaf	*Cx. quinquefasciatus*	Karmegam et al. (1997)
	Euphorbia hirta	Stembark	*Cx. quinquefasciatus*	Rahuman and Venkatesan (2008)
	E. tirucalli	Stem bark	*Cx. quinquefasciatus*	
	Acalypha alnifolia	Leaf	*An. Stephensi* *Ae. aegypti* *Cx. quinquefasciatus*	Kovendan (2012)
	Acalypha indica	Leaf	*An. stephensi*	Govindarajan et al. (2008)
	Cleistanthus collinus	Leaf	*An. gambiae*	
	Ricinus communis	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
Fabaceae	*Abrus precatorius*	Shoot	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Acacia nilotica	Leaf	*An. gambiae*	Kumar and Dutta (1987)
	Cassia obtusifolia	Seed	*Ae. aegypti* *Cx. pipiens pallens*	Jang et al. (2002)
	Croton bonplandianum	Shoot	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Vicia tetrasperma	Seed	*Cx. pipiens pallens*	Jang et al. (2002)
Geraniaceae	*Pelargonium citrosum*	Whole Plant	*Ae. aegypti*	Zaridah et al. (2006)
Labiatae	*Endostemon tereticaulis*	Aerial Parts	*An. gambiae*	Odalo et al. (2005)
	Lavandula afficinalis	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
	Leucas aspera	Whole	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Mentha arvensis	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
	Mentha piperita	Aerial Parts	*Ae. aegypti* *An. Tessellatus* *Cx. quinquefasciatus*	Hori (2003)
	Minthostachys setosa	Whole Plant	*Ae. aegypti*	Ciccia et al. (2000)

	Moschosma polystachyum	Leaf	*Cx. quinquefasciatus*	Zaridah et al. (2006)
	Ocimum basilicum	Aerial Parts	*An. stephensi* *Ae. aegypti* *Cx. quinquefasciatus* *Cx. pipiens*	Kalyanasundaram and Babu (1982), Nerio et al. (2010)
	Ocimum gratissimum	Leaf	*Cx. gelidus* *Cx. quinquefasciatus*	Kamaraj et al. (2010)
	Ocimum sanctum	Leaf	*Ae. aegypti* *Cx. quinquefasciatus*	Anees (2008)
	Origanum majoranal	Leaf	*Cx. pipiens*	Soliman and El-Sherif (1995)
	Plectranthus longipes	Aerial Parts	*An. gambiae*	Nerio et al. (2010)
	Pogostemon cablin	Leaf	*Ae. aegypti* *Cx. quinquefasciatus* *An. dirus*	Trongtokit et al. (2005)
	Rosmarinus officinalis	Shoot	*An. stephensi* *Ae. aegypti* *Cx. quinquefasciatus*	Prajapati et al. (2005)
	Thymus capitatus	Whole Plant	*Cx. pipiens*	Mansour et al. (2000)
Lauraceae	*Cinnamomum iners*	Leaf	*Ae. aegypti*	Zaridah et al. (2006)
	Cinnamomum kuntsleri	Leaf	*Ae. aegypti*	
	Cinnamomum pubescens	Leaf & Bark	*Ae. aegypti*	
	Cinnamomum scortechinii	Bark	*Ae. aegypti*	
	Cinnamomum sintoc	Bark, Leaf	*Ae. aegypti*	
	Cinnamomum zeylanicum	Bark, Leaf	*An. stephensi* *Ae. aegypti*	Prajapati et al. (2005)

			Cx. quinquefasciatus	
Leguminosae	*Millettia dura*	Seed	*Ae. aegypti*	Yenesew et al. (2003)
	Cassia obtusifolia	Seed	*Ae. aegypti*	Yang et al. (2003)
			Ae. togoi	
	Acacia ferruginea	Leaf	*Cx. quinquefasciatus*	
	Caesalpinea sp.	Bark	*Cx. quinquefasciatus*	
	Cassia obtusifolia	Leaf	*An. stephensi*	
	Denis sp.	Root	*An. stephensi*	
	Erythrina mulungu	Stem bark	*An. stephensi*	Rajkumar and Jebanesan (2009)
	Pterodon polygalaeflorus	Seed	*An. stephensi*	
Liliaceae	*Gloriosa superb*	Whole	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Aloe barbadensi	Leaf	*An. stephensi*	Maurya et al. (2007)
Lythraceae	*Pemphis acidula*	leaf	*Cx. quinquefasciatus*	Samidurai et al. (2009)
			Ae. aegypti	
Meliaceae	*Azadirachta indica*	Leaf & Seed	*Ae. aegypti*	Monzon et al. (1994)
			Cx. quinquefasciatus	
	Khaya senegalensis	Seed	*Cx. annulirostris*	Shaalan et al. (2003)
	Lansium domesticum	Leaf	*Ae. Aegypti*	Monzon et al. (1994)
			Cx. quinquefasciatus	
	Melia azadirachta	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
			Cx. pipiens molestus	
	Azadirechta indica	Leaf	*Ae. aegypti*	Mgbemena (2010)
			Cx. quinquefasciatus	
	Dysoxylum malabaricum	Leaf	*An. stephensi*	Senthil Nathan et al. (2008)
	Melia volkensii	Seed & Fruit	*Cx. pipiens molestus*	
			Ae. aegypti	Al-Sharook et al. (1991)
			An. arabiensis	
Menispermaceae	*Abuta grandifolia*	Fruit	*Ae. aegypti*	Ciccia et al. (2000)

Moringaceae	*Moringa oleifera*	Bark	*Cx. gelidus*	Kamaraj and Rahuman (2010)
Myrtaceae	*Eucalyptus camaldulensis*	Fruit	*Cx. pipiens*	Erler et al. (2006)
	Eugenia caryophyllus	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
	Eucalyptus globules	Whole Plant	*An. stephensi* *Ae. albopictus*	Soliman and El-Sherif (1995)
	Syzygium aromaticum	Leaf	*Ae. aegypti* *Cx. quinquefasciatus* *An. dirus*	Trongtokit et al. (2005)
Oleaceae	*Jasminum fructicans*	Leaf	*Cx. pipiens*	Soliman and El-Sherif (1995)
Papaveraceae	*Argemone mexicana*	Leaf	*Cx. quinquefasciatus*	Karmegam et al. (1997)
Pinaceae	*Cedrus deodara*	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
Piperaceae	*Piper longum*	Fruit	*Cx. pipiens pallens*	Vasudevan et al. (2009)
	Piper nigrum	Fruit	*Cx. pipiens pallens* *Ae. aegypti* *Ae. togoi*	Moawed (1998)
	Piper longum	Fruit exocarp	*Ae. aegypti*	Chaithong et al. (2006)
	P. ribesoides	Fruit exocarp	*Ae. aegypti*	
	P. sarmentosum	Fruit exocarp	*Ae. aegypti*	
Plumbaginaceae	*Plumbago dawei*	Root	*An. gambiae*	Dorni et al. (2007)
	Plumbago stenophylla	Root	*An. gambiae*	
	Plumbago zeylanica	Root	*An. gambiae*	Maniafu et al. (2009)
Poaceae	*Cymbopogon citratus*	Whole Plant	*Cx. quinquefasciatus*	Zaridah et al. (2006)

	Cymbopogon flexuosus	Whole Plant	*An. stephensi*	Sakthivadivel and Daniel (2008)
	Cymbopogon martini	Whole Plant	*An. stephensi*	
	Sorghum bicolour	Seedling	*Cx. pipiens*	Jackson et al. (1990)
	Vetiveria zizanioides	Rhizome	*Cx. pipiens*	Soliman and El-Sherif (1995)
Rubiaceae	*Spermacoce hispida*	Whole	*Cx. quinquefasciatus*	Nazar et al. (2009)
Rutaceae	*Citrus limon*	Peel	*Cx. pipiens*	Thomas, and Callaghan (1999)
	Zanthoxyllum acanthopodium	Stem	*Ae. aegypti*	Zaridah et al. (2006)
	Feronia limonia	Leaf	*Cx. quinquefasciatus* *An. stephensi*	Rahuman et al. (2000)
	Citrus sinensis	Fruit peel	*An. subpictus*	Bagavan et al. (2009)
	Atlantia monophylla	Leaf	*An. stephensi*	Sivagnaname and Kalyanasundaram (2004)
Simaroubaceae	*Quassia amara*	Whole Plant	*Cx. quinquefasciatus*	Rajkumar and Jebanesan (2005)
Solanaceae	*Solanum indicum*	Shoot	*Cx. quinquefasciatus*	Nazar et al. (2009)
	S. elaeagnifolium	Berry	*An. labranchiae*	Markouk et al. (2000)
	S. sodomaeum	Seed	*An. labranchiae*	Markouk et al. (2000)
	S. xanthocarpum	Leaf	*Cx. quinquefasciatus*	Rajkumar and Jebanesan (2005)
	S. xanthocarpum	Fruits	*Ae. aegypti*	Kumar et al. (2012)
	Withania somnifera	Leaf	*Cx. quinquefasciatus*	Karmegam et al. (1997)
	Solanum anthocarpum	Root	*Cx. pipiens pallens*	Mohan et al. (2006)
	Solanum nigrum	Dried fruit	*An. Culicifacies* *An. stephensi* *Cx. quinquefasciatus* *Ae. aegypti*	Raghavendra et al. (2009)
	S. xanthocarpum	Root	*Cx. pipiens pallens*	Mohan et al. (2006)

	Solanum villosum	Leaf	*An. subpictus*	Chowdhury et al. (2009)
	Cestrum diurnum	Leaf	*An. stephensi*	Ghosh & Chandra (2006)
	Solanum villosum	Berry	*Ae. aegypti*	Chowdhury et al. (2008a)
	Solanum nigrum	Leaf	*Cx. quinquefasciatus*	Rawani et al. (2010)
	Solanum villosum	Leaf	*An. Stephensi* *Cx. quinquefasciatus*	Chowdhury et al. (2008b)
	Solanum nigrum	Dried fruit	*An. culicifacies* A *An. Culicifacies* C *An. Stephensi* *Cx. quinquefasciatus* *Ae. aegypti*	Raghavendra et al. (2009)
Thymelaeaceae	*Aquilaria malaccensis*	Wood	*Ae. aegypti*	Zaridah et al. (2006)
	Dirca palustris	Seed	*Ae. aegypti*	Ramsewak et al. (1999)
Umbelliferae	*Angelico glauca*	Aerial Parts	*Ae. aegypti* *Cx. fatigans*	Sharma et al. (1994)
	Centella asiatica	Leaf	*Cx. quinquefasciatus*	Rajkumar and Jebanesan (2005)
	Pimpinella anisum	Seed	*Cx. pipiens*	Erler et al. (2006)
Valerianaceae	*Valarian wallichii*	Rhizome	*Ae. Aegypti* *Cx. fatigans*	Sharma et al. (1994)
Verbenaceae	*Aloysia citriodora*	Whole Plant	*Ae. aegypti*	Gillij et al. (2008)
	Clerodendrun inerme	Leaf	*Cx. quinquefasciatus*	
	Stachytarpheta jamaicensis	Shoot	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Vitex nequrdo	Whole Plant	*Cx. quinquefasciatus*	Kalyanasundaram and Babu (1982)
Zingiberaceae	*Curcuma domestica*	Rhizome	*An. culicifacies*	Ranaweera (1996)
	Curcuma aromatica	Rhizome	*Ae. aegypti*	Choochate et al. (2005)
	Kaempferia galanga	Whole	*Cx. quinquefasciatus*	Nazar et al. (2009)
	Zingiber officinalis	Tubers	*Cx. quinquefasciatus*	Pushpanathan et al. (2008)

PLANT DERIVED MOSQUITOSIDAL AGENTS

Natural product literature provides a growing research on plant derived mosquitosidal agents. Mosquitoes in the larval stage are attractive targets for pesticides because they breed in water and, thus, are easy to deal with them in this habitat. Some of new significant larvicidal insect growth regulators such as methoprene, pyriproxyfen, diflubenzuron, and endotoxins obtained from *Bacillus thuringiensis israelensis* and *B. sphaericus* have been developed. The plant *Azardichita indica* has gained wide acceptance in some countries as an antifeedant (Isman 1997). Many of essential oils such as citronella, calamus, thymus, and eucalyptus have been found promising in killing of mosquito larva (Shaalan et al. 2005; Rahuman et al. 2008; James 1992; Hemingway 2004; Wandscheer et al. 2004). Hence, in the coming sections numerous plants derived natural products with mosquitosidal potentials have been discussed. In order to highlight any possible mechanism based activity the review has been organized in accordance to chemical structural classes.

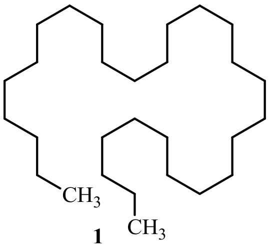
Alkanes, alkenes, alkynes and simple aromatics

Octacosane **(1)**, a hydrocarbon isolated from *Moschosma polystachyum*, exhibits significant larvicidal activity against *Cx. quinquefasciatus* mosquito with LC_{50} value of 7.2±1.7 mg/L (Rajkumar and Jebanesan 2004). The *(E)*-6-hydroxy-4,6-dimethyl-3-heptene-2-one **(2)** isolated from *Ocimum sanctum*, displays toxicity against fourth-instar larvae of *Ae. aegypti* with LD_{100} value of 6.25 μg/mL in 24 h (Kelm and Nair 1998). Among the acetylenic compounds, falcarinol **(3)** and falcarindiol **(4)** isolated from *Cryptotaenia Canadensis*, demonstrate strong activity against *Cx. pipiens* larvae (Kern and Cardellina 1982; Miyazawa et al. 1996). The more lipophilic compound **3** exerts strong toxicity than the more polar acetylene **4** with LC_{50} values of 3.5 and 2.9 ppm in 24 h and 48 h, respectively (Eckenbach at al. 1999). The volatile aromatics, 4-ethoxymethylphenol **(5)**, 4-butoxymethylphenol **(6)**, vanillin **(7)**, 4-hydroxy-2-methoxycinnamaldehyde **(8)**, and 3,4-dihydroxyphenylacetic acid **(9)**, isolated from *Vanilla fragrans*, show very efficient mortality against mosquito larvae.

The compounds **5-8** display 100% larval mortality at 0.5, 0.4, 2.0 and 1.0 mg/mL concentrations, respectively while compound **9** shows 17% larval mortality at a concentration of 1.0 mg/mL (Sun et al. 2001). The hexane extract of *Delphinium cultorum* containing ethylmethylbenzene **(10)**, 1-isopentyl-2,4,5-trimethylbenzene **(11)**, 2-(hex-3-ene-2-one)phenyl methyl ketone **(12)**, *E* & *Z* 3-butylidene-3*H*-isobenzofuran-1-one (**13** and **14**) and 2-penten-1-ylbenzoic acid (**15**), exhibits 100% mortality against *Ae. aegypti* larvae at 10 mg/mL in 2 h (Miles et al. 2000).

The *trans*-asarone (**16**) isolated from seeds of *Daucus carota*, shows 100% mortality of fourth-instar larvae of *Ae. aegypti* at 200 μg/mL concentration (Momin and Nair 2002). The compound **17** isolated from rhizomes *of Curcuma longa*, display 100% mortality against *A. aegyptii* larvae with LD_{100} value of 50 μg/mL in 18 h (Lee et al. 2001). Similarly, compound **18** isolated from *Ocimum sanctum*, displays activity against fourth-instar larvae of *Ae. aegypti* with LD_{100} value of 200 μg/mL in 24 h (Kelm and Nair 1998). The 5-allyl-2-methoxyphenol **(19)** isolated from seeds of *Apium graveolens*, exhibit 100% mortality on fourth-instar *Ae. aegypti* larvae at 200 μg/mL concentration (Momin et al. 2000). The *trans*-anethole **(20)**, methyl eugenol **(21)** and iso-methyl eugenol **(22)** isolated from *Myrica salicifolia*, exhibit 100% mortality with LD_{100} value of 20, 60 and 80 ppm in 24 h against 4th instar larvae of *Ae. aegypti* (Kelm et al. 1997). Methyl-phydroxybenzoate (**23**) isolated from *Vitex trifolia*, shows 100% larval mortality at 20 ppm against *Cx. quinquefasciatus* and *Ae. aegypti* with LC_{50} values of 5.77 and 4.74 ppm, respectively (Kannathasan et al. 2011).

The stilbenes **24-30** isolated from the root bark of *Lonchocarpus chiricanus* possess larvicidal activities against *Ae. aegypti*. Among these, compound **28** exhibits highest activity at 3.0 ppm while **25** & **26** at 6.0 ppm concentration display pronounced affect by kill all the larvae in 24 h. The compounds **24**, **27**, **29** and **30** at about 50 ppm concentration display moderate activity against larvae of *Ae. aegypti* (Ioset et al. 2001).



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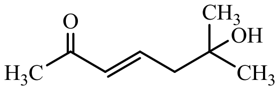

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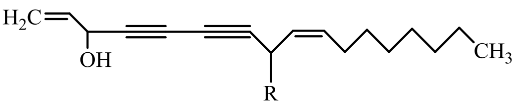

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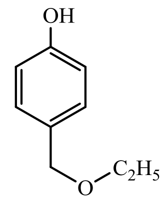
4 R = OH



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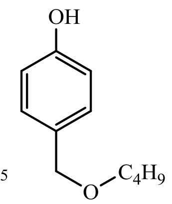

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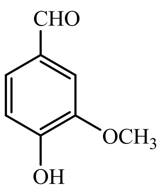

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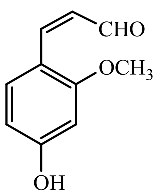

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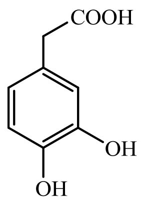

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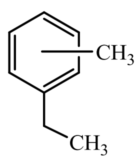

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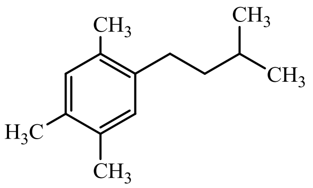

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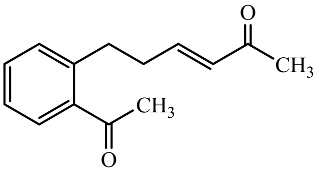

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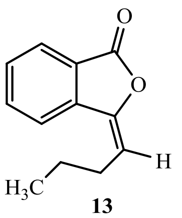

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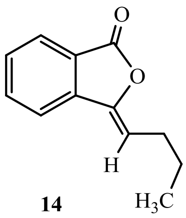

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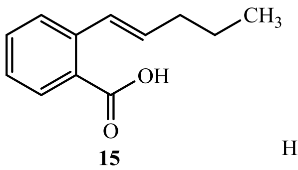

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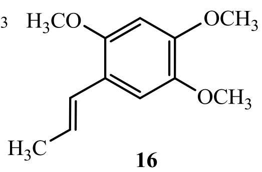

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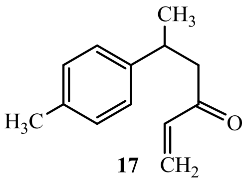

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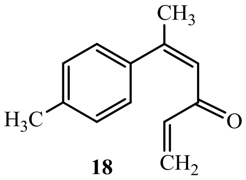

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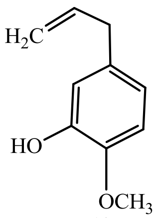

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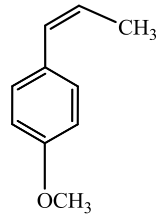

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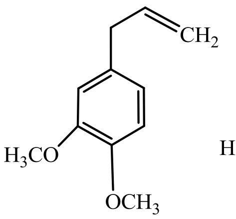

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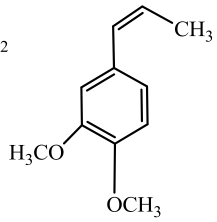

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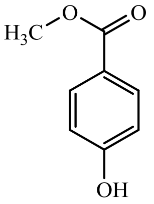

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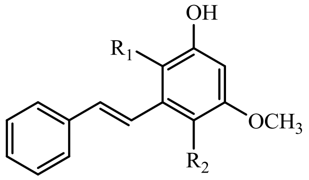
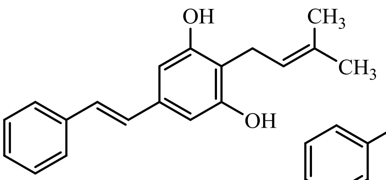


24 R$_1$ = H; R$_2$ = -CH$_2$CHC(CH$_3$)$_2$
25 R$_1$ = R$_2$ = -CH$_2$CHC(CH$_3$)$_2$



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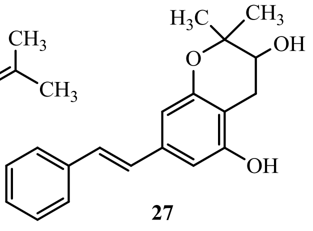

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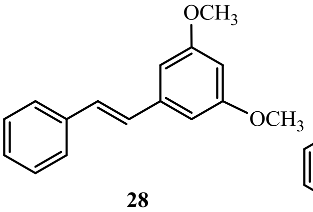

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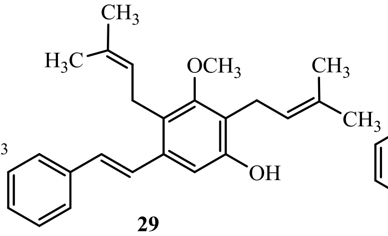

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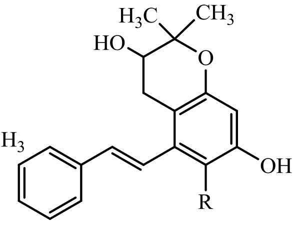
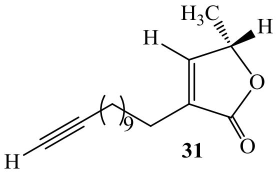


30 R = -CH$_2$CHC(CH$_3$)$_2$

Lactones

The lactones **31** and **32**, isolated from *Hortonia floribunda, H. angustifolia and H. ovalifolia,* exhibit potent larvicidal activity against the second instar larvae of *Ae. aegypti* with LC$_{50}$

values of 0.41 and 0.47 ppm, respectively (Ratnayake et al. 2001). The 3-*n*-butyl-4,5-dihydrophthalide **(33)** isolated from seeds of *Apium graveolens* shows 100% mortality on fourth-instar *Ae. aegypti* larvae at 25 *μ*g/mL concentration (Momin et al. 2000). The sedanolide **(34)** isolated from seeds *An. graveolens* exhibits 100% mortality at 50 *μ*g/mL concentrations against fourth-instar larvae of *Ae. aegyptii* (Momin and Nair 2001).



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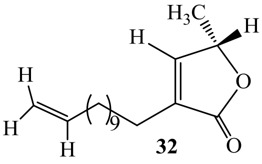

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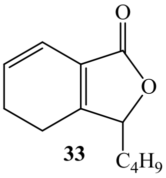

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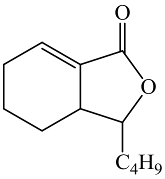

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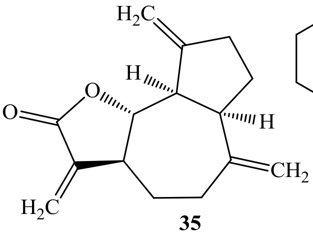

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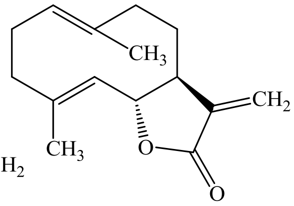

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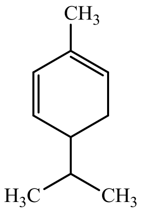
Essential oils and fatty acids

The essential oil obtained from *Saussurea lappa* exhibits significant larvicidal effect against *A. albopictus* (LC_{50} = 12.41 μg/mL). The dehydrocostus lactone **(35)** and costunolide **(36)**, identified from essential oil of *S. lappa* exhibit strong larvicidal activity against *A. albopictus* with LC_{50} values of 2.34 and 3.26 μg/mL, respectively (Liu et al. 2012). Likewise, *α*-phellandrene **(37)**, limonene **(38)**, *p*-cymene **(39)**, *γ*-terpinene **(40)**, terpinolene **(41)** and *α*-terpinene **(42)** isolated from leaves of *Eucalyptus camaldulensis* possess significant activity against fourth-instar larvae of *Ae. aegypti* and *Ae. albopictus*. The compound **42** exerts the strongest activity against *Ae. aegypti* larvae with LC_{50} value of 14.7 *μ*g/mL (LC_{90} = 39.3 *μ*g/mL), following the compounds **37** (LC_{50} = 16.6 *μ*g/mL, LC_{90} = 36.9 *μ*g/mL), **38** (LC_{50} = 18.1 *μ*g/mL, LC_{90} = 41.0 *μ*g/mL), **39** (LC_{50} = 19.2 *μ*g/mL, LC_{90} = 41.3 *μ*g/ mL), **41** (LC_{50} = 28.4 *μ*g/mL, LC_{90} = 46.0 *μ*g/mL) and **40** (LC_{50} = 30.7 *μ*g/mL, LC_{90} > 50.0 *μ*g/mL) in 24 h (Jantan et al. 2005). Benzaldehyde **(43)**, 4-hydroxybenzaldehyde **(44)**, benzenepropanal **(45)**, cinnamic acid **(46)**, cinnamyl alcohol **(47)**, bornyl acetate **(48)**, *β*-caryophyllene **(49)**, caryophyllene oxide **(50)** and linalool **(51)**, isolated from *Cinnamomum osmophloeum* display strong activity against *Ae. aegypti* larvae with LD_{50} value of 50 μg/mL, while **52** exhibits significant larvicidal effect with LD_{50} value of 33 μg/mL (Cheng et al. 2009). The *n*-hexadecanoic acid **(53)** isolated from *Feronia limonia* leaves shows activity against fourth instar larvae of *Cx. quinquefasciatus*, *An. stephensi* and *Ae. aegypti*, with LC_{50} values of 129.24, 79.58 and 57.23 ppm, respectively (Rahuman et al. 2000).



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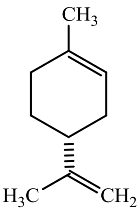

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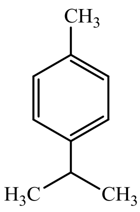

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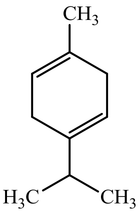

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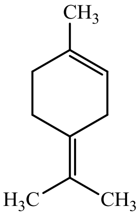

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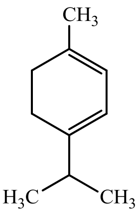

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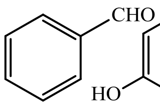

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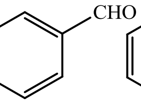

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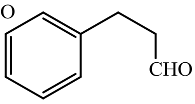

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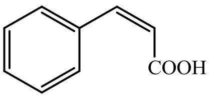

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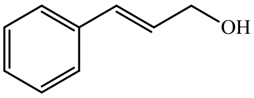

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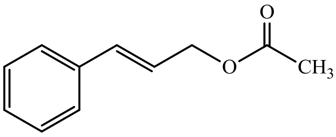

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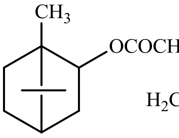

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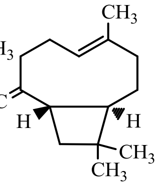

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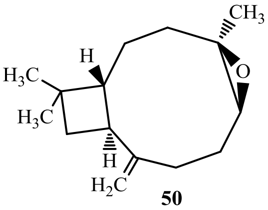

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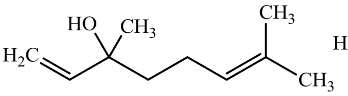

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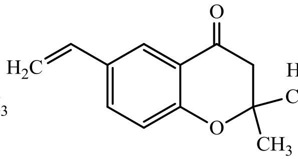

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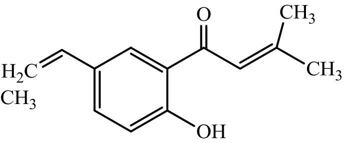

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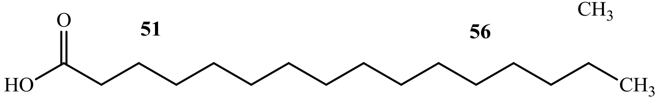

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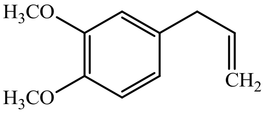
$H_3C(H_2C)_4(HC{=}CHCH_2)_2(CH_2)_5CH_2COOH$

58



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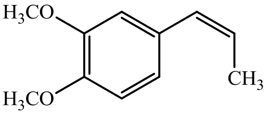

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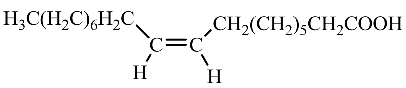

$H_3C(H_2C)_6H_2C\text{–}C(H){=}C(H)\text{–}CH_2(CH_2)_5CH_2COOH$

59

The aromatics, *O*-methyleugenol **(54)** and *O*-methylisoeugenol **(55)** isolated from stem and root barks of *Uvariodendron pycnophyllum*, exhibit activity against mosquito larvae with LC_{50} value of 43 and 59 ppm in 24 h, respectively (Kihampa et al. 2010). Likewise, 2,2-

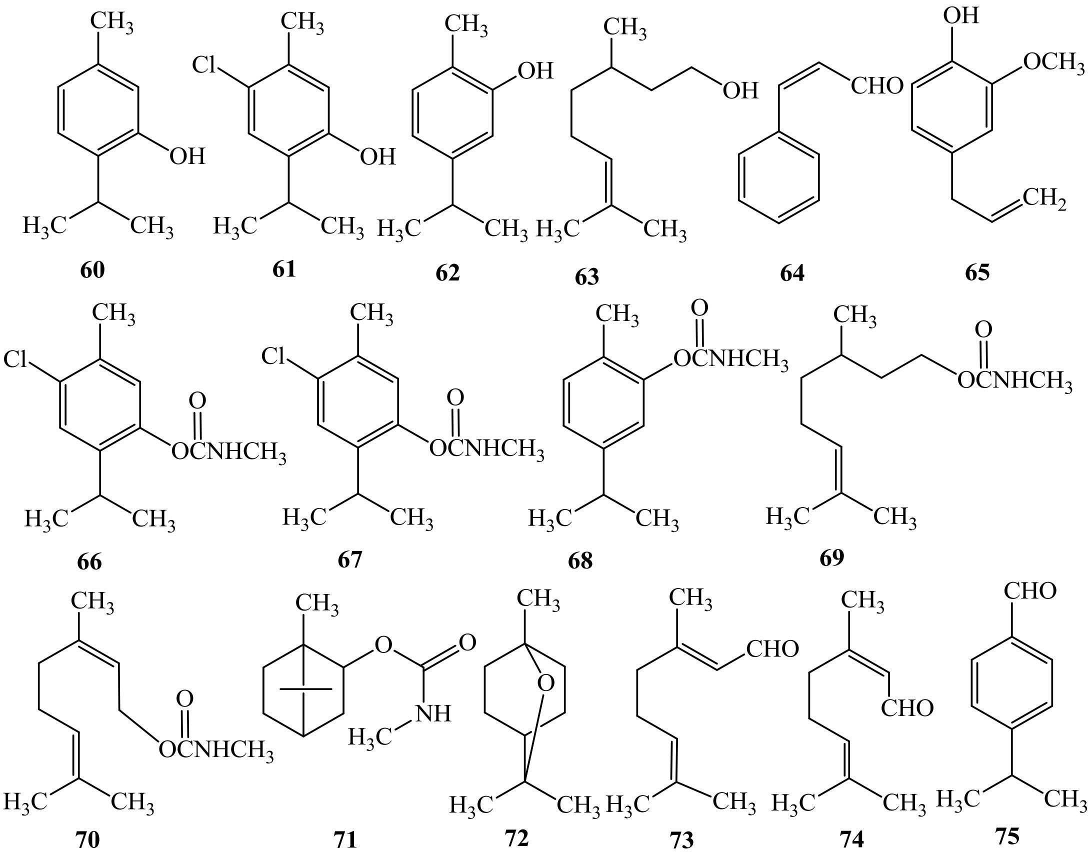
dimethyl-6-vinylchroman-4-one **(56)** and 2-senecioyl-4-vinylphenol **(57)** isolated from the roots of *Eupatorium betonicaeforme*, possess significant moquitosidal properties. The compound **56** shows efficient larvicidal potential causing 84% larval mortality at 12.5 μg/mL concentrations while **57** displays 40-100% mortality at 5-100 μg/mL concentrations (Albuquerque et al. 2004). The fatty acid constituents, linoleic acid **(58)**, and oleic acid **(59)** isolated from *Dirca palustris*, exhibit mosquitocidal activity against fourth instar *Ae. aegypti* larvae with LD_{50} values of 100 μg/mL at 24 h (Ramsewak et al. 2001).

Terpenoids

Monoterpenes

The monoterpenoids, thymol (**60**), cholorothymol (**61**), carvacrol (**62**), β-citronellol (**63**), cinnamaldehyde (**64**), and eugenol (**65**) isolated from a number of plant species, possess mosquitocidal activity against forth instar larvae of *Cx. pipiens* with LC_{50} values of 37.95, 14.77, 44.38, 89.75, 58.97 and 86.22 μg/mL, respectively. The *N*-methyl carbamate derivatives of **60-63**, i.e. **66-69** display high toxicities against forth instar larvae of *Cx. pipiens* with LC_{50} values of 7.83, 11.78, 4.54, 15.90 μg/mL, respectively. Likewise, *N*-methyl carbamate derivatives of geraniol (**70**) and borneol (**71**) also exhibit significant activity against forth instar larvae of *Cx. pipiens* with LC_{50} values of 24.08 and 33.00 μg/mL, respectively (Radwan et al. 2008).

The 1,8-cineole (**72**) isolated from leaves of *Hyptis martiusii* displays significant insecticidal effect against *Ae. aegypti* larvae at 25 (10%), 50 (53%), 100 (100%) mg/mL concentrations (Jo et al. 2003). Other monoterpenoids, geranial (**73**), and neral (**74**) isolated from *Magnolia salicifolia* exhibit 100% mortality with LD_{100} value of 100 ppm in 24 h against 4th instar *Ae. aegypti* (Kelm et al. 1997). Cuminaldehyde (**75**) occurring in plant species, exhibits significant larvicidal and adulticidal toxicity with LC_{50} values of 38.94 mg/L in 24h against *Cx. pipiens* larvae (Zahran HE-DM and Abdelgaleil SAM et al. 2010).



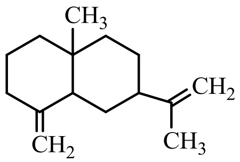
60 61 62 63 64 65

66 67 68 69

70 71 72 73 74 75

Sesquiterpenes

The *β*-selinene **(76)** isolated from seeds of *Apium graveolens* shows 100% mortality against fourth-instar larvae of *Ae. aegypti* at 50 *μ*g/mL concentrations (Momin et al. 2000). The pregeijerene **(77)**, geijerene **(78)**, and germacrene-D (**79**) isolated from leaves of *Chloroxylon swietenia*, possess activity against *An. gambiae, Cx. quinquefasciatus* and *Ae. aegypti*. The compound **79** with LD_{50} values of 1.8, 2.1 and 2.8×10^{-3} exerts highest activity followed by **77** (LD_{50} values of 3.0, 3.9 and 5.1×10^{-3}) while **78** (LD_{50} values of 4.2, 5.4 and 6.8×10^{-3}) displays lowest activity against *An. gambiae, Cx. quinquefasciatus* and *Ae. aegypti* (Kiran and Devi 2007). The sesquiterpene lactones, **80** and **81** isolated from leaves, stem bark, flowers, and fruits of *Magnolia salicifolia* exhibit significant toxicity against *Ae. aegypti* larvae. The lactone **80** with LD_{100} value of 15 ppm kills all the mosquito larvae of *Ae. aegypti* in 24 h while **81** exhibits 100% mortality with LD_{100} value >50 ppm in 24 h (Lee et al. 1971). The sesquiterpene **81** does not show mosquitocidal activity at 50 ppm, thus suggesting the presence of a double bond rather than an epoxide at C-4 and C-5 in **80** is essential for mosquitocidal activity (Kelm et al. 1997). The sesquiterpenes, elemol (**82**), *β*-eudesmol (**83**), carotol (**84**), and patchoulol (**85**) occurring in plants *Amyris balsamifera*, and *Daucus carota*, show >90% mortality against *Cx. pipiens pallens* at 0.1 mg/mL (Park and Park 2012).



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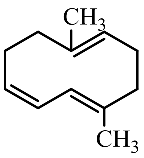

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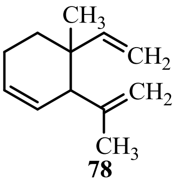

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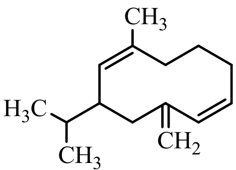

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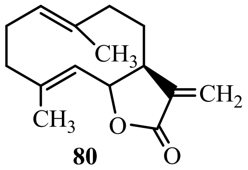

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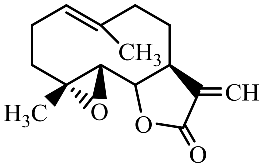

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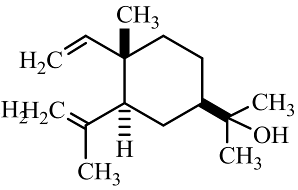

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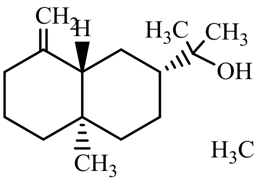

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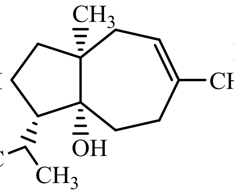

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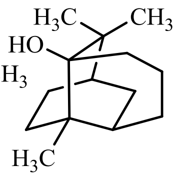

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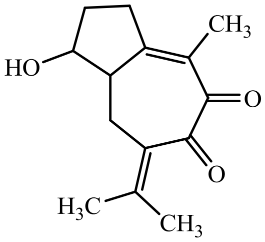

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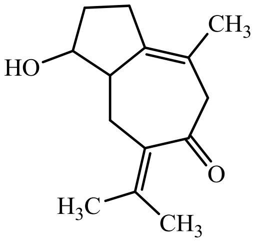

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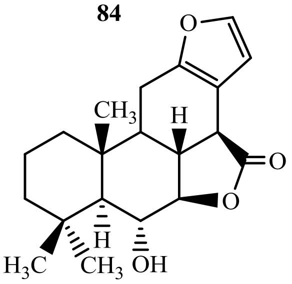

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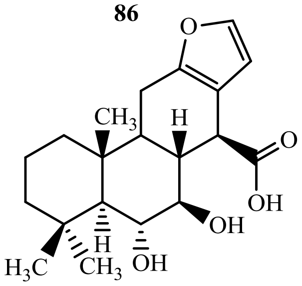

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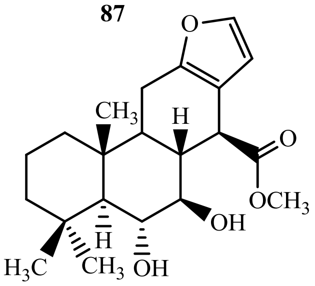

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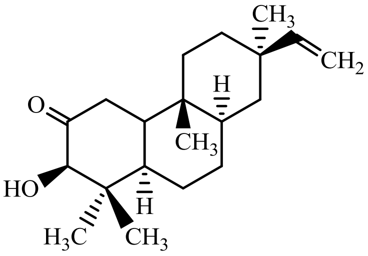


91

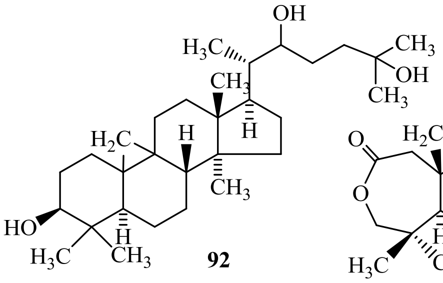
The guanine type sesquiterpenes, 9-oxoneoprocurcumenol (**86**), and neoprocurcumenol (**87**) isolated from *Curcuma aromatica*, exhibit significant toxicity on mosquito larvae of *Cx. quinquefasciatus* (Madhu et al. 2010). Between the two, the compound **86** exerts significant toxicity ($P < 0.01$) on mosquito larvae with LC_{50} value of 5.81 ppm and LC_{90} being 9.99 ppm compared to **87** with 13.69 and 23.92 ppm of LC_{50} and LC_{90} values, respectively.

Diterpenes

The diterpenes, **88-90** isolated from *Pterodon polygalaeflorus*, exhibit significant activity against 4th instar larvae of *Ae. aegypti* with LC_{50} values of 50.08, 14.69 and 21.76 μg/mL, respectively (Omena et al. 2006). Likewise, hugorosenone **(91)** isolated from the *Hugonia castaneifolia* displays larvicidal effect against *An. gambiae* larvae with LC_{50} values of 0.3028 and 0.0986 mg/mL at 24 and 48 h, respectively (Baraza et al. 2008).

Triterpenes

The triterpenes, 3β,24,25-trihydroxycycloartane **(92)** and beddomeilactone **(93)** isolated from *Dysoxylum species* (*D. malabaricum*, *D. beddomei* etc.) possess strong larvicidal, pupicidal and adulticidal activity. These compounds also affect the reproductive potential of adults by acting as oviposition deterrents. The compound **92** at a concentration of 10 ppm kills more than 90% of pupae and 85% of adult mosquitoes. Similarly, compound **93** at the same concentration results in more than 95% of pupal and larval mortality and >90% mortality in case of adult *An. stephensi* (Nathan et al. 2008)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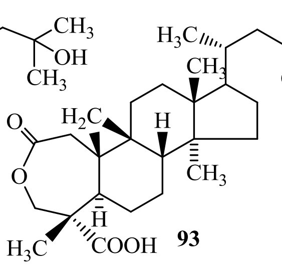
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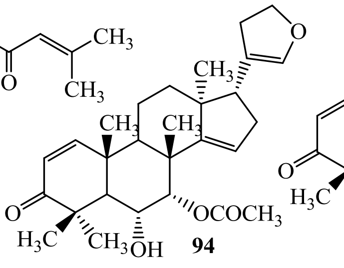
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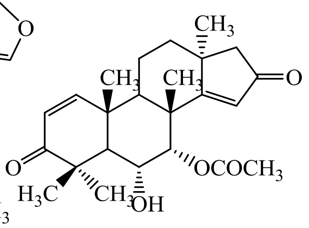
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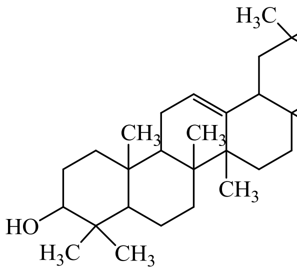
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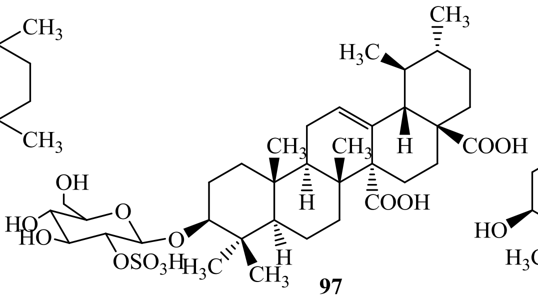
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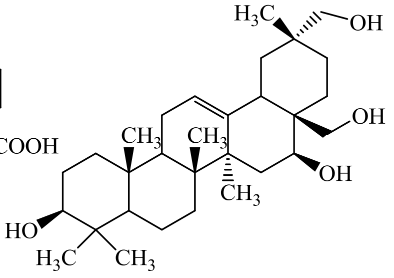
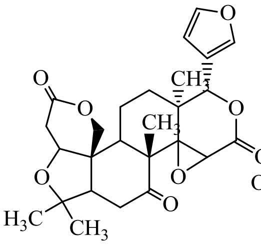

98

The compounds, 22,23-dihydronimocinol (**94**) and desfurano-6*R*-hydroxyazadiradione (**95**), isolated from leaves of *Azadirachta indica*, exhibit significant mortality for fourth instar larvae of *An. stephensi* with LC_{50} values of 60 and 43 ppm, respectively (Siddiqui et al. 2002). The β-amyrin **(96)** isolated from stem of *Duranta repens* display strong activity against first to fourth instars larvae of *Cx. quinquefasciatus* with LC_{50} value of 7.75, 16.11, 28.63 and 26.53 ppm, respectively in 24 h (Nikkon et al. 2010). The ursane-type triterpene saponin **97** isolated from aerial parts of *Zygophyllum coccineum*, exhibits significant adult mortality of 90% and 80% against *Ae. aegypti* and *Cx. quinquefasciatus* at 3.1 and 0.5 μL concentrations, respectively (Amin et al. 2012). The gymnemagenol (**98**) isolated from *Gymnema sylvestre* shows larvicidal against the fourth-instar larvae of *An. subpitcus* and *Cx. quinquefasciatus* with LC_{50} values of 22.99 ppm and 15.92 ppm, respectively (Khanna et al. 2011).

Tetranortriterpenoids

The limonin **(99)**, nomilin **(100),** and obacunone **(101)**, isolated from the seeds of *Citrus reticulate* (Champagne et al. 1992), exhibit mosquitocidal activity against fourth instar larvae of *Cx. quinquefasciatus* at a concentration of 59.57, 26.61 and 6.31 ppm, respectively (Jayaprakasha et al. 1997). The limonoids **102-104**, isolated from the root bark of *Turraea wakefieldii* show strong larvicidal activity against late third or early fourth-instar larvae of *An. gambiae*. In SAR, strong activities of **102**, **103**, and **104** with LD_{50} values of 7.83, 7.07, and 7.05 ppm, respectively indicate that the epoxidation of the C-14, C-15 double bond or de-acetylation of the 11-acetate group does not alter the larvicidal activity (Ndungu et al. 2003). Other limonoids, azadirachtin **(105)**, salannin **(106)**, deacetylgedunin **(107)**, 17-hydroxyazadiradione **(108)**, gedunin **(109)**, and deacetylnimbin **(110)**, isolated from *Azadirachta indica* possess significant activity against *An. stephensi* larvae. Among these, the compound **105** with EC_{50} value of 0.014, 0.021, 0.028 and 0.034 ppm, **106** with EC_{50} value of 0.023, 0.036, 0.047 and 0.061 ppm, **107** with EC_{50} value of 0.028, 0.041, 0.0614 and 0.078 ppm, **108** with EC_{50} value of 0.047, 0.054, 0.076 and 0.0104 ppm, **109** with EC_{50} value of 0.058, 0.073, 0.095 and 0.0117 ppm and **110** with EC_{50} value of 0.055, 0.067, 0.091 and

0.0113 ppm, show activity against first, second, third and fourth instar larvae of *An. stephensi*, respectively.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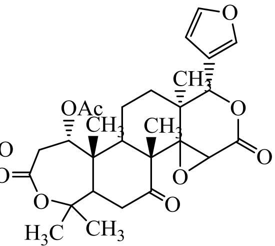
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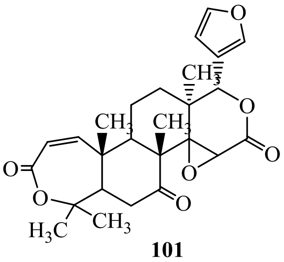
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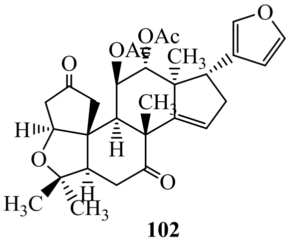
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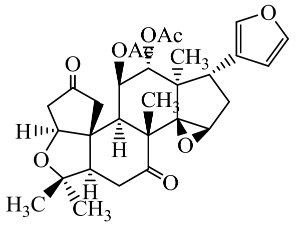
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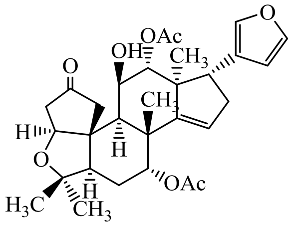
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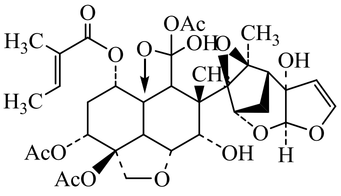
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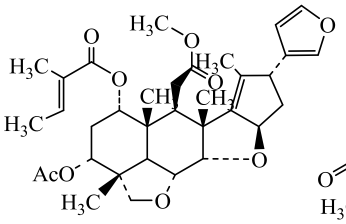
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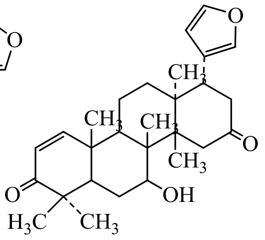
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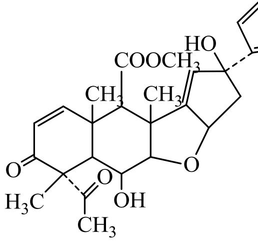
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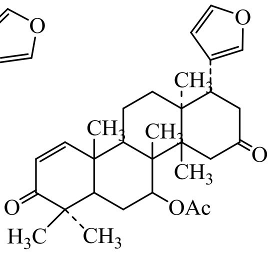
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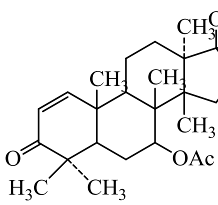
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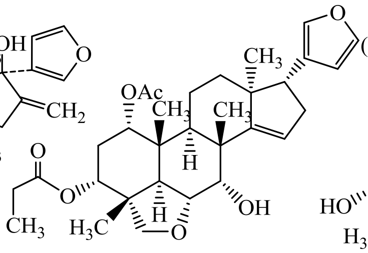
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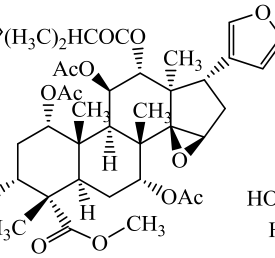
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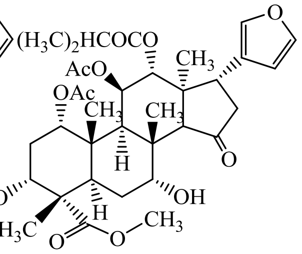
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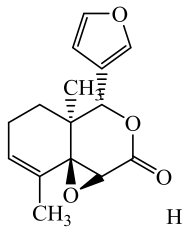
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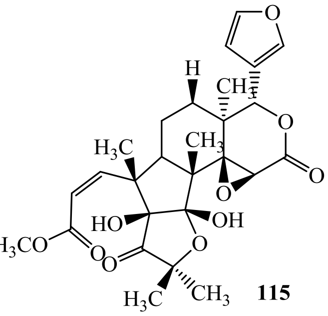
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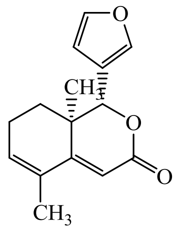
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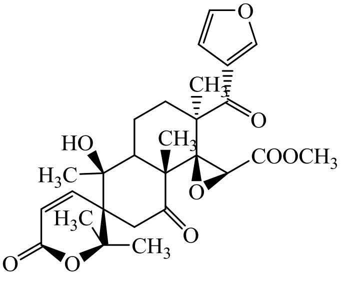
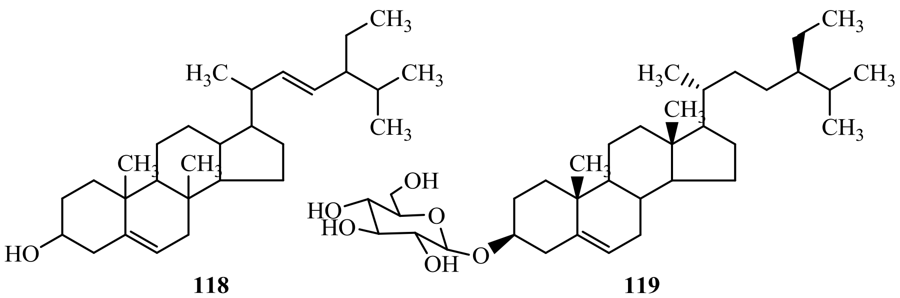

117

The metabolite **105** exerts 100% larval mortality at a concentration of 1.0 ppm, thus, demonstrates that the use of *A. indica* products may have benefits in mosquito control programs (Nathan et al. 2005). The compounds **111-113** isolated from *Turraea* species (*T.*

wakefieldii, *T. floribunda* etc.), exhibit toxicity against *An. gambiae* larvae with LD_{50} values of 7.1, 4.0, and 3.6 ppm, respectively (Ndungu et al. 2004). Other limonoids calodendrolide (**114**), harrisonin (**115**), pedonin (**116**), and pyroangolensolide (**117**) isolated from root bark of *Harrisonia abyssinica* and *Calodendrum capense*, exhibit toxicity against 2nd instar larvae of *Ae. aegypti* in the order: **114** (13.2 μm) > **117** (16.6 μm) > **115** (28.1 μm) > **116** (59.2 μm). Also, compound **114** results in 100% mortality at all concentrations, while **117** shows 100% mortality up to concentration of 50 μm (Kiprop et al. 2007).

Steroids

The compound stigmasterol (**118**), isolated from *Uvariodendron pycnophyllum* and many other plant species, exhibit larvicidal activity at different levels with LC_{50} value of 46 ppm in 24 h (Kihampa et al. 2010). Likewise, β-sitosterol-3-*O*-β-D-glucoside (**119**) isolated from *Acanthus montanus* results in 100% mortality against adult *Ae. aegypti* at 1.25 μg/mL concentration (Amin et al. 2012).



118 **119**

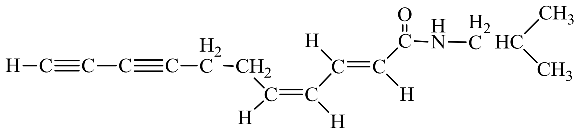
Alkaloids

Alkamides

The alkamides, undeca-2*E*-4*Z*dien- 8,10-diynoic acid isobutylamide (**120**), undeca-2*Z*,4*E*-dien-8,10-diynoic acid isobutylamide (**121**), dodeca-2*E*,4*Z*-dien-8,10-diynoic acid isobutylamide (**122**), undeca-2*E*,4*Z*-dien-8,10-diynoic acid 2-methylbutylamide (**123**), dodeca-2*E*,4*Z*-dien-8,10-diynoic acid 2-ethylbutylamide (**124**), and a mixture of dodeca-2*E*,4*E*,8*Z*,10*E*-tetraenoic acid isobutylamide **(125)** and dodeca-2*E*,4*Z*,8*Z*,10*Z*-tetraenoic acid isobutylamide (**126**) isolated from roots of *Echinacea purpurea* and other species, display significant activity against *Ae. aegypti* larvae. A mixture of compounds **125** and **126**, exert most effective mosquitocidal activity at 100 μg/mL concentration with 87.5% larval mortality in 15 min while **120** display 100% mortality at same concentration in 2 h.

The alkamides **121** and **122** exhibit 50% mortality at 100 μg/mL concentration in 9 h while **123** and **124** show least activity with 10% mortality at 100 μg/mL concentrations in 24 h (Clifford et al. 2002). Among isobutyl amides, pellitorine (**127**), guineensine (**128**), pipercide (**129**), and retrofractamide-A (**130**) isolated from *Piper nigrum* fruits, exhibit toxicity against *Cx*. *Pipiens* larvae in the order: **129 (**0.004 ppm) > **130** (0.028 ppm) > **128** (0.17 ppm) > **127** (0.86 ppm). These compounds also possess activity against *Ae. aegypti* larvae in which **130** exerts pronounced activity at a concentration of 0.039 ppm in compared to compounds **129** (0.1 ppm), **128** (0.89 ppm) and **127** (0.92 ppm). The SAR indicates that the *N*-isobutyl amine moiety might play a crucial role in the larvicidal activity, but the methylenedioxyphenyl moiety does not appear essential for toxicity (Park et al. 2002). The compound **131** isolated from *Piper longum*, exhibits larval toxicity against *Cx.* species with LC_{50} values of 0.58 and 1.88 ppm, respectively (Madhu et al. 2011).

120



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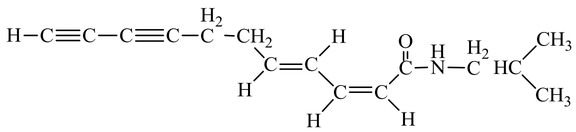

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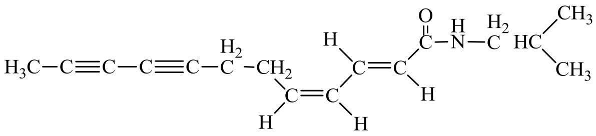

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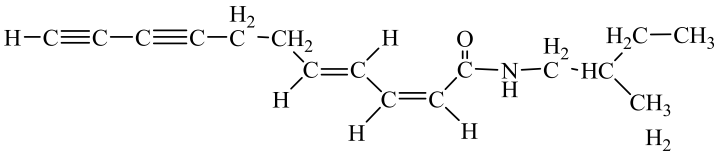

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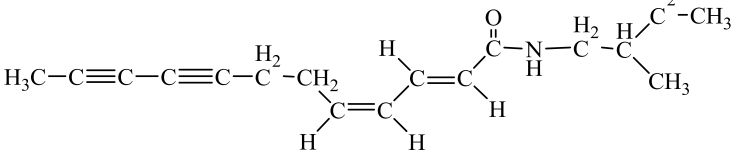

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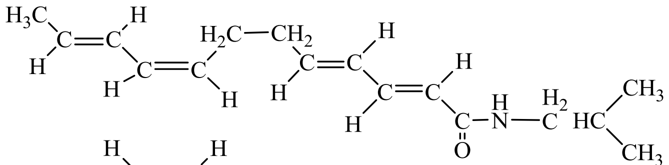

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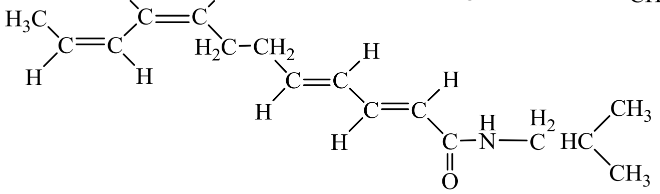

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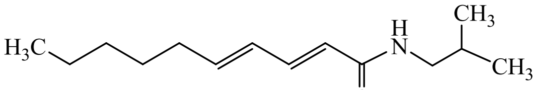

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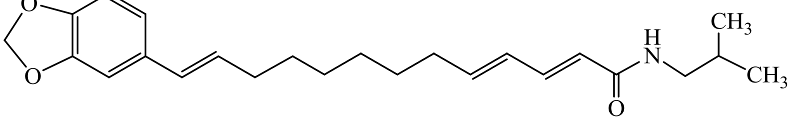

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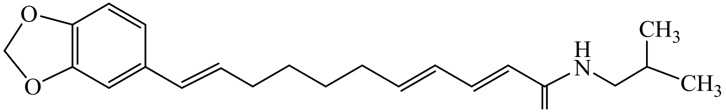

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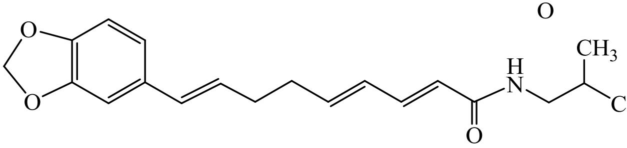

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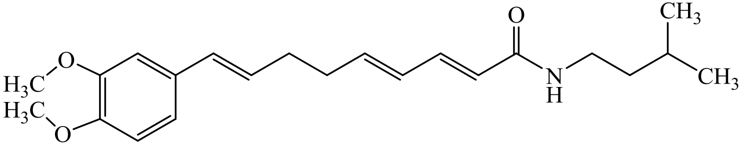
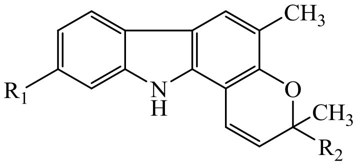


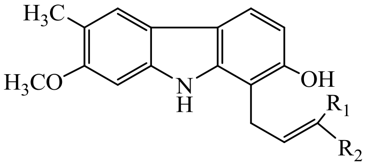
Carbazole alkaloids

Among carbazoles, mahanimbine (**132**), murrayanol (**133**), and mahanine (**134**) isolated from leaves of *Murraya koenigii*, display promising mosquitocidal activity against *Ae. aegypti* (Ramsewak et al. 1999). The alkaloid **132** exhibits 100% mortality at 100 μg/mL concentration while **133** and **134** at 12.5 μg/mL concentration display 100% mortality (Nair et al. 1989; Roth et al. 1998).

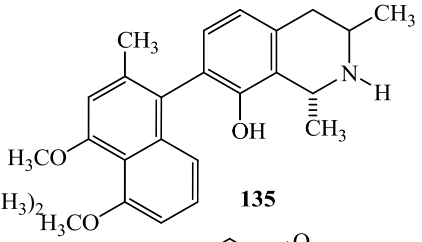
Naphthylisoquinoline alkaloid

The alkaloid, dioncophylline-A **(135)** isolated from *Triphyophyllum peltatum* (Bringmann et al. 1990), displays promising activity against different larval stages of *An. stephensi* with LD_{50} values of 0.5, 1.0 and 2.0 mg/L at 3.33, 2.66 and 1.92 h, respectively. In each instar larval stage, the LC_{50} values decrease as a function of time indicating that **135** continues to exert its action during at least 48 h (Franqois et al. 1996).





132: $R_1 = H$; $R_2 = CH_2CH_2CH{=}C(CH_3)_2$ **133**: $R_1 = CH_3$; $R_2 = CH_2CH_2CH{=}C(CH_3)_2$
134: $R_1 = OH$; $R_2 = CH_2CH_2CH{=}C(CH_3)_2$



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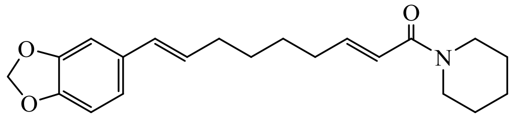

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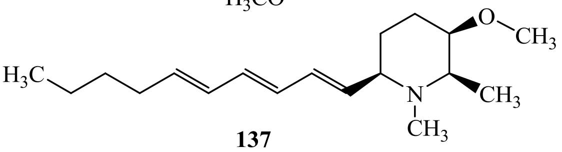
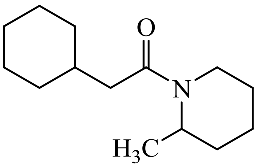


137

Piperidine alkaloids

The alkaloid, pipernonaline **(136)** isolated from fruits of *Piper longum* exhibits activity against the fourth-instar larvae of *Ae. aegypti* (Yang et al. 2002) and *Cx. pipiens* (Lee 2000) in 24 h with LC_{50} values of 0.25 and 0.21 mg/L, respectively. Similarly, *N*-methyl-6β-(deca-l',3',5'-trienyl)-3-β--methoxy-2-β-methylpiperidine **(137)** isolated from stem bark of *Microcos paniculata*, shows significant insecticidal activity against second instar larvae of *Ae. aegypti* with LC_{50} value of 2.1 ppm at 24 h (Bandara et al. 2000). Insecticidal activity evaluation of piperidine derivatives **138-170**, against female adults of *Ae. aegypti* following SAR studies using piperine (*E,E*)-1-piperoyl-piperidine as standard insecticide (LD_{50} value of 8.13 μg per mosquito) reveal that different moieties (ethyl-, methyl-, and benzyl-) attached to the piperidine ring are responsible for different toxicities (i.e. **138**, 1.77; **139**, 2.74; **140**, 8.76; **141**, 1.20; **142**, 1.09; **143**, 1.13; **144**, 4.14; **145**, 1.92; **146**, 2.07; **147**, 1.80; **148**, 4.90; **149**, 4.25; **150**, 2.63; **151**, 6.71; **152**, 1.22; **153**, 1.67; **154**, 0.94; **155**, 1.56; **156**, 1.83; **157**, 0.84; **158**, 29.20; **159**, 14.72; **160**, 19.22; **161**, 12.89; **162**, 0.80; **163**, 1.38; **164**, 3.59; **165**, 1.32; **166**, 2.07; **167**, 7.43; **168**, 1.54; **169**, 2.72, and **170**, 14.72 μg) against *Ae. aegypti*.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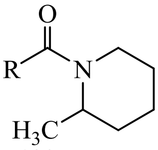
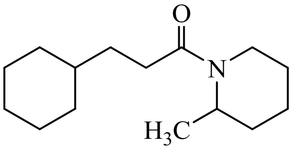

139 R = C_9H_{19}
140 R = $C_{11}H_{23}$
141 R = C_6H_{13}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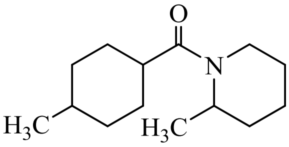
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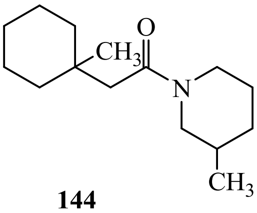
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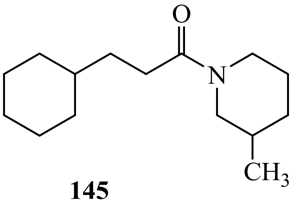
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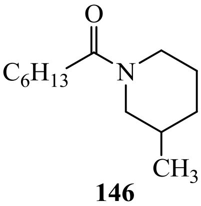
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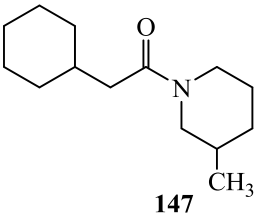
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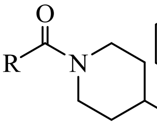
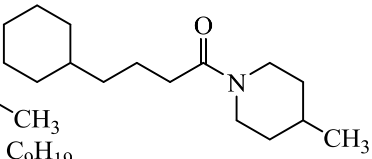

148 R = C_9H_{19}
151 R = $C_{11}H_{23}$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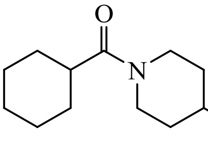
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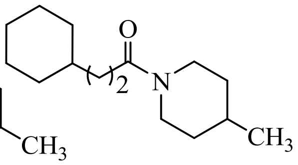
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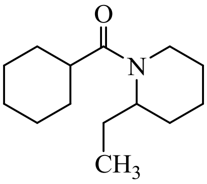
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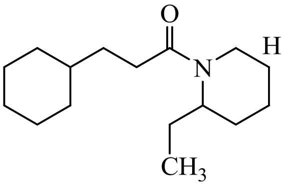
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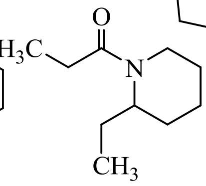
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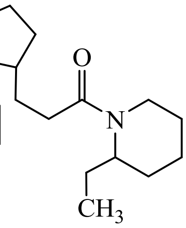
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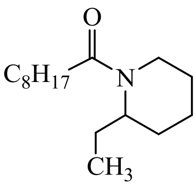
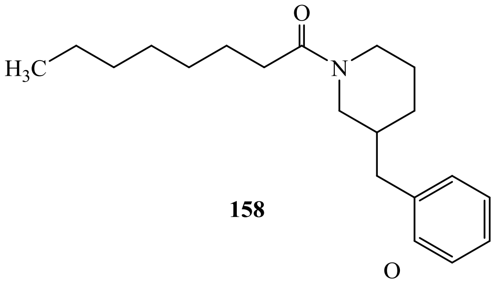

157

The 3-methylpiperidines **144-147** exhibit slightly lower toxicities than that of 2-methyl-piperidines **138-143** with LD_{50} values ranging from 1.80-4.14 μg. However, there is no significant difference found between the toxicities of 3-methyl piperidines **144-147** and 4-methyl piperidines **148-152**, whose LD_{50} values range from 1.22-6.71 μg while the saturated long chain derivatives of 4-methyl-piperidine **148** & **151** show lower toxicity compared to others with LD_{50} values of 4.90 and 6.71 μg, respectively (Pridgeon et al. 2007). Further, SAR among the piperidines with two different moieties (ethyl- and benzyl-) attached to the carbons of the piperidine ring indicates that 2-ethyl-piperidines **153-157** show higher toxicity than the benzyl-piperidines **(158-161)** with LD_{50} values ranging from 0.84-1.83 and 12.89-

29.20 μg, respectively. The results of SAR suggest that ethyl-piperidines generally exhibit higher toxicities than methyl-piperidines, followed by benzyl-piperidines whose toxicities are lowest.



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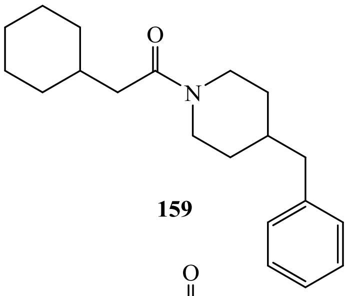

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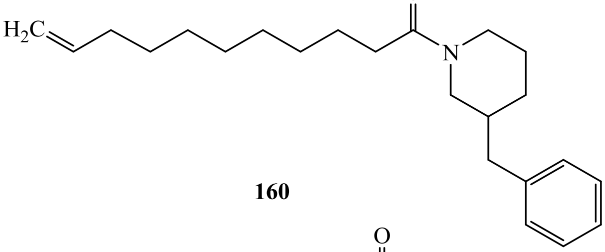

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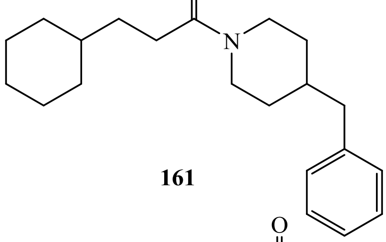

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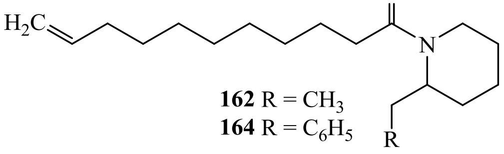
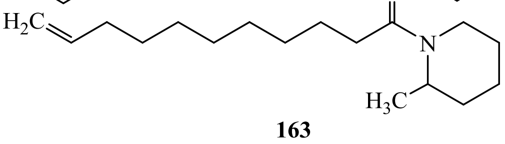


162 R = CH_3
164 R = C_6H_5



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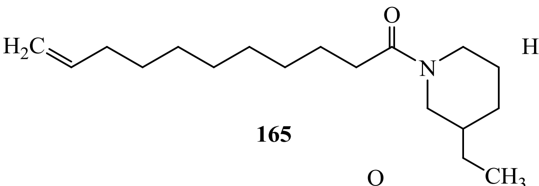

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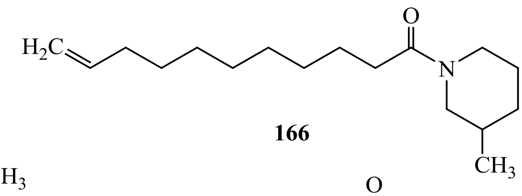

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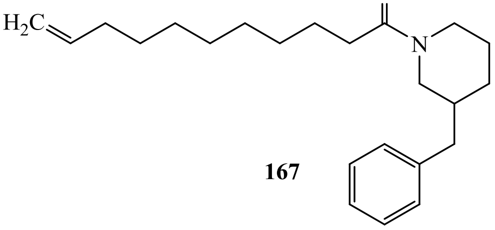

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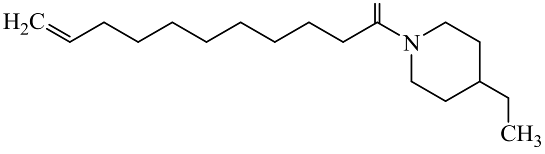

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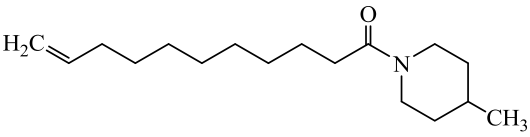

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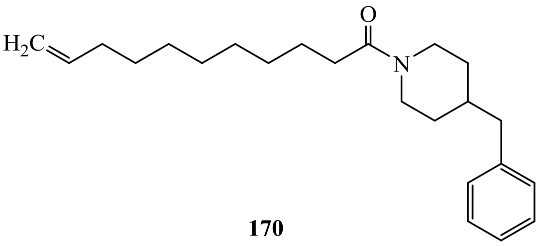


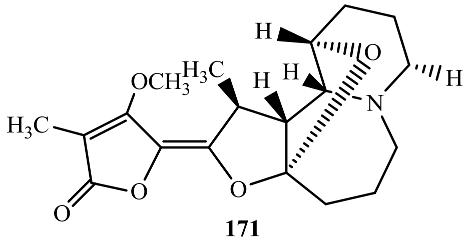
170

Among 1-undec-10-enoyl-piperidines **159-164** having three different moieties at the second carbon of the piperidine ring, the compound **162** displays highest toxicity with LD_{50} value of

0.80 μg, compared to **163** (LD_{50} value of 1.38 μg) and **164** (LD_{50} value of 3.59 μg). Similarly, among compounds **165-167** containing three different moieties attached to the third carbon of the piperidine ring, the compound **165** exhibits highest toxicity (LD_{50} value of 1.32 μg), followed by **166** and **167** with LD_{50} values of 2.07 and 7.43 μg, respectively. Likewise, among compound **168-170** bearing three different moieties attached to the fourth carbon of the piperidine ring, the compound **168** shows highest toxicity (LD_{50} value of 1.54 μg), following **169** (LD_{50} value of 2.72 μg) and **170** (LD_{50} value of 14.72 μg).

Stemona alkaloids

The *Stemona* alkaloids, stemocurtisine **(171)**, stemocurtisinol **(172)**, and oxyprotostemonine **(173)** isolated from roots of *Stemona curtisii*, exhibit potency against mosquito larvae *An. minimus* with LC_{50} values of 18, 39, and 4 ppm, respectively. Among these, **173** show highest potency with LC_{50} value of 4 ppm (Mungkornasawakul et al. 2004).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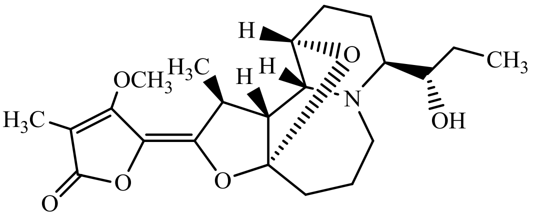
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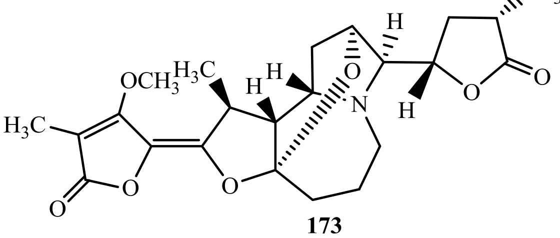
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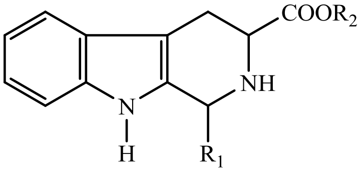
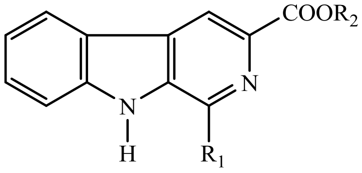

174 $R_1 = CH_3$, $R_2 = H$
175 $R_1 = C_6H_5$, $R_2 = H$
176 $R_1 = H$, $R_2 = H$
177 R_1 = trichloromethyl, $R_2 = H$
178 R_1 = 3-methoxy-4-hydroxyphenyl, $R_2 = H$
179 $R_1 = CH_3$, $R_2 = CH_3$
180 $R_1 = C_6H_5$, $R_2 = CH_3$
181 R_1 = 3-methoxy-4-hydroxyphenyl, $R_2 = CH_3$
182 R_1 = trichloromethyl, $R_2 = CH_3$
183 $R_1 = H$, $R_2 = CH_3$


184 $R_1 = CH_3$, $R_2 = CH_3$
185 R_1 = 4-chlorophenyl, $R_2 = CH_3$
186 $R_1 = C_6H_5$, $R_2 = CH_3$
187 R_1 = 2-hydroxyphenyl, $R_2 = CH_3$
188 R_1 = 1-phenyl-3-methyl-5-chloropyrazol-4yl, $R_2 = CH_3$
189 $R_1 = CH_3$, $R_2 = H$

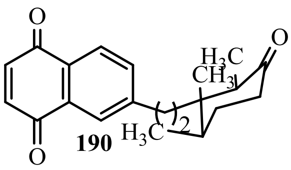
Carboline alkaloids

The 1,3-substituted *β*-carboline derivatives **174-189** related to harmine (a natural insecticide isolated from *Peganum harmala*), show significant cytotoxicity against fourth instar larvae of *Cx. pipiens quinquefasciatus*. The results show that compound 1-phenyl-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylic acid (**175**) and methyl 1-phenyl-*β*-carboline-3-carboxylate (**186**) exhibit best larvicidal potential with $LC_{50/90}$ values of 20.82/88.29 and 23.98/295.13 mg/L, respectively after 24 h of treatment. Other metabolites display 15-40% mortality at a concentration of 100 mg/L in 24 h (Zeng et al. 2010).

Naphthoquinones

The cordiaquinones, **190-193** isolated from the roots of *Cordia curassavica*, show toxicity against yellow fever-transmitting *Ae. aegypti* larvae. The quinones **190** and **192** with 25.0 μg/mL concentrations result in 100% larval mortality while **191** and **193** with 12.5 μg/mL concentrations kill all the *Ae. aegypti* larvae in 24 h (Ioset et al. 2000). Likewise, the compounds **194-196** isolated from the roots of *Cordia linnaei*, exhibit larvicidal potency against *Ae. aegypti* at 12.5, 50.0 and 25.0 μg/mL concentrations, respectively (Ioset et al. 1998). The naphthoquinone, plumbagin **(197)** isolated from *Plumbago zeylanica* (Kishore et al. 2010) and other plant species (Mishra et al. 2010a; Mishra et al. 2010b; Mishra and Tiwari 2011) exhibit larvicidal activity against *An. gambiae* with LC_{50} value of 1.9 μg/mL (Maniafu et al. 2009; Adikaram et al. 2002). The compound lapachol **(198)** and its synthetic derivatives **(199-201)** possess toxicity against fourth instar larvae of *Ae. aegypti*. The quinone **198** with LC_{50} value of 15.24 μM exerts higher activity in compared to **201** (19.45 μM)**, 199** (33.94 μM) and **198** (108.7 μM). Similarly, juglone **(202)** and its synthetic derivatives **(203-211)** display significant toxicity against fourth instar larvae of *Ae. aegypti*. The bromo-naphthoquinone **208** with LC_{50} value of 3.46 μM exhibits the best larval toxicity in compared to **205** (4.64 μM), **206** (3.98 μM), **207** (36.48 μM), **208** (3.46 μM), **209** (24.79 μM) and **210**

(21.62 μM) while **202** and derivatives **203**, **204** and **211** display relatively weak toxicity with LC_{50} values of 20.61, 21.08, 42.12 and 86.93 μM, respectively (Ribeiro et al. 2009).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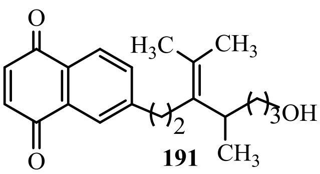
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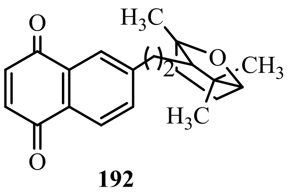
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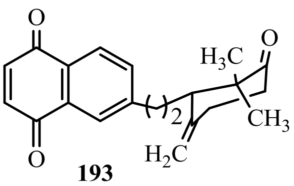
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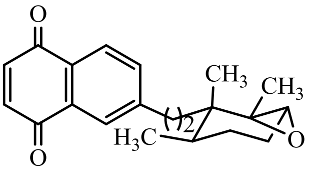
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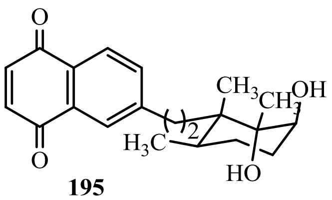
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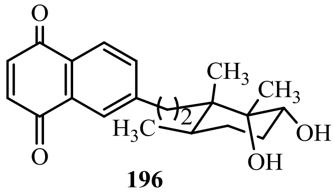
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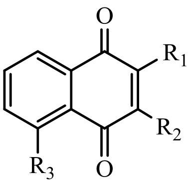
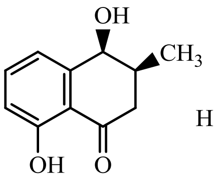


197: $R_1 = CH_3$, R_2 =H, R_3 = OH
198: R_1 = OH, $R_2 = CH_2CHC(CH_3)_2$, R_3 = H
199: R_1 = OAc, $R_2 = CH_2CHC(CH_3)_2$, R_3 = H
200: R_1 = OLi, $R_2 = CHCHCH(CH_3)_2$, R_3 = H
201: R_1 = OH, $R_2 = CH_2CH_2\ CH(CH_3)_2$, R_3 = H
202: R_1 = H, R_2 = H, R_3 = OH
203: R_1 = H, R_2 = H, R_3 = OAc
204: R_1 = H, R_2 = H, $R_3 = OCH_3$
205: R_1 = Br, R_2 = H, R_3 = OH
206: R_1 = Br, R_2 = H, R_3 = OAc
207: R_1 = Br, R_2 = H, $R_3 = OCH_3$
208: R_1 = H, R_2 = Br, R_3 = OH
209: R_1 = H, R_2 = Br, R_3 = OAc
210: R_1 = H, R_2 = Br, $R_3 = OCH_3$
211: $R_1 = CH_3$, R_2 = H, R_3 = H
212: $R_1 = CH_3$, $R_2 = OCH_3$, R_3 = OH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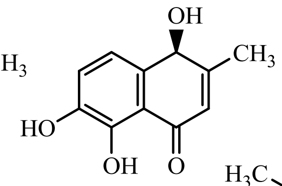
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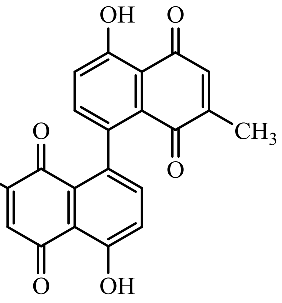
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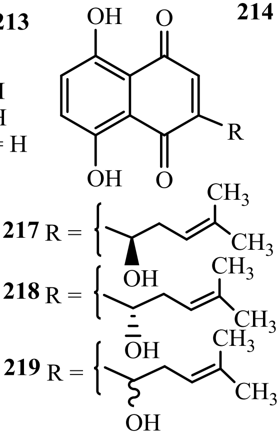
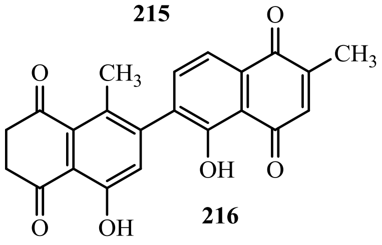

217 R =
218 R =
219 R =

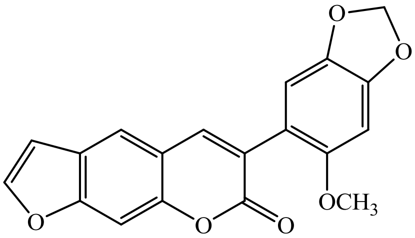

216

Some other naphthoquinones (**212-216**) isolated from *Plumbago capensis*, display a varying degrees of mosquitocidal potentials i.e. LC_{50} value ranging from 1.26-40.66 μg/mL against fourth instar larvae of *Ae. aegypti*. Among these the compound **213** exhibits strongest activity (IC_{50} = 1.26 μg/mL) against larvae of *Ae. aegypti* (Sreelatha et al. 2010) while compound **212** and **213** exhibit moderate larvicidal activity. The shikonin **(217)**, alkannin **(218),** and shikalkin **(219)** isolated from root of *Lithospermum erythrorhizon* (Chen et al. 2003), *Alkanna tinctoria* (Urbanek et al. 1996), and young leaves and stems of *L. officinale* (Haghbeen et al. 2006), display toxicities against mosquito larvae. The quinone **217** at a concentration of 3.9 mg/L show high toxicity against mosquito larvae followed by **219** and **218** at 8.73 and 12.35 mg/L concentrations, respectively. The SAR studies indicate that the naphthoquinones compared to other natural compounds, are very toxic against mosquito larvae and would be a potential source of natural larvicidal substances (Michaelakis et al. 2009). However, it is difficult to discuss the SAR criteria responsible for the mosquitocidal activities in this set of compounds, presence of reduced quinine ring (ring B), hydroxyl group at C-4 and methyl group at C-3 appears to be important in imparting the mosquitocidal activity compared to others.

Coumarins

The coumarin, pachyrrhizine **(220)** isolated from *Neorautanenia mitis* possess significant activity with LC_{50} value of 0.007 mg/mL against adult mosquitoes of *An. gambiae*. Similary, marmesin **(221)** isolated from *Aegle marmelos* exhibits toxicity against *An. gambiae* adults with LC_{50} and LC_{90} values of 0.082 and 0.152 mg/L, respectively (Joseph et al. 2004). Other coumarins **222-234** isolated from *Cnidiummon nieri* fruit, show insecticidal activity against susceptible *Cx. pipiens pallens* and *Ae. aegypti* larvae. The imperatorin **(231)** (LC_{50} = 2.88 mg/L) shows 2.4, 4.5 and 4.6 times more toxicity than isopimpinellin **(232)**, isoimperatorin **(233)**, and osthole **(228)**, respectively. The angelicin **(234)**, psoralen **(227)**, 7-ethoxycoumarin **(225)**, herniarin **(224)**, and xanthotoxin **(229)** exhibit moderate toxicity with LC_{50} values ranging from 22.84-39.35 mg/L. The limettin **(226)**, bergapten **(230)** and coumarin **(222)** display moderate toxicity (LC_{50} = 57.03-73.95 mg/L) while umbelliferone **(223)** exibits lowest toxicity with LC_{50} value of 132.65 mg/L. The SAR study indicates that the chemical structure, alkoxy substitution, and length of the alkoxyl side chain at C-8 position are essential for imparting toxicity (Wang et al. 2012).

Some other monobromo and tribromo derivatives of 4-methyl-7-hydroxy coumarin **(235-238)**, exhibit insecticidal activity *Cx. quinquefasciatus* and *Ae. aegypti*. Among these, compound 3,6,8-tribromo-7-hydroxy-4methyl-chromen-2-one **(235)** displays most potent activity with LC_{50} value of 1.49 and 2.23 ppm against fourth instar larvae of *Cx. quinquefasciatus* and *Ae. aegypti*, respectively. It shows 100% larval mortality at a concentration of 25 ppm against *Ae. aegypti*, and at 10 ppm concentration causes complete lysis of *Cx. quinquefasciatus* larvae. The 3,6,8-tribromo-4-methyl-2'-oxo-2H-chromen-7-yl acetates **235** and **236** show remarkable ovicidal activity and cause significant reduction of 80-85% hatching in eggs of *Cx. quinquefasciatus* and *Ae. aegypti* at 100 ppm concentrations. The hatched larvae show 100% mortality in the successive instars. The compounds 3-bromo-7-hydroxy-4-methyl-chromen-2-one **(237)** and 3-bromo-4-methyl-2'-oxo-2H-chromen-7-yl acetate **(238)**, exhibit moderate activity against both mosquito species i.e. at 77.99 & 89.60 ppm against *Ae. aegypti*, and 46.06 & 72.65 ppm concentrations against *Cx. quinquefasciatus* (Deshmukh et al. 2008). The 4-hydroxy coumarin derivatives, brodifacoum **(239)** and *cis*flocoumafen **(240)** show strong activity against the F_{21} laboratory strain of *Ae. aegypti* with LC_{50} values of 8.23 and 9.34 ppm, respectively (Jung et al. 2011).



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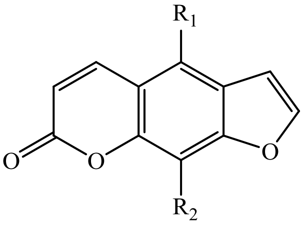
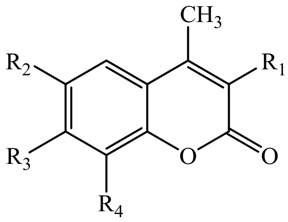
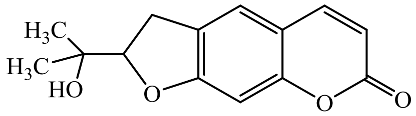


229: $R_1 = H, R_2 = OCH_3$
230: $R_1 = OCH_3, R_2 = H$
231: $R_1 = H, R_2 = OCH_2CHC(CH_3)_2$
232: $R_1 = R_2 = OCH_3$
233: $R_1 = OCH_2CHC(CH_3)_2, R_2 = H$



235: R1 = R2 = R4 = Br, R3 = OH
236: R1 = R2 = R4 = Br, R3 = OAc
237: R1 = Br, R2 = R4 = H, R3 = OH
238: R1 = Br, R2 = R4 = H, R3 = OAc



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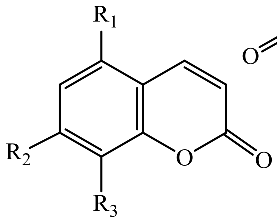
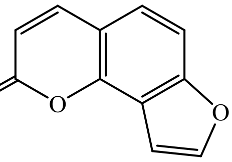


222: $R_1 = H, R_2 = H$
223: $R_1 = H, R_2 = OH$
224: $R_1 = H, R_2 = OCH_3$
225: $R_1 = H, R_2 = OC_2H_5$
226: $R_1 = R_2 = OCH_3$
228: $R_1 = H, R_2 = OCH_3, R_3 = CH_2CHC(CH_3)_2$



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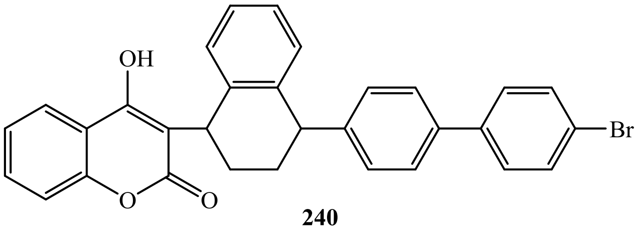

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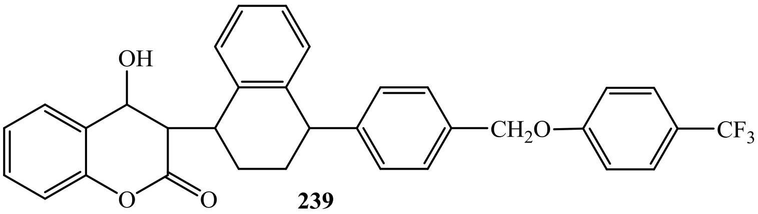
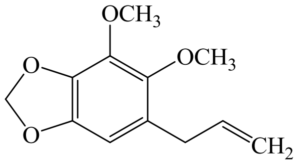


239

Phenylpropanoid

The phenylpropanoid dillapiol (**241**) isolated from leaves of *Piper aduncum* and its semi-synthetic derivatives **242-254**, show lethality against adults of female *Ae. aegypti*. The metabolites **241** and **242** exhibit 100% mortality at 0.57 μg/cm^2 surface density after 45 min. The compounds **243-246** exert 80%~98% lethalities against female adults of *Ae. aegypti* after 90 min. Additionally, dillapiol oxide (**248**) kills about 51% and acetonide **250** kills 29% of mosquitoes after 90 min of exposure. Other dillapiols **251-254** possess low mortality (4-11%) against these mosquito species. The SAR study suggests that C-3 side chain is important for the toxic effects of these substances against *A. aegypti* adult females. The compounds isodillapiol **(242)**, methyl ether **(243)**, propyl ether **(245)**, and butyl ether **(246)** exhibit greater mosquitocidal potential than **241**, and their activities fall in order: **242** > **246** > **243** > **245** > **241** (Pinto et al. 2012).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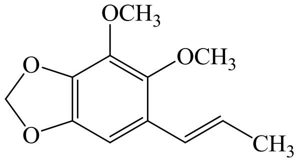
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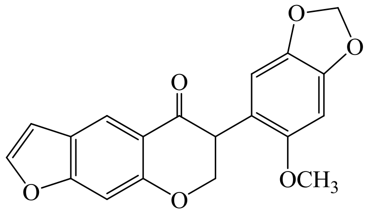
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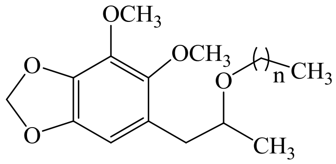
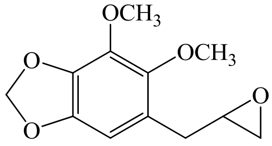

243: n = 0
244: n = 1
245: n = 2
246: n = 3
247: n = 7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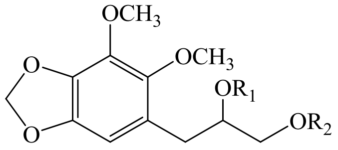
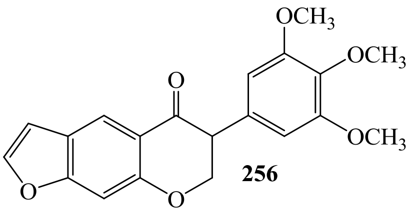

249 $R_1 = R_2 = H$,
250 $R_1, R_2 = {>}C(CH_3)_2$
251 = $R_1 = COCH_3$, $R_2 = COCH_3$
252 = $R_1,R_2 = {>}C{=}O$,
253 $R_1 = H$, $R_2 = CH_2C_6H_5$
254 = $R_1 = H$, $R_2 = COCH_3$


256

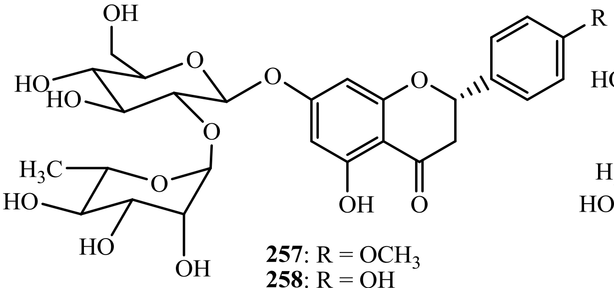
Flavonoids and isoflavonoids

The isoflavonoids, neotenone **(255),** and neorautanone **(256)** isolated from *Neorautanenia mitis*, display activity against adults of *An. gambiae* with LD_{50} values of 0.008 and 0.009

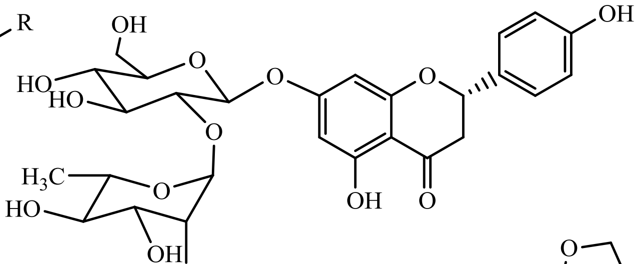
mg/mL, respectively (Puyvelde et al. 1987). The flavonoids, poncirin (**257**), rhoifolin (**258**) and naringin (**259**) isolated from *Poncirus trifoliata*, show larvicidal activity against *Ae. aegypti* with LC_{50} values of 0.082-0.122 mg/L and LC_{90} values 0.152-0.223 mg/L after 24h (Rajkumar and Jebanesan 2008). Other flavonoids, linaroside (**260**), homoplantagenin (**261**), 5,7,3'-trihydroxy-6,4'-dimethoxy flavone-7-*O*-glucoside (**262**) isolated from *Acanthus montanus* exhibit mosquitocidal activity against adult *Ae. aegypti* at a concentration 1.25 *μ*g/mL (Amin et al. 2012).

Pterocarpans

The pterocarpans, neoduline **(263)**, 4-methoxyneoduline **(264)**, and nepseudin **(265)** isolated from tubers of *Neorautanenia mitis*, exhibit mosquitocidal activity against *An. gambiae* and *Cx. quinquefaciatus* larvae with LD_{50} values 0.005, 0.011 and 0.003 mg/mL, respectively (Joseph et al. 2004; Breytenbach and Rall 1980).



257: R = OCH_3
258: R = OH



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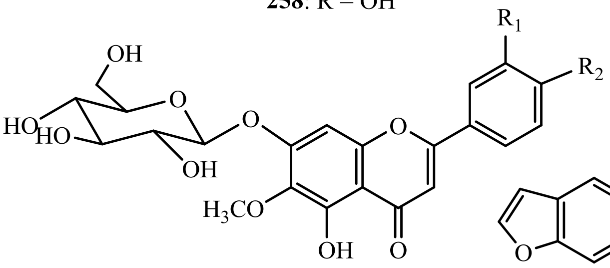
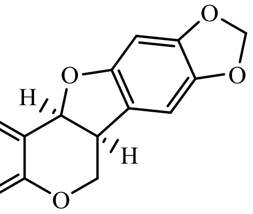


260: R_1 = H, R_2 = OCH_3
261: RI = H, R_2 = OH
262: R_1 = OH, R_2 = OCH_3



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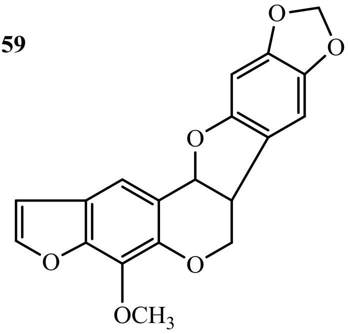

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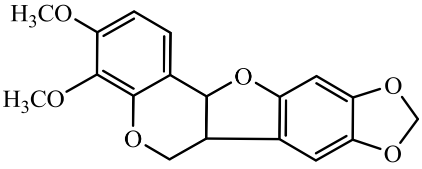

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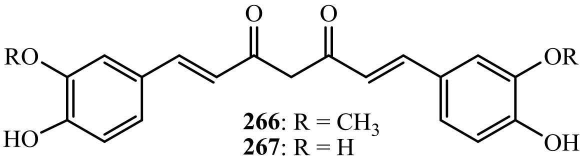
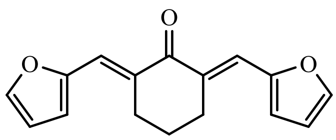


266: R = CH_3
267: R = H

Curcuminoid and phenolic acid

The curcumin (**266**) isolated from *Curcuma longa* and its synthetic derivative di-*O*-demethylcurcumin (**267**), show significant larvicidal activity against *Cx. pipiens* with LC$_{50}$ value of 19.07 and 12.42 mg/L, respectively (Sagnou et al. 2012). However, based on the LC$_{90}$ values, compound **267** shows greater activity (LC$_{90}$ = 29.40 mg/L) than **266** (LC$_{90}$ = 61.63 mg/L). Other curcumin analogs **268-270** exhibit larvicidal activities against fourth instar larvae *Ae. aegypti* with LC$_{50}$ values ranging from 17.29-27.90 μM (Anstrom et al. 2012).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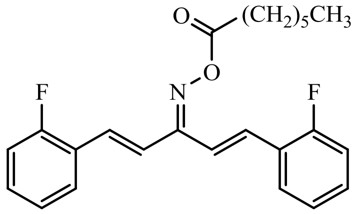
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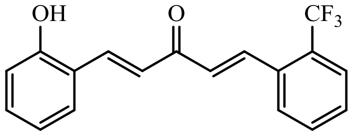
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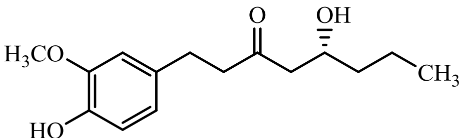
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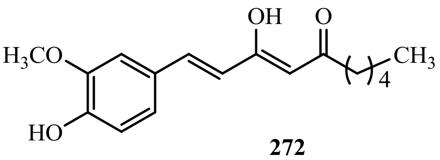
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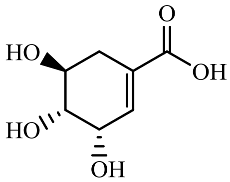
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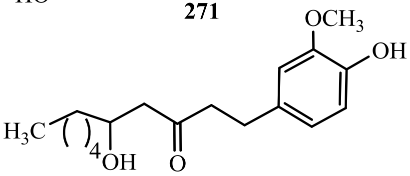
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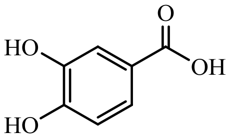
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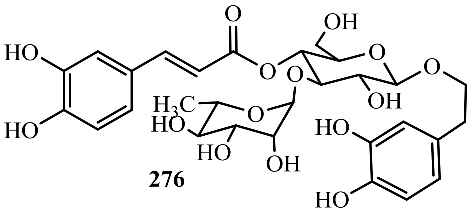
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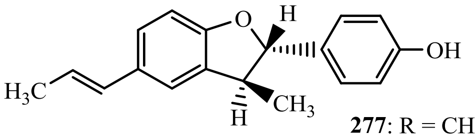
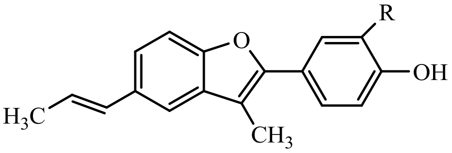

277: R = CH=CH-CH$_3$
279: R = CHO


278: R = OCH$_3$
280: R = H

The zingiber metabolites, 4-gingerol **(271)**, 6-dehydrogingerdione **(272)**, and 6-dihydrogingerdione **(273)** isolated from rhizomes of *Zingiber officinale*, exhibit larvicidal activities against fourth instar larvae of *Ae. aegypti* with LC$_{50}$ values of 4.25, 9.80, and 18.20 ppm, respectively. These metabolites also display larvicidal activity against *Cx.*

quinquefasciatus with LC_{50} values of 5.52 **(271)**, 7.66 **(272)**, 27.24 **(273)** ppm (Rahuman et al. 2008). The shikimic acid (**271**), protochatecuic acid (**272**), and acetoside (**273**) isolated from *Acanthus montanus*, show 40% mosquitocidal activity against *Ae. aegypti* adult at a concentration 1.25 μg/mL while **273** exhibit 70% mosquitocidal activity at a concentration 1.25 μg/mL (Amin et al. 2012).

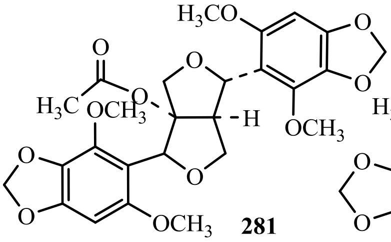
Lignans

The lignans, conocarpan **(277)**, eupomatenoid-5 **(278)**, eupomatenoid-6 **(279)**, and decurrenal **(280)** isolated from *Piper decurrens* possess significant mortality at 10 μg/mL concentrations against mosquito larvae (Chauret et al. 1996). Similarly, compound leptostachyol acetate (**281**) and 8'-acetoxy-2,2',6-trimethoxy-3,4,4',5'-dimethylenedioxyphenyl-7,7'-dioxabicyclo-[3.3.0]octane (**282**) isolated from the roots of *Phryma leptostachya asiatica*, exhibit insecticidal activity against third instar larvae of *Cx. pipiens pallens*, *Ae. aegypti* and *Ochlerotatus togoi*. Among these, compound **282** shows relatively weak insecticidal activity while compound **281** with LC_{50} values of 0.41, 2.1, and 2.3 ppm exhibits strong activity against *Cx. pipiens pallens*, *Ae. aegypti*, and *O. togoi*, respectively (Park et al. 2005).

Other lignans i.e. phrymarolin-I **(283)**, haedoxane-A **(284)**, and haedoxane-E **(285)** isolated from *Phryma leptostachya*, show high larvicidal activity against fourth instar larvae of *Cx. pipiens pallens* at 24 h with LC_{50} values of 1.21, 0.025, and 0.15 ppm, and LC_{90} values of 5.03, 0.085 and 0.37 ppm, respectively (Xiao et al. 2012).

Rotenoids

The compounds deguelin (**286**), 12a-hydroxy-α-toxicarol (**287**), tephrosin (**288**), α-toxicarol (**289**), and 6a, 12a-dehydro-α-toxicarol (**290**) isolated from roots of *Tephrosia toxicaria*, show larvicidal activity against *Ae. aegypti* with LC_{50} of 3.38 ± 2.02, 3.22 ± 1.37, 6.31 ± 0.69 and 24.55 ± 0.13 ppm, respectively. The metabolite **290** displays weaker activity than **286-289** with LC_{50} >50 ppm. The SAR study indicates that the presence or absence of the double bond between C-6a and C-12a is responsible for difference in toxicity (Nunes e Vasconcelos et al. 2012).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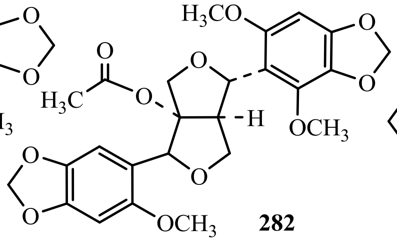
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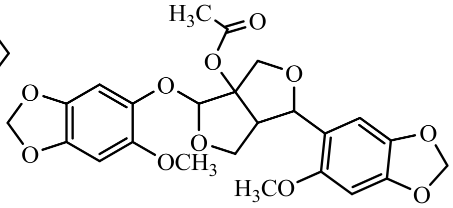
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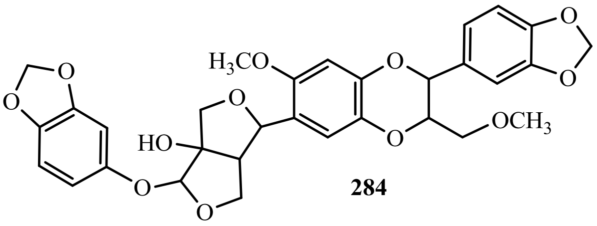
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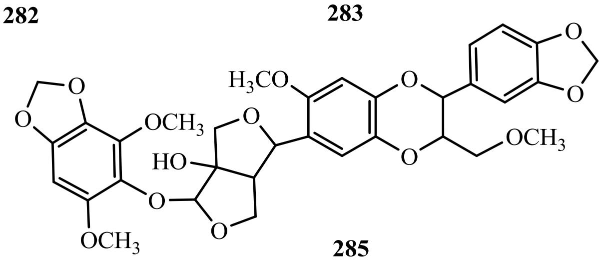
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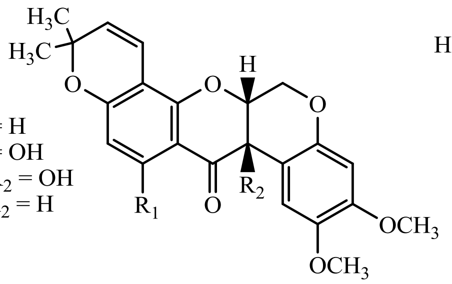
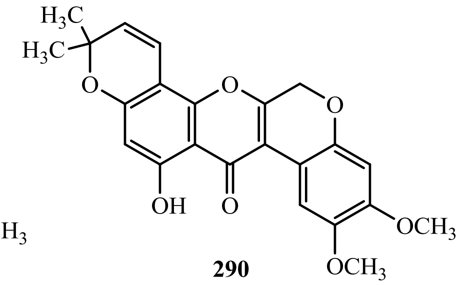
286 $R_1 = R_2 = H$
287 $R_1 = R_2 = OH$
288 $R_1 = H, R_2 = OH$
289 R_1 OH, $R_2 = H$

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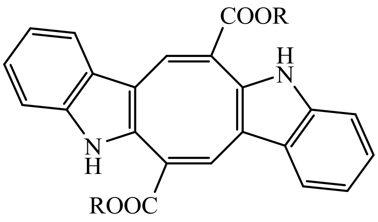
Mosquitocides from microorgainsms

An algal metabolite caulerpin (**291**), isolated from *Caulerpa racemosa*, shows larvicidal activity against second, third and fourth instar larvae of *Cx. pipiens* mosquito with LC_{50} of 1.42, 1.81, 1.99 ppm, respectively. Likewise, caulerpinic acid (**292**) isolated from same plant species, exhibits activity with LC_{50} of 3.04, 3.90, and 4.89 ppm against second, third and fourth instar larvae, respectively (Alarif et al. 2010).


291 $R = CH_3$, **292** $R = H$

Conclusive remarks

Our ancestors exclusively depended on the use of plant-derived products to repel or kill mosquitoes and other blood-sucking insects. Modern synthetic chemicals could provide immediate results for the control of insects/mosquitoes; on the contrary they bring irreversible environmental hazard, severe side effects and pernicious toxicity to human being and beneficial organisms. In concern to the quality and safety of life and the environment, the emphasis on controlling mosquito vectors has shifted steadily from the use of conventional chemicals toward alternative insecticides that are target-specific, biodegradable, and environmentally safe, and these are generally botanicals in origin. Therefore, right now use of eco-friendly and cost-free plant based products for the control of insects/mosquitoes is inevitable. Efforts should be made to promote the use of easy accessible and affordable traditional insect/mosquito repellent plants.

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