The present invention includes insecticidal carbamates that are useful, for example, for the control of insects, such as mosquitoes, which can be used in applications where exposure to and/or contact with humans is likely. The insecticides of the present invention include phenyl N-methyl carbamates and compositions comprising them that exhibit species-selective inhibition of acetylcholinesterase (AChE) and are preferably toxic to mosquitoes but not humans. Of particular interest are compounds of Formula (I) and Formula (II):

![Formula (I)](image1)

![Formula (II)](image2)

Compounds of Formula (I) and Formula (II) are especially suitable for insecticide treated nets and indoor residual spraying for mosquito control.

12 Claims, 3 Drawing Sheets
Figure 1. Excellent correlation of Ag ace-1S and Ag hmg AChE IC₅₀ values

$$r^2 = 0.937$$

![Graph showing correlation between log Ag homogenate IC₅₀ (nM) and log Ag ace-1S IC₅₀ (nM)]
Figure 2. Plot of $\log([g\text{ acce-IS IC}_{50}])$ vs $\log([g\text{ hmg AChE IC}_{50}])$.

$\mathbf{r}^2 = 0.954$

Log Homogenate IC$_{50}$ (nM)

Log acce-IS IC$_{50}$ (nM)
Figure 3. Residual AChE activity vs carbamate concentration for 1b (left) and 2b (right)

**Compound 1b**
- Human IC50: 3,627 nM (3,182-4,134) Hill: 1.06 \( r^2 0.99 \)
- *An. gambiae ace1-S* (GCGH) IC50: 2.9 nM (2.8-3.1) Hill: 0.91 \( r^2 0.99 \)

**Compound 2b**
- Human IC50: 98,820 nM (89,110-109,600) Hill: 1.52 \( r^2 0.98 \)
- *An. gambiae ace1-S* (GCGH) IC50: 10 nM (7-14) Hill: 0.63 \( r^2 0.98 \)
INSECTICIDAL CARBAMATES EXHIBITING SPECIES-SELECTIVE INHIBITION OF ACETYLCHOLINESTERASE (AChE)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application relies on the disclosure and claims the benefit of the filing date of U.S. Provisional Application No. 60/971,614 filed Sep. 12, 2007 and U.S. Provisional Application No. 61/034,260 filed Mar. 6, 2008, the disclosures of which are incorporated herein by reference in their entireties.

STATEMENT OF GOVERNMENT INTEREST

This invention was funded in part by a Grant from the Foundation for the National Institutes of Health, Inc. through the Grand Challenges in Global Health initiative, with funds provided by the Bill & Melinda Gates Foundation. The Foundation for the National Institutes of Health was established by the United States Congress to support the mission of the National Institutes of Health—improving health through scientific discovery. The Foundation identifies and develops opportunities for innovative public-private partnerships involving industry, academia, and the philanthropic community. A non-profit, 501(c)(3) corporation, the Foundation raises private-sector funds for a broad portfolio of unique programs that complement and enhance NIH priorities and activities.

BACKGROUND OF THE INVENTION

1. Field of the Invention
   The present invention relates to the fields of chemistry and biology and more particularly to the field of insecticides. The present invention includes insecticidal carbamates that are useful, for example, for the control of insects, such as mosquitoes, which can be used in applications where exposure to and/or contact with humans is likely. The insecticides of the present invention exhibit species-selective inhibition of acetylcholinesterase (AChE) and are toxic to mosquitoes but not humans.

2. Description of Related Art
   Malaria is a global scourge. Over three billion people are at risk of infection by the malaria parasites Plasmodium falciparum and Plasmodium vivax, which cause an estimated one million deaths annually. For many in sub-Saharan Africa, especially children, insecticide treated nets (ITNs) provide the only means of defense against Anopheles gambiae, the mosquito vector of the parasites. Carbamate insecticides work by inhibiting acetylcholinesterase (AChE), and are commonly used to control agricultural pests and disease vectors. Human toxicity (resulting from concurrent potent inhibition of human AChE), however, has thus far discouraged deployment of insecticidal carbamates on ITNs. Currently, pyrethroid insecticides have filled this gap. It would thus be desirable to improve current ITN performance by identifying classes of carbamates that possess excellent target selectivity for Anopheles gambiae AChE (AgAChE) over human AChE (hAChE). Such highly selective carbamates would be ideally suited for safe deployment on ITNs, but up to the inventors’ work in this area such compounds have been unavailable. The present inventors have identified certain carbamates that are much more potent at AgAChE than at hAChE. This difference in potency for the two species is unanticipated and potentially very useful.

SUMMARY OF THE INVENTION

The present invention addresses at least some of the needs discussed above by providing carbamate insecticides that can be used in close proximity to humans. In particular, the present invention provides phenyl N-methyl carbamates that are lethal to insects, including mosquitoes. Preferred phenyl N-methyl carbamates and compositions of the present invention include compounds that are lethal to insects, including mosquitoes, but that are not lethal to humans, including when applied in appropriate doses.

The present invention includes N-methyl carbamates of Formulas (I) and (II):

Formula (I)

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{CH}_3 & \quad \text{O}
\end{align*}
\]

Formula (II)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{O}
\end{align*}
\]
With respect to the compounds of Formula (I):
R is chosen from C(R1)(R2)(R3) and Si(R1)(R2)(R3'),
wherein
R1 is chosen from methyl, ethyl, n-alkyl (C3-C10),
—(CH2)n-aryl, —CF3, and —CF2CF3,
wherein n is 0 to 10 and aryl is chosen from phenyl, 1-naphthyl, and 2-naphthyl, and 2-naphthyl, each of which is unsubstituted or substituted with three or fewer substituents chosen from bromo, carboxethoxy, carboxemethoxy, chloro, cyano, ethoxy, ethyl, fluoro, iodo, isopropoxy, isopropyl, methoxy, methyl, nitro, thiophenyl, thioisopropyl, and thionylethyl;
R2 is chosen from methyl, ethyl, n-alkyl (C3-C10), branched (C3-C10) alkyl, —(CH2)n-aryl, —CF3, and —CF2CF3, wherein n and aryl are as defined above;
R3 is chosen from methyl, ethyl, n-alkyl (C3-C10), halogen (fluoro, chloro, bromo, and iodo), —CF3, —CF2CF3, OR4, C(O)R4, C(O)OR4, and C(O)NR4R5, wherein
R4 is chosen from methyl, ethyl, n-alkyl (C3-C10), halogen (fluoro, chloro, bromo, and iodo), and OR4, wherein R5 is as defined above;
R23 is hydrogen or when appropriate is no substituent.

For example, substituents for the substituted aryl group identified above with respect to Formula (I) include —Br, —CO2CH2CH3, —CO2CH2, —Cl, —CN, —OCH2CH2, —CH2CH3, —F, —I, —Oi-Pr, —i-Pr, —OCF3, —CH2, —NO2, —SCH2CH3, —Si—Pr, and —SCH2. Also, as described above with respect to Formula (I), three or fewer of such substituents can be present on the phenyl, 1-naphthyl, or 2-naphthyl, meaning that the aryl can be unsubstituted (i.e., comprising hydrogen) or substituted with up to and including three substituents. The substituents can be distributed at any position of the aryl and, in the case of 1-naphthyl or 2-naphthyl, the substituents can be distributed at any position of either of the naphthyl rings. Further, the "1-" or "2-" of the naphthyl refers to the position of the naphthyl ring where the naphthyl attaches to the remainder of the compound. For example, 1-naphthyl and 2-naphthyl refer to the following:

![Naphthyl structures](image)

Of particular interest are compounds of Formula (I) chosen from N-methyl 3-(tert-butyl)phenyl carbamate, N-methyl 3-(ethylmethylisyl)phenyl carbamate, and N-methyl 3-(trimethylisyl)phenyl carbamate.

With respect to the compounds of Formula (II):
A is chosen from O and S;
R1 is chosen from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, —CF3, —CF2CF3, —CH2, —CH3H2, —CH2CH2CH3, —C(CH3)2, —CH2CH2CH2CH3, and —(CH2)n(CH2CH3);
R2 is chosen from methyl, ethyl, propyl, butyl, —CF3, and —CF2CF3; and
R3 is hydrogen or when appropriate is no substituent.

The N-methyl carbamates of Formula (II) of the present invention include, for chiral compounds, racemates and enantiomers, and when R21 is chosen from —CHCH3,
The present invention includes compounds of Formula (I):

\[
H - N - CH_3
\]

[Formula (I)]

wherein:

- \( R \) is chosen from \( C(R_1)(R_2)(R_3) \) and \( Si(R_1)(R_2)(R_3') \), wherein
- \( R_1 \) is chosen from methyl, ethyl, n-alkyl (\( C_3-C_{10} \)), branched (\( C_3-C_{10} \)) alkyl, \( -(CH_2)_n- \) aryl, \(-CF_3\), and \(-CF_2CF_3\), wherein \( n \) is 0 to 10 and aryl is chosen from phenyl, 1-naphthyl, and 2-naphthyl, each of which is unsubstituted or substituted with three or fewer substituents chosen from bromo, carbethoxy, carboxethoxy, chloro, cyano, ethoxy, ethyl, fluoro, iodo, isopropoxy, isopropyl, methoxy, methyl, nitro, thiocyano, and thiomethyl;
- \( R_2 \) is chosen from methyl, ethyl, n-alkyl (\( C_3-C_{10} \)), branched (\( C_3-C_{10} \)) alkyl, \( -(CH_2)_n- \) aryl, \(-CF_3\), and \(-CF_2CF_3\), wherein \( n \) and aryl are as defined above;
- \( R_3 \) is chosen from methyl, ethyl, n-alkyl (\( C_3-C_{10} \)), \( -(CH_2)_n- \) aryl, \(-CF_3\), \(-CF_2CF_3\), OR, \( C(O)R \), \( C(O)OR_4 \), and \( C(O)NR_5R_6 \), wherein \( R_4 \) is chosen from methyl, ethyl, n-alkyl or branched alkyl (\( C_3-C_{10} \)), and \( -(CH_2)_n- \) aryl, wherein \( n \) and aryl are as defined above, and
- \( R_5 \) is chosen from hydrogen, methyl, and ethyl; and
- \( R_3' \) is chosen from methyl, ethyl, n-alkyl (\( C_3-C_{10} \)), \( -(CH_2)_n- \) aryl, \(-CF_3\), \(-CF_2CF_3\), OR, \( C(O)R \), \( C(O)OR_4 \), and \( C(O)NR_5R_6 \), wherein

Methods of making compounds of Formula (I) are also included in the present invention, wherein the methods comprise:

- deprotonating a phenol with \( KOt-Bu \) or \( NaH \) in THF to obtain a deprotonated phenol;
- carboxamoylating said deprotonated phenol by reacting said deprotonated phenol with \( N-H \) carboxamoyl chloride; and
- isolating the resultant compound to obtain a compound of Formula (I):

\[
H - N - CH_3
\]

[Formula (I)]

wherein:

- \( R \) is chosen from \( C(R_1)(R_2)(R_3) \) and \( Si(R_1)(R_2)(R_3') \), wherein
- \( R_1 \) is chosen from methyl, ethyl, n-alkyl (\( C_3-C_{10} \)), \( -(CH_2)_n- \) aryl, \(-CF_3\), and \(-CF_2CF_3\), wherein \( n \) is 0 to 10 and aryl is chosen from phenyl, 1-naphthyl, and 2-naphthyl, each of which is unsubstituted or substituted with three or fewer substituents chosen from bromo, carbethoxy, carboxethoxy, chloro, cyano, ethoxy, ethyl, fluoro, iodo, isopropoxy, isopropyl, methoxy, methyl, nitro, thiocyano, and thiomethyl;
The present invention further includes insecticidal compositions comprising one or more compounds of Formula (I):

\[
\begin{align*}
R & \text{ is chosen from } C(R_1)(R_2)(R_3) \text{ and } Si(R_1)(R_2)(R_3'), \\
R_1 & \text{ is chosen from methyl, ethyl, } n\text{-alkyl } (C_3-C_{10}), \\
R_2 & \text{ is chosen from methyl, ethyl, } n\text{-alkyl } (C_3-C_{10}), \\
R_3 & \text{ is chosen from methyl, ethyl, } n\text{-alkyl } (C_3-C_{10}), \\
R_4 & \text{ is chosen from hydrogen, methyl, and ethyl; and} \\
R_4' & \text{ is chosen from methyl, ethyl, } n\text{-alkyl } (C_3-C_{10}), \\
\end{align*}
\]

Formulas (I)

wherein:

- \( R \) is chosen from \( C(R_1)(R_2)(R_3) \) and \( Si(R_1)(R_2)(R_3') \),
- \( R_1 \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \),
- \( R_2 \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \),
- \( R_3 \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \),
- \( R_4 \) is chosen from hydrogen, methyl, and ethyl; and
- \( R_4' \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \),

The compounds and compositions are useful for controlling mosquitoes for example when used with a substrate, especially in close proximity to humans. One such substrate for example are nets comprising one or more compounds of Formula (I) or a composition comprising one or more compounds of Formula (I):

- Ethoxy, ethyl, fluoro, iodo, isopropoxy, isopropyl, methoxy, methyl, nitro, thioethoxy, thiopropoxy, isopropyl, methoxy, methyl, nitro, thioisopropyl, and thiomethyl;
- \( R_2 \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \), branched \( (C_3-C_{10}) \) alkyl, \(-CH_2)n-aryl, \(-CF_3\), and \(-CF_2CF_3\), wherein \( n \) and \( aryl \) are as defined above;
- \( R_3 \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \), fluoro, chloro, bromo, iodo, \(-CF_3\), \(-CF_2CF_3\), ORg, \( C(O)R_g \), \( C(O)OR_g \), and \( C(O)NR_g R_g' \), wherein
- \( R_4 \) is chosen from methyl, ethyl, \( n\)-alkyl or branched alkyl \( (C_3-C_{10}) \), and \(-CH_2)n-aryl \), wherein \( n \) and \( aryl \) are as defined above, and
- \( R_4' \) is chosen from methyl, ethyl, \( n\)-alkyl \( (C_3-C_{10}) \), fluoro, chloro, bromo, iodo, and \( OR_g \), wherein \( R_4' \) is as defined above.

Further applications that the compounds and compositions of the present invention are useful for include applying one or more compounds of Formula (I) in accordance with the invention, as well as for indoor residual spraying and nets and/or other substrates comprising insecticidal carbamates include N-methyl 3-(ethyldimethylsilyl)phenyl carbamate is a preferred compound of Formula (I). Further, for example, preferred compounds of Formula (I) for compositions according to the invention, as well as for indoor residual spraying and nets and/or other substrates comprising insecticidal carbamates include N-methyl 3-(3,3,3-trifluoro-2-methylpropan-2-yl)phenyl carbamate; N-methyl 3-(3,3,3-trifluoro-2-(trifluoromethyl)butan-2-yl)phenyl carbamate; Compounds of Formula (I), wherein \( R_1 \), \( R_2 \), and/or \( R_3 \) comprise a \(-CF_3\) or \(-CF_2CF_3\) group, may be desirable for increased resistance to oxidative detoxification mechanisms in the insect thus conferring greater toxicity to mosquitoes. Example compounds include 3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,1,3,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,1,3,3,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,1,3,3,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,1,3,3,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; and 3-(1,1,1,3,3,3,3,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate, for example.
more compounds of Formula (I) or compositions comprising them in the context of indoor residual spraying or treating of nets.

The methods, compositions, substrates, and nets according to the invention can comprise a synergist for increasing the lethality of a compound of Formula (I), such as for example, piperonylbutoxide.

The present invention further includes compounds of Formula (II):
The methods, compositions, substrates, and nets according to the invention can comprise a synergist for increasing the lethality of a compound of Formula (II), such as for example, piperonyl butoxide.

Materials and methods relating to compounds of Formula (I). Synthesis of inhibitors: Carbamates were prepared from the corresponding phenols as described below. The phenol precursors for compounds 1a, 4a-12a were commercially available (Aldrich). The phenol precursor for compound 2a was prepared by the literature method from 3-bromophenol and Me3SiCl (Wilbur, D. S.; Stone, W. E.; Anderson, K. W. Regiospecific Incorporation of Bromine and Iodine into Phenols Using (Trimethylsilyl)phenol Derivatives. J. Org. Chem. 1983, 48, 1542-1544): the phenol precursor for 3a was prepared similarly using EtMeSiCl, more details for which are provided in Example I. The phenol precursor for 13a was prepared by a multistep method, which is also described below. In general, synthesis of N-methyl carbamates 1a-13a was achieved by deprotonating the phenols with K(Ot-Bu) or NaH in THF, followed by the addition of N-methyl carbamoyl chloride.

Synthesis of N,N-dimethylcarbamate 1g was similarly achieved using N,N-dimethylcarbamoyl chloride. Synthesis of N-ethyl and N-hexyl carbamates 1b and 1c was achieved using EtN(i-Pr)2 as base and the corresponding isocyanates as electrophiles. Purified yields for the carbamoylation steps ranged from 60-90%. N-isopropyl carbamate 1d, N-propargyl carbamate 1e and N-(1-benzyltetrahydro-1,3,4-oxathiolanyl)ethyl carbamate 1f were prepared as described below. Carbamates 1a (Kolbezen, et al., 1954); 2a (Metcalfe, R. L.; Fukuto, T. R. Silicon-containing carbamates: insecticides. J. Econ. Ent. 1965, 58, 1151 (“Metaf 11965”)); 4a-5a (Metcalfe, R. L.; Fukuto, T. R. Carbamate Insecticides, Effects of Chemical Structure on Intoxication and Detoxication of Phenyl N-Methylcarbamates in Insects. J. Agric. Food Chem. 1965, 13, 220-231 (“Metaf 11965”)); 6a (Kohn et al., 1965); 7a-11a (Metaf 11965); 1h (Kolbezen et al., 1954); 1c (Yu, C.-C.; Kearns, C. W.; Metcalfe, R. L. Acetylcholinesterase inhibition by substituted phenyl N-alkyl carbamates. J. Agric. Food Chem. 1972, 20, 537-540); and 1g (Metcalfe, 1971) have been previously described. Detailed procedures for new compounds follow below.

**EXAMPLE I**

Preparation of N-methyl 3-ethylidimethylsilylphenyl carbamate (3a)

3-bromophenoxyethyldimethylsilane: To a stirred solution of 3-bromophenol (0.60 g, 3.47 mmol) in dry THF (15 mL) under nitrogen was added Et3N (0.48 mL, 3.47 mmol). A yellow solution formed immediately; after cooling to 0° C., dimethylethylsilyl chloride (0.45 g, 0.49 mL, 3.47 mmol) was added by syringe over a period of 10 minutes. The yellow color disappeared in 10 minutes, and a white cloudy solution formed. After 3 hr the thick reaction mixture was filtered, washed with 15 mL of hexane, and filtered again. Concentration gave a clear oil (quantitative weight recovery) that was used in the next step without purification.

3-ethylidimethylsilylphenol: In a 100 mL flame-dried three-necked flask, fitted with refluxing condenser and dropping funnel, magnesium (92 mg, 3.82 mmol), iodine (1 mg) and dry THF (6 mL) were placed under nitrogen. A clear yellow solution formed immediately; after cooling to 0° C., dimethylethylsilyl chloride (0.45 g, 0.49 mL, 3.47 mmol) was added by syringe over a period of 10 minutes. The yellow color disappeared in 10 minutes, and a white cloudy solution formed. After 3 hr the thick reaction mixture was filtered, washed with 15 mL of hexane, and filtered again. Concentration gave a clear oil (quantitative weight recovery) that was used in the next step without purification.

3-ethyldimethylsilylphenol: In a 100 mL flame-dried three-necked flask, fitted with refluxing condenser and dropping funnel, magnesium (92 mg, 3.82 mmol), iodine (1 mg) and dry THF (6 mL) were placed under nitrogen. A light brown solution formed, the mixture was heated to reflux, and a solution of 3-bromophenoxydimethylsilane (0.899 g, 3.47 mmol) in THF (20 mL) was added by dropping funnel over 2 hr. The reaction mixture was refluxed overnight and cooled to room temperature. Ethyl(dimethylethylsiloxane (0.681 g, 0.78 mL, 5.55 mmol) was then added by syringe. The reaction
mixture was brought to reflux again for 6 hr, and allowed to stir overnight at room temperature. The reaction was then quenched with 1N HCl and the reaction concentrated in vacuo. Extraction with CH$_2$Cl$_2$, aqueous workup, and column chromatography (n-hexane/ethyl acetate 8:1) yielded 3-ethynylphenol (0.130 g, 0.73 mmol, 21%) as a colorless oil.

N-methyl 3-((1-benzyl-1H-1,2,3-triazol-4-yl)phenyl carbamate: To a stirred suspension of solution of sodium hydride (31 mg, 60%, 1.28 mmol) in THF (6 mL) was added 3-ethynylphenol (115 mg, 0.64 mmol) at room temperature. The cloudy suspension turned clear and after 30 min, N-methyl carbamoyl chloride (151 mg, 1.41 mmol) was added by syringe. A white cloudy solution formed again in 10 min. After stirring overnight, the reaction was quenched with water, concentrated in vacuo, and extracted with CH$_2$Cl$_2$. The organic layer was dried with sodium sulfate, concentrated and purified by column chromatography (n-hexane/ethyl acetate 10:1) to yield N-methyl 3-(ethynylphenyl)phenyl carbonate (405 mg, 1.34 mmol). The reaction mixture was brought to reflux again for 6 hr, and allowed to stir overnight at room temperature. The reaction mixture was neutralized by 1 N HCl and evaporated, and concentrated in vacuo to give a 218.5 mg of an oil that was chromatographed on silica w/2.5:1 hexane:ethyl acetate to give a feathery white solid.

**EXEMPLARY I**

Preparation of N-methyl-3-fluoro-5-trifluoromethylphenyl carbamate (12a)

An oven-dried 25 mL round bottom flask was charged with 251 mg (1.39 mmol) 3-fluoro-5-trifluoromethylphenol and purged with nitrogen. After cooling to 0°C, 1.6 mL 1 M KOT-Bu in THF (1.6 mmol) was added by syringe. After stirring for 20 min, 196 mg (2.1 mmol) N-methylcarbamoyl chloride was added by syringe and the reaction was allowed to warm to room temperature. After 18 hrs the reaction was concentrated in vacuo and the residue was taken up in CH$_2$Cl$_2$, washed with 0.25 M HCl, H$_2$O, and brine. The organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to give a residue that was chromatographed on silica w/2.5:1 hexane:ethyl acetate to give a feathery white solid (195 mg, 59% yield). $^1$H NMR (CDCl$_3$) δ 2.92 (s,3H), 5.00 (7-let, 1H), 132.77 (d, J$_{CF}$= 8.5 Hz), 152.40 (d, J$_{CF}$= 10 Hz), 154.02, 154.60 (d, J$_{CF}$= 24.8 Hz).

**EXEMPLARY III**

Preparation of N-methyl-3-(1-benzyl-1H-1,2,3-triazol-4-yl)phenyl carbamate (13a)

3-ethynylphenol: To a stirred solution of PdCl$_2$(PPh$_3$)$_2$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), and Et$_3$N (0.303 g, 0.42 mL, 3 mmol) in 10 mL of THF under nitrogen was added 3-iodophenol (0.440 g, 2 mmol) by syringe. The reaction mixture was cooled to 0°C, and trimethylsilylacetylene (0.206 g, 0.30 mL, 2.1 mmol) was added dropwise over 30 min. The reaction mixture was stirred at room temperature overnight and was filtered through Celite to remove Pd and Cu catalysts. Column chromatography (n-hexane/Acetone 6:1) yielded 3-((1-benzyl-1H-1,2,3-triazol-4-yl)phenyl)phenyl (380 mg, 2.0 mmol, >99%) as a light brown oil. This compound was diluted with THF (6 mL) and MeOH (6 mL), and 10% aqueous KOH (6 mL) was added. After stirring for 2 hr, the reaction mixture was neutralized by 1 N HCl and evaporated, extracted with CH$_2$Cl$_2$, and dried (Na$_2$SO$_4$). Column chromatography (n-hexane/Acetone 5:1) yielded 3-ethynylphenol (162.8 mg, 70%) as a yellow oil.
To a stirred solution of N-propargyl-3-t-butylphenyl carbamate 1e (48.9 mg, 0.21 mmol) and benzyl alcohol (31 mg, 0.23 mmol) in 1:1 t-butanol:water (2 mL) was added sodium ascorbate (4.2 mg, 0.021 mmol), followed by CuSO4.5H2O (0.52 mg, 0.0021 mmol). The reaction mixture was stirred for 24 h, evaporated, extracted with CH2Cl2, dried, and purified by column chromatography (n-hexane/ethyl acetate 1:1) to yield the desired product (47.4 mg, 0.13 mmol, 60%).

**Materials and Methods Relating to Compounds of Formula (II)**


**General Procedure for O-alkylation of catechols.**

2p: 2-(2-ethylbutylthio)phenyl-N—methylcarbamate. An oven-dried 5 mL round-bottom was charged with 2-(2-ethylthio)phenol 16p (152 mg, 0.941 mmol) and a magnetic stir bar, sealed with a septum, purged with N2, and cooled to 0° C.: 1.0 mL 1M KOT-Bu in THF (1.0 mmol) was then added via syringe. After stirring for 30 min, N-methylcarbamoyl chloride (135 mg, 1.4 mmol) was added as a solution in 1 mL THF; after 15 min the ice bath was removed and the reaction was allowed to stir at room temperature for 24 h. Workup was performed by removal of solvent in vacuo, addition of dichloromethane (25 mL), and filtration and washed with saturated sodium bicarbonate (25 mL) while stirring. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel w/ 6:1 hexane/ethyl acetate to afford a pale yellow oil that crystallized into an off-white solid weighing 454 mg (86% yield).

**General procedure for the preparation of N-methylcarbamoyl-ethyl phenol.** An oven-dried 5 mL round-bottom flask was charged with 2-(2-ethylthio)phenol 16p (152 mg, 0.941 mmol) and a magnetic stir bar, sealed with a septum, purged with N2, and cooled to 0° C. A solution of 1M KOT-Bu in THF (1.0 mmol) was then added via syringe. After stirring for 30 min, N-methylcarbamoyl chloride (135 mg, 1.4 mmol) was added as a solution in 1 mL THF; after 15 min the ice bath was removed and the reaction was allowed to stir at room temperature for 24 h. Workup was performed by removal of solvent in vacuo, addition of dichloromethane (25 mL), and filtration and washed with saturated sodium bicarbonate (25 mL) while stirring. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel w/ 6:1 hexane/ethyl acetate, affording a pale oil weighing 1.314 g (83% yield).

**Supplier Sources**

- 1M KOT-Bu in THF (1.0 mmol)
- Dichloromethane (25 mL)
- Saturated sodium bicarbonate (25 mL)

**General procedure for the S-alkylation of 2-mercaptophenol**

General procedure for the S-alkylation of 2-mercaptophenol with saturated alkyl halides. 1p: 2-(2-ethylthio)phenol. An oven-dried 50 mL round-bottom flask was charged with 2-mercaptophenol (1.00 g, 7.56 mmol), DMF (dried, 8.0 mL) and sodium bicarbonate (950 mg, 11.3 mmol) while purging with nitrogen. 1-Bromo-2-ethylbutane (2.25 g, 13.6 mmol) was added and the reaction was stirred at 55° C. for 18 hours. The reaction was cooled, diluted with 1:1 sat’d NaCl: 1M HCl (80 mL) extracted with EtOAc (3×50 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexane/ethyl acetate), affording a pale oil weighing 1.314 g (83% yield).

**Suppliers**

- 2-mercaptophenol (1.00 g, 7.56 mmol)
- DMF (dried, 8.0 mL)
- Sodium bicarbonate (950 mg, 11.3 mmol)
- 1-Bromo-2-ethylbutane (2.25 g, 13.6 mmol)
- 1M HCl (80 mL)
- EtOAc (3×50 mL)
flask was charged with catechol (4.99 g, 45.3 mmol), DMF (45 mL) and Cs₂CO₃ (14.7 g, 45.1 mmol) and purged with nitrogen. 2-Ethyl-1-bromobutane (5.90 g, 35.7 mmol) was added and the reaction was heated at 80°C for 18 hours. After cooling to room temperature the reaction was diluted in 250 mL of 1:1 M HCl:sat’d brine and extracted with EtOAc (3×50 mL). The combined organic layers were washed with saturated NaCl (1×25 mL), dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (5:1 hexane:EtOAc afforded a colorless oil weighing 4.25 g (61% yield). ¹H NMR (CDCl₃): δ 0.94 (t, J = 7.42 Hz, 6H), 1.45-1.51 (m, 4H), 1.71 (s, J = 3.51 Hz, 1H), 6.81-6.88 (m, 3H), 6.92 (d, J = 7.42 Hz, 2H), 7.05 (s, J = 3.51 Hz, 1H), 7.30 (d, J = 7.42 Hz, 2H); ¹³C NMR (CDCl₃): δ 11.29, 23.46, 27.84, 41.11, 67.08, 113.32, 120.51, 123.17, 126.43, 140.51, 151.52, 155.13.

EXAMPLE X

3b: 2-(ethylthio)phenyl-N-methylcarbamate. White solid; 83% yield; ¹H NMR (CDCl₃): δ 0.92 (t, J = 7.70 Hz, 6H), 1.38-1.52 (m, 4H), 1.64 (s, J = 6.35 Hz, 1H), 2.88 (d, J = 4.95 Hz, 3H), 3.87 (d, J = 5.80 Hz, 2H), 6.89 (t, J = 7.70 Hz, 1H). ¹³C NMR (CDCl₃): δ 11.29, 23.46, 27.84, 41.11, 70.68, 113.32, 120.51, 123.17, 126.43, 140.51, 151.52, 155.13.

EXAMPLE XI

4p: 2-(methylthio)phenol. This compound was prepared in 57% yield from 2-mercaptophenol and 1-chloro-2-methylbutane according to the procedure for 1p in Example VIII. ¹H NMR (CDCl₃): δ 0.66 (t, J = 4.85 Hz, 3H), 1.00 (d, J = 6.60 Hz, 3H), 1.18-1.27 (m, 1H), 1.46-1.58 (m, 2H), 2.55 (dd, J = 7.15, J = 12.35, 1H), 2.70 (dd, J = 5.75, J = 6.25, 1H), 2.86 (m, J = 1.1 Hz, 1H), 8.68 (dt, J = 1.1 Hz, 4.93 Hz, 1H), 6.98 (dd, J = 1.1 Hz, J = 8.25 Hz, 1H), 7.24 (dt, J = 1.65 Hz, J = 7.40 Hz, 1H), 7.45 (dd, J = 1.65 Hz, J = 7.07 Hz, 1H); ¹³C NMR (CDCl₃): δ 11.26, 18.74, 28.56, 34.80, 44.36, 114.77, 119.98, 120.81, 130.83, 135.80, 155.80; HRMS (FAB): 196.09219 calcd for C₃H₃₂NO₂S[M⁺]+ found 196.0896 (—2.5 ppm, —0.6 mmu).

EXAMPLE XII

5p: 2-(isopropylthio)phenol. This compound was prepared in 51% yield from 2-mercaptophenol and isopropyl iodide according to the procedure for 1p in Example VIII. Colorless oil; ¹H NMR (CDCl₃): δ 1.25 (d, J = 6.85 Hz, 3H), 3.09 (s, J = 6.60 Hz, 1H), 6.83 (s, 1H), 6.87 (dd, J = 3.10 Hz, J = 7.45 Hz, 1H), 6.99 (dd, J = 0.10 Hz, J = 7.45 Hz, 1H), 7.00 (t, J = 7.95 Hz, 1H); ¹³C NMR (CDCl₃): δ 23.36, 40.66, 114.71, 118.02, 120.61, 131.44, 137.00, 157.56; HRMS (FAB): 169.06872 celd for C₁₁H₁₃NO₂S [M⁺]+ found 169.06956 (3.1 ppm, 0.5 mmu).

EXAMPLE XIII

6b: 2-(isobutylthio)phenyl-N-methylcarbamate. White solid; 92% yield; ¹H NMR (CDCl₃): δ 1.28 (d, J = 6.85 Hz, 3H), 2.90 (d, J = 4.95 Hz, 3H), 3.37 (s, J = 6.60 Hz, 1H), 7.27 (dd, J = 1.65 Hz, J = 7.70 Hz, 1H); ¹³C NMR (CDCl₃): δ 23.29, 27.98, 37.50, 123.24, 126.05, 127.87, 129.14, 132.73, 150.57, 154.89; HRMS (FAB): 226.09018 calcd for C₁₃H₁₅NO₂S [M⁺]+ found 226.0896 (—2.5 ppm, —0.6 mmu).

EXAMPLE XIV

7p: 2-(neopentylthio)phenol. This compound was prepared in 58% yield from 2-mercaptophenol and neopentyl iodide according to the procedure for 1p in Example VIII. ¹H NMR (CDCl₃): δ 1.05 (s, J = 7.45 Hz, 3H), 3.19 (s, 3H), 5.10 (s, J = 7.45 Hz, 1H), 6.83-6.87 (m, 1H), 6.96 (dd, J = 2.12 Hz, J = 7.95, 1H), 7.21-7.26 (m, 1H), 7.46-7.48 (m, 1H); ¹³C NMR (CDCl₃): δ 28.90, 32.56, 52.64, 114.82, 120.94, 130.74, 135.61, 156.60, 158.89; HRMS: 240.10583 calcd for C₁₃H₁₅NO₂S [M⁺]+ found 240.10578 (—0.5 ppm, —0.1 mmu).

EXAMPLE XV

8p: 2-(methylallylthio)phenol. This compound was prepared in 65% yield from 2-mercaptophenol and methylallyl chloride according to the procedure for 1b in Example VII. Brown Oil; ¹H NMR (CDCl₃): δ 1.86 (s, J = 3.11 Hz, 3H), 4.52 (s, 1H), 4.73 (s, 1H), 6.64 (s, 1H), 6.85 (dd, J = 1.35 Hz, J = 7.40 Hz, 1H), 6.97 (dd, J = 1.1 Hz, J = 8.00 Hz, 1H), 7.25 (dt, J = 1.4, J = 7.7, 1H), 7.39 (dd, J = 1.7 Hz, J = 7.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 20.91, 44.49, 114.74, 114.92, 118.84, 120.67, 121.35, 136.31, 140.32, 157.08.

8b: 2-(methylallylthio)phenyl-N-methylcarbamate. Yellow oil; 82% yield; ¹H NMR (CDCl₃): δ 0.83 (s, J = 3.11 Hz, 3H), 2.89 (d, J = 19.25 Hz, 3H), 3.47 (s, 3H), 4.82 (d, J = 11.25 Hz, 2H), 5.04 (s, J = 11.25 Hz, 3H), 7.34 (d, J = 7.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 21.31, 27.95, 41.09, 56.34, 114.33, 122.98, 126.02, 127.43, 131.15, 140.00, 149.80, 154.77; HRMS (FAB): 237.08235 calcd for C₁₃H₁₅NO₂S [M⁺]+ found 237.08333 (4.0 ppm, 0.9 mmu).

EXAMPLE XVI

9p: 2-(cyclohexylmethylthio)phenol. This compound was prepared in 87% yield from 2-mercaptophenol and cyclohexylmethyl bromide according to the procedure for 1p in Example VIII. Colorless oil; ¹H NMR (CDCl₃): δ 9.91-9.99,
19
19.0
19.1
19.2
19.3
19.4
19.5
19.6
19.7
19.8
19.9
20
20.0
20.1
20.2
20.3
20.4
20.5
20.6
20.7
20.8
20.9
tosylate according to the general procedure for 2p in Example IX, except that potassium carbonate was used in place of cesium carbonate. Yellow oil: 1H NMR (CDCl₃): δ 1.33 (m, 2H), 1.58-1.69 (m, 4H), 1.82-1.89 (m, 2H), 2.04 (s, J=7.70 Hz, 2H), 2.10 (s, J=7.35 Hz, 2H), 2.87 (d, J=7.70 Hz, 2H), 3.00 (d, J=7.70 Hz, 2H), 2.94-3.00 (m, 2H), 3.65 (s, J=7.70 Hz, 2H), 6.90 (s, J=7.70 Hz, 1H), 9.47 (s, 2H), 13C NMR (CDCl₃): δ 25.35, 29.54, 39.11, 73.20, 111.78, 114.49, 120.16, 121.40, 149.50, 146.16.
12b: 2-(cyclopentylmethoxy)phenyl-N-methylcarbamate. White solid; 85% yield; 1H NMR (CDCl₃): δ 1.35-1.41 (m, 2H), 1.53-1.66 (m, 4H), 1.75-1.83 (m, 2H), 2.35 (s, J=7.70 Hz, 1H), 2.89 (d, J=4.95 Hz, 2H), 6.90 (t, J=7.65 Hz, 1H), 6.94 (d, J=8.25 Hz, 1H), 7.08 (d, J=7.95 Hz, 1H), 7.14 (t, J=7.40 Hz, 1H); 13C NMR (CDCl₃): δ 25.65, 27.88, 29.33, 39.12, 72.83, 113.59, 120.62, 123.18, 126.42, 140.49, 151.48, 155.15.

EXAMPLE XX

13b: 2-isobutoxyphenyl-N-methylcarbamate. White solid; 90% yield; 1H NMR (CDCl₃): δ 1.05 (d, J=1.95 Hz, 6H), 2.13 (s, J=6.60 Hz, 3H), 3.61 (d, J=6.60 Hz, 3H), 6.56-6.68 (m, 3H), 6.83-6.95 (m, 1H); 13C NMR (CDCl₃): δ 19.23, 27.92, 28.47, 75.02, 113.53, 120.65, 123.24, 126.47, 140.52, 151.47, 155.22.

EXAMPLE XXI

14p: 2-(2-chloroallylthio)phenol. This compound was synthesized in 49% yield from 2-mercaptophenol and 2-chloroallyl chloride according to the general procedure for 16p in Example VI. Pale oil; 1H NMR (CDCl₃): δ 3.48 (d, J=6.7 Hz, 2H), 4.91 (d, J=0.65 Hz, 1H), 5.15 (d, J=1.35 Hz, 1H), 6.69 (s, 1H), 6.87 (dt, J=1.40 Hz, J=7.42 Hz, 1H), 6.99 (dd, J=1.35, J=8.25 Hz, 1H), 7.27 (dt, J=1.65 Hz, J=7.82 Hz, 1H), 7.45 (dd, J=1.65 Hz, J=7.70 Hz, 1H); 13C NMR (CDCl₃): 45.30, 115.08, 115.98, 131.72, 131.91, 136.59, 137.67, 137.56; HRMS (FAB): 200.00586 calculated for C₁₅H₁₄NO₂S [M⁺] found 200.00586 (2.3 ppm, 0.3 mu).

14b: 2-(2-chloroallylthio)phenyl-N-methylcarbamate. Pale Oil; 58% yield; 1H NMR (CDCl₃): δ 2.92 (d, J=4.65 Hz, 3H), 3.66 (s, 2H), 5.09 (s, 1H), 5.22 (d, J=15.15 Hz, 2H), 7.15-7.40 (m, 3H), 7.41 (d, J=7.70 Hz, 1H); 13C NMR (CDCl₃): δ 27.97, 42.04, 115.24, 123.23, 126.21, 127.70, 128.76, 132.90, 131.51, 141.99, 150.69; HRMS (FAB): 258.03556 calculated for C₁₅H₁₄NO₂S₂Cl [M⁺⁺] found 258.03574 (0.6 ppm, 0.2 mu).

EXAMPLE XXII

15p: 2-(2-bromoallylthio)phenol. This compound was prepared from 2-mercaptophenol and 2-bromoallyl bromide in 58% yield according to the general procedure given for 16p in Example VII. Yellow oil; 1H NMR (CDCl₃): δ 3.57 (s, 2H), 5.33 (d, J=14.55 Hz, 2H), 6.69 (d, J=2.50 Hz, 1H), 6.87 (t,
21

J=7.40 Hz (1H), 6.99 (d, J=8.25 Hz, 1H), 7.28 (t, J=7.70 Hz, 1H), 7.45 (d, J=7.70 Hz, 1H); 13C NMR (CDCl₃): δ 47.63, 115.12, 120.39, 120.93, 124.92, 128.39, 131.89, 136.60, 157.56; HRMS (FAB): 243.9557 calculated for C₁₃H₁₄BrOS [M⁺] found 243.9557.

15b: 2-(2-bromoallylthio)phenyl-N-methylcarbamate. Yellow oil; 35% yield; 1H NMR (CDCl₃): δ 2.92 (d, J=4.95 Hz, 3H), 3.76 (s, 2H), 5.09 (s, 1H), 5.44 (s, 1H), 5.69 (s, 1H), 7.15-7.29 (m, 3H), 7.40 (d, J=1.40 Hz, J=7.70 Hz); 13C NMR (CDCl₃): δ 27.98, 44.04, 119.61, 123.23, 126.24, 126.31, 128.38, 128.68, 132.67, 150.55, 154.80.

EXEMPLARY XXIII

17p: (E)-2-(but-2-enythio)phenol. This compound was prepared in 97% yield according to the general procedure for 16p in Example VII. Colorless oil; 1H NMR (CDCl₃): δ 1.61 (d, J=8.8 Hz, 3H), 3.26 (d, J=7.40 Hz, 2H), 5.26-5.33 (m, 1H), 5.43-5.50 (m, 1H), 6.73 (s, J=10.87 Hz, 1H), 6.99 (d, J=1.10 Hz, 8.25 Hz, 1H), 7.27 (d, J=1.65 Hz, J=7.40 Hz, 1H), 7.43 (dd, J=1.65 Hz, J=7.70 Hz, 1H); 13C NMR (CDCl₃): δ 17.79, 39.40, 114.69, 118.57, 120.59, 125.77, 128.88, 131.27, 166.57, 157.28.

EXEMPLARY XXIV

18p: 2-(3-methyl-2-enylthio)phenol. This compound was prepared in 99% yield from 2-mercaptopropenol (and 2-(but-2-enyl) bromide in 97% yield according to the general procedure for 16p in Example VII. Colorless oil; 1H NMR (CDCl₃): δ 1.61 (d, J=8.0 Hz, 3H), 1.66 (s, 3H), 3.50 (d, J=8.00 Hz, 2H), 5.21-5.26 (m, 1H), 6.82 (s, 1H), 7.20-7.24 (m, 3H), 7.34 (dd, J=2.00 Hz, J=8.00 Hz, 1H); 13C NMR (CDCl₃): δ 17.85, 27.94, 35.49, 122.98, 126.73, 126.01, 127.09, 129.60, 130.93, 149.43, 154.79; HRMS (FAB): 238.09018 calculated for C₁₁H₁₂NO₅S [M⁺] found 238.08942 (+3.3 ppm, +0.08 mnu).

EXEMPLARY XXV

19p: 2-(benzylthio)phenol. This compound was prepared in 78% yield from 2-mercaptopropenol and benzyl bromide according to the procedure for 16p in Example VII. Pale oil; 1H NMR (CDCl₃): δ 1.66 (d, J=6.05 Hz, 3H), 2.92 (d, J=5.00 Hz, 3H), 3.49 (d, J=6.90 Hz, 2H), 5.08 (s, 1H), 5.80-5.85 (m, 1H), 6.70-6.72 (m, 1H), 7.13-7.24 (m, 3H), 7.34 (dd, J=2.00 Hz, J=8.00 Hz, 1H); 13C NMR (CDCl₃): δ 17.25, 25.70, 34.79, 114.56, 118.66, 119.14, 120.53, 131.31, 136.87, 137.25, 154.47; HRMS (FAB): 194.07654 calculated for C₁₁H₁₀OS [M⁺] found 194.07717 (+0.29 ppm, 0.06 mnu).

EXEMPLARY XXV

22b: 2-isopropylphenyl-N-methylcarbamate. Yellow solid; 80% yield; 1H NMR (CDCl₃): δ 1.21 (d, J=6.90 Hz, 6H), 2.88 (d, J=4.95 Hz, 3H), 3.12 (s, J=6.85 Hz, 1H), 5.05 (s, 1H), 7.04-7.07 (m, 1H), 7.17-7.19 (m, 2H), 7.28-7.30 (m, 2H), 7.42 (d, J=1.05 Hz, J=7.95 Hz, 1H), 7.72 (d, J=1.65 Hz, J=7.70 Hz, 1H), 7.37 (dd, J=1.65 Hz, J=7.97 Hz, 1H); 13C NMR (CDCl₃): δ 27.90, 30.32, 34.63, 124.20, 125.34, 126.94, 127.05, 141.34, 149.67, 155.36; HRMS (FAB): 208.13376 calculated for C₁₁H₁₄NO₂ [M⁺] found 208.1342 (2.1 ppm, 0.04 mnu).

EXEMPLARY XXX

23b: 2-tert-butylphenyl methacrylate. White solid; 67% yield; 1H NMR (CDCl₃): δ 1.36 (s, 9H), 2.93 (d, J=3.45 Hz, 3H), 5.03 (s, 1H), 7.05 (d, J=1.35 Hz, J=7.95 Hz, 1H), 7.14 (d, J=1.35 Hz, J=7.95 Hz, 1H), 7.22 (d, J=1.65 Hz, J=7.70 Hz, 1H), 7.37 (dd, J=1.65 Hz, J=7.97 Hz, 1H); 12C NMR (CDCl₃): δ 27.90, 30.32, 34.63, 124.20, 125.34, 126.94, 127.05, 141.34, 149.67, 155.36; HRMS (FAB): 208.13376 calculated for C₁₁H₁₄NO₂ [M⁺] found 208.1342 (2.1 ppm, 0.04 mnu).

8c: 2-(3-thio-2-methylpropanoyl)phenyl-N-ethylcarbamate. A 25 ml round-bottom flask was charged with 8p (0.198 g, 1.10 mmol, THF (10 mL) and purged with nitrogen. Diisopropylamine (0.2 ml, 1.15 mmol, 1.05 equiv.) was added via syringe followed by ethyl isocyanate (3.5 mL, 44.56 mmol, 6 equiv). After 4 h, the reaction was diluted with CH₂Cl₂ (60 mL), washed successively with 0.25 M HCl (2×60 mL), water (3×60 mL) and brine (60 mL). After drying over MgSO₄ (anhydrous), the solution was filtered, concentrated in vacuo, and the residue was purified by flash (15% ethyl acetate/hexane) to afford the desired product as a colorless oil, 202.5 mg, 0.806 mmol (73% yield). 1H NMR (CDCl₃): δ 1.18 (t, J=7.2 Hz, 3H, major amide conformer, CH₂CH₃), 1.24 (br.t, shoulder to triplet at δ 1.18, J=6.8 Hz, CH₂CH₃), 2.14 (s, 3H, methyl, CH₃).
Anopheles gambiae. Filterpaper assays were performed to determine the susceptibility or resistance of adult mosquitoes at the bottom of the tubes at 27°C. Batches of 15-20 non-blood fed females, 3-5 days old, were impregnated with 2 mL of each dilution and dried for 24 hours before testing. Insecticide concentrations are reported as ug/cm². The negative control was either 95% ethanol or water and mortality was recorded.

EXAMPLE XXXI

8d. 2-(3-thio-2-methylpropenyl)phenyl-N,N-hexylcarbamate. This compound was prepared from 8p and hexyl isocyanate in 47% yield according to the procedure for 8c. Colorless oil; 1H NMR (CDCl₃): δ 0.90 (t, J=5.5 Hz, 3H, hexyl CH₃), 1.31-1.40 (m, 6H, hexyl CH₂), 1.57 (quintet, J=5.8 Hz, 2H, NCH₂CH₃), 1.85 (d, J=6.0 Hz, 3H, C—CH₃), 3.27 (q, J=6.7 Hz, minor amide conformer, 2H, NHCHZCH₃), 3.36-3.41 (m, minor amide conformer, 2H, NCH₂CH₃), 3.48 (s, 2H, SCH₂), 4.82 (d, J=1.4 Hz, 1H, C—CH), 4.84 (s, 1H, C—CH), 5.13 (br.s, 1H, NH), 7.09-7.13 (m, 2H, Ar), 7.19-7.22 (m, 1H, Ar), 7.30-7.32 (m, 1H, Ar); 13C NMR (100 MHz, CDCl₃) (ppm); HRMS (FAB+, Direct) m/z calcd for C₁₇H₂₆N₀₂ $ (M+H⁺) 308.1684, found 308.1688 (100%).

Mosquito rearing and toxicity tests. The G3 strain of Anopheles gambiae, originally obtained from MR4, the National Institutes of Health (NIH), was used in all toxicity tests. The genotype is wild type and was selected and used for enzymatic assays. As used in the context of this application, this protein is referred to as “Ag ace-1” to represent that it is the insecticide-susceptible AgAChE enzyme encoded by ace-1.

Enzyme inhibition assays. Inhibition of AChE (Ag homogenate, Ag ace-1S and hAChE) was determined at pH 7.8 using the Ellman assay in a microtiter plate format. The Ag homogenate was prepared from 10 Anopheles gambiae mosquitoes with 1 mL ice-cold 0.1 M Na₂HPO₄ buffer (adjusted with 0.1 M NaH₂PO₄ to pH 7.8) containing 0.1% Triton X-100 in a glass homogenizer. The crude homogenate was then centrifuged for 10 min at 4°C in a microcentrifuge, and the supernatant was transferred to a
clean 1.5 mL microcentrifuge tube and stored on ice prior to use. Recombinant AgAChE (Ag ace-1S described above) was obtained in the form of a centrifuged cell lysate and diluted 10:1 with buffer prior to use. Recombinant hAChE (lyophilized powder, Sigma C1682) with a quoted specific activity of 2790 units/mg was diluted to 600 U/mL with buffer, frozen, and stored at −80°C. Immediately prior to assay, a frozen hAChE sample was thawed and diluted 1000-fold with buffer before use.

AChE inhibition of seven common commercial carbamate insecticides at three enzyme sources (Ag hmg, Ag ace-1S, and hAChE) were examined. As can be seen in Table 1, IC50 values of these seven commercial carbamates are similar at Ag hmg and Ag ace-1S, suggesting that Ag ace-1S is the major ACh-hydrolyzing enzyme present in the Ag hmg. AChE inhibition of the following carbamates were examined:

TABLE 1

Low Anopheles gambiae/human selectivity of AChE inhibition by common insecticidal carbamates

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>hAChE recomb IC50 (nM)</th>
<th>Ag hmgIC50 (nM)</th>
<th>Ag ace-1S IC50 (nM)</th>
<th>Live Mosquito Contact Toxicity MC (ug/cm²) for 100% lethality at 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldicarb</td>
<td>4,421</td>
<td>4624 (0.95x)</td>
<td>10,890 (0.41x)</td>
<td>0.55</td>
</tr>
<tr>
<td>Bendiocarb</td>
<td>270</td>
<td>65 (4.1x)</td>
<td>142 (1.9x)</td>
<td>0.55</td>
</tr>
<tr>
<td>Carbaryl</td>
<td>2,844</td>
<td>262 (11x)</td>
<td>515 (5.5x)</td>
<td>2.7</td>
</tr>
<tr>
<td>Carbofuran</td>
<td>61</td>
<td>22 (2.8x)</td>
<td>49 (1.2x)</td>
<td>0.55</td>
</tr>
<tr>
<td>Carbosulfan</td>
<td>5,920</td>
<td>4,099 (1.4x)</td>
<td>10,850 (0.54x)</td>
<td>1.1</td>
</tr>
<tr>
<td>Methonyl</td>
<td>626</td>
<td>716 (0.87x)</td>
<td>1,762 (0.36x)</td>
<td>2.7</td>
</tr>
<tr>
<td>Propoxur</td>
<td>444</td>
<td>371 (1.2x)</td>
<td>213 (2.1x)</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*Enzyme source is WT Anopheles gambiae homogenate; values in parenthesis are IC50 ratios (hAChE/Ag hmg).

Enzyme source is recombinant Anopheles gambiae AChE, WT (susceptible) strain; values in parenthesis are IC50 ratios (hAChE/Ag ace-1S).

Minimum concentration (ug/cm²) to cause 100% lethality of Anopheles gambiae at 24 h under standard WHO contact toxicity conditions (1 hr exposure to treated filter paper).

As can be seen, selectivity for AgAChE over hAChE inhibition is low with these compounds. The most selective compound is Carbaryl, which ranges from 5.5-11-fold selective.

Carbamates of Formula (I). We then prepared a range of 3-substituted phenyl N-methylcarbamates 1a-13a conforming to the following general formula:

We assayed compounds having various substituents, R₉ and R₆, in the three enzyme screen. The compounds tested and their corresponding results are provided in Table 2.
As shown in Table 2, Ag hmg IC₅₀ values are quite similar to those obtained with the recombinant Ag ace-1S. FIG. 1 provides a plot of log(Ag ace-1S IC₅₀ (nM)) vs log(Ag hmg IC₅₀ (nM)) for all the commercial and synthesized inhibitors described in Tables 1 and 2. The r² value of 0.937 provides further confirmation that the major AChE-hydrolyzing enzyme in the Ag hmg is ace-1S.

The most striking feature to emerge in Table 2, however, is the highly potent and selective AgAChE inhibition obtained with inhibitors 1a-3a. Human/Ag IC₅₀ ratios range from 38 to 130-fold based on recombinant Ag ace-1S, and 85 to 110-fold based on Ag hmg data. The contact toxicity of these inhibitors was also excellent. In the presence of synergist piperonyl butoxide, a one hour exposure to filter paper treated with carbamate 1a at 0.28 μg/cm² kills 100% of Anopheles gambiae within 24 hours. Similarly, one hour exposure to filter paper treated with 2a and 3a at 2.8 μg/cm² kills 80 and 60% of Ag mosquitoes within 24 hours.

The present inventors have, thus, identified that the substituent at C3 plays a role in AgAChE potency and selectivity. Interestingly, as the size of the 3-alkyl group is decreased from t-Bu (1a) to i-Pr (4a) to Et (5a), both AgAChE inhibition potency and selectivity decrease significantly. Lower inhibition potency is also seen for 3-phenyl (6a) and 3-halo (7a-9a) substituted carbamates, although the 3-iodo substituted carbamate 9a offers significant selectivity. Keeping the 3-t-butyl group constant, carbamates 1c-1h were prepared to assess the effect of the N-alkyl group on AChE inhibition potency (Table 3).

### TABLE 2

| Compound | R₉ | R₈ | hAChE recomb. IC₅₀ (nM) | Ag WT hmg IC₅₀ (nM) | Ag ace-1S IC₅₀ (nM) | Live Mosquito Contact Toxicity MC for 100% lethality at 24 hr
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>t-Bu</td>
<td>157</td>
<td>7 (85x)</td>
<td>1.1 (0.28)</td>
<td>1.1 (0.28)</td>
</tr>
<tr>
<td>2a</td>
<td>SiMe₃</td>
<td>H</td>
<td>532</td>
<td>5.6 (95x)</td>
<td>4.1 (130x)</td>
<td>5.6</td>
</tr>
<tr>
<td>3a</td>
<td>SiEtMe₂</td>
<td>H</td>
<td>285</td>
<td>2.7 (110x)</td>
<td>2.2 (130x)</td>
<td>11 (60% lethal at 2.8)</td>
</tr>
<tr>
<td>4a</td>
<td>i-Pr</td>
<td>H</td>
<td>175</td>
<td>27 (5.8)</td>
<td>12 (13x)</td>
<td>56</td>
</tr>
<tr>
<td>5a</td>
<td>Et</td>
<td>H</td>
<td>2,500</td>
<td>630 (4.0)</td>
<td>392 (6.4x)</td>
<td>11</td>
</tr>
<tr>
<td>6a</td>
<td>Ph</td>
<td>H</td>
<td>38,880</td>
<td>18,350 (2.1x)</td>
<td>12,080 (3.2x)</td>
<td>11</td>
</tr>
<tr>
<td>7a</td>
<td>Cl</td>
<td>H</td>
<td>86,000</td>
<td>26,000 (3.3x)</td>
<td>16,590 (5.2x)</td>
<td>11</td>
</tr>
<tr>
<td>8a</td>
<td>Br</td>
<td>H</td>
<td>&gt;100,000</td>
<td>23,970 (4.2x)</td>
<td>7,607 (13x)</td>
<td>11</td>
</tr>
<tr>
<td>9a</td>
<td>I</td>
<td>H</td>
<td>67,200</td>
<td>5,419 (13x)</td>
<td>18,227 (37x)</td>
<td>11</td>
</tr>
<tr>
<td>10a</td>
<td>Me</td>
<td>H</td>
<td>17,410</td>
<td>2,778 (6.2x)</td>
<td>1,040 (17x)</td>
<td>56</td>
</tr>
<tr>
<td>11a</td>
<td>t-Bu</td>
<td>H</td>
<td>5,166</td>
<td>5,318 (1.0x)</td>
<td>2,469 (2.1x)</td>
<td>None at 11</td>
</tr>
<tr>
<td>12a</td>
<td>CF₃</td>
<td>F</td>
<td>&gt;100,000</td>
<td>&gt;100,000 (Ha)</td>
<td>78,480 (Ha)</td>
<td>None at 11</td>
</tr>
<tr>
<td>13a</td>
<td>1-benzyl-triazol-4-yl</td>
<td>H</td>
<td>&gt;100,000</td>
<td>336,000 (Ha)</td>
<td>None at 11</td>
<td></td>
</tr>
</tbody>
</table>

*Enzyme source is Anopheles gambiæ homogenate; values in parenthesis are hAChE/Ag hmg; nd means not applicable, because the ratio cannot be determined.

**TABLE 3**

<table>
<thead>
<tr>
<th>Variation of N-alkyl group</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₇</th>
<th>R₈</th>
<th>hAChE recomb. IC₅₀ (nM)</th>
<th>Ag WT hmg IC₅₀ (nM)</th>
<th>Live Mosquito Contact Toxicity MC for 100% lethality at 24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>265</td>
<td>3.1</td>
<td>1.1 (0.28)</td>
</tr>
<tr>
<td>1h</td>
<td>Et</td>
<td>H</td>
<td>2,408</td>
<td>3,997</td>
<td>11</td>
</tr>
<tr>
<td>1c</td>
<td>n-hexyl</td>
<td>H</td>
<td>696</td>
<td>&gt;100,000 (Ha)</td>
<td>13% lethal at 11</td>
</tr>
</tbody>
</table>
### TABLE 3-continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>R&lt;sub&gt;7&lt;/sub&gt;</th>
<th>R&lt;sub&gt;8&lt;/sub&gt;</th>
<th>hAChE recomb. IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>Ag WT hmg&lt;sup&gt;a&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>Live Mosquito Contact Toxicity MC for 100% leathality at 24 hr&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>i-Pr</td>
<td>H</td>
<td>181,000</td>
<td>538,000</td>
<td>None at 11</td>
</tr>
<tr>
<td>1e</td>
<td>Propargyl</td>
<td>H</td>
<td>205</td>
<td>339</td>
<td>56</td>
</tr>
<tr>
<td>1f</td>
<td>(1-benzyl-triazol-4-yl)methyl</td>
<td>H</td>
<td>&gt;10,000</td>
<td>&gt;10,000</td>
<td>56</td>
</tr>
<tr>
<td>1g</td>
<td>Me</td>
<td>Me</td>
<td>4,036</td>
<td>5,945</td>
<td>20% lethal at 11</td>
</tr>
</tbody>
</table>

<sup>a</sup>Enzyme source is WT Anopheles gambiae homogenate; values in parenthesis are IC<sub>50</sub> ratios (hAChE:Ag WT).

<sup>b</sup>Minimum concentration (ug/cm<sup>2</sup>) to cause 100% lethality of Anopheles gambiae at 24 h under standard WHO contact toxicity conditions (1 hr exposure to treated filter paper). Values in parenthesis represent data in the presence of a synergist (piperonyl butoxide 0.3 mg/mL).

As can be seen, AgAChE inhibition is sensitive to the nature of the N-alkyl group. A methyl group (1a) gives the highest inhibition potency, as has been seen in numerous previous studies of Musca domestica (i.e. housefly) AChE (MdaChE). (Kolberzen, 1954 and Metcalf, 1971.)

As Table 4 illustrates, however, carbamate 1a is much more potent at Ag hmg AChE (3 nM) than at Mda homogenate AChE (400 nM). This >100-fold difference in potency for two insect species is unanticipated and leads to the 85-fold selectivity for Ag hmg AChE relative to hAChE noted above in Table 2.

### TABLE 4-continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>R&lt;sub&gt;9&lt;/sub&gt;</th>
<th>R&lt;sub&gt;6&lt;/sub&gt;</th>
<th>Ag WT hmg&lt;sup&gt;a&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>Md WT hmg&lt;sup&gt;b&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldicarb</td>
<td>Na</td>
<td>na</td>
<td>4,624</td>
<td>84,000</td>
</tr>
<tr>
<td>Carbaryl</td>
<td>Na</td>
<td>na</td>
<td>262</td>
<td>900</td>
</tr>
<tr>
<td>Propoxur</td>
<td>Na</td>
<td>na</td>
<td>371</td>
<td>670</td>
</tr>
</tbody>
</table>

<sup>a</sup>Enzyme source is Anopheles gambiae homogenate

<sup>b</sup>Enzyme source is Musca domestica head homogenate; data from Metcalf.

Similarly, carbamate 2a (2921-34-8) is reported to be a 700 nM inhibitor at Mda hmg AChE. (Metcalf I 1965.) The 100-fold greater potency of 2a at Ag hmg AChE is again unexpected. A less dramatic but still significant enhancement in potency is seen for carbamate 4a: it is 340 nM at MdaChE, but 27 nM at AgAChE. (Metcalf II 1965.) Finally, not all the inhibitors in Table 4 are more potent at AgAChE than MdaChE. A dramatic reversal in inhibition potency is seen for 11a (tradename butacarb): it is 5,318 nM at AgAChE, but 78 nM at Mda hmg AChE. (Metcalf II 1965.) Thus, as can be seen, neither MdaChE nor bovine AChE IC<sub>50</sub> values are predictive of AgAChE IC<sub>50</sub> values.

Consequently, the high selectivity shown by the present inventors for Ag relative to hAChE seen with inhibitors 1a-3a is unprecedented, could not have been predicted, and is thus non-obvious. The common structural feature these three inhibitors share is the presence of a trialkylmethyl or trialkylsilyl group at the meta-position of a phenyl N-methylcarbamate.

Carbamates of Formula (II). We then prepared a range of 2-substituted phenyl N-methylcarbamates 1b-23b, and assayed them in the three enzyme screen (Table 5).
<table>
<thead>
<tr>
<th>Compound</th>
<th>R_{12}</th>
<th>hMChE recomh IC_{50} (nM)</th>
<th>Ag WT hmg IC_{50} (nM)</th>
<th>Ag ace- IS IC_{50} (nM)</th>
<th>Live mosquito toxicity MC (ug/cm²) for 100% lethality at 24 hr²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td></td>
<td>3430</td>
<td>3 (1210x)</td>
<td>2.9 (1250x)</td>
<td>27% at 11</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td>95,820</td>
<td>69 (1400x)</td>
<td>10 (9,900x)</td>
<td>27% at 11, 53% at 11 (±PBO)</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>55,380</td>
<td>51,750 (11x)</td>
<td>nd</td>
<td>0% at 11</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td>3540</td>
<td>30 (118x)</td>
<td>27 (131x)</td>
<td>70% at 11</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>943</td>
<td>33 (29x)</td>
<td>nd</td>
<td>2.8</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>8114</td>
<td>109 (74x)</td>
<td>nd</td>
<td>11</td>
</tr>
<tr>
<td>7b</td>
<td></td>
<td>13,940</td>
<td>732 (19x)</td>
<td>287 (40x)</td>
<td>33% at 11</td>
</tr>
<tr>
<td>8b</td>
<td></td>
<td>9,55</td>
<td>124 (77x)</td>
<td>165 (58x)</td>
<td>2.8</td>
</tr>
<tr>
<td>Compound</td>
<td>R&lt;sub&gt;12&lt;/sub&gt;</td>
<td>hMChE recomb. IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>Ag WT IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>Ag ace-IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>Live mosquito toxicity MC (ug/cm²) for 100% lethality at 24 hr&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
<td>---------------------------------</td>
<td>----------------------------</td>
<td>---------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>9b</td>
<td></td>
<td>10,600</td>
<td>17,500 (0.61x)</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>10b</td>
<td></td>
<td>&gt;100,000</td>
<td>&gt;100,000 (0.61x)</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>11b</td>
<td></td>
<td>6,880</td>
<td>1,070 (6.2x)</td>
<td>391 (18x)</td>
<td>nd</td>
</tr>
<tr>
<td>12b</td>
<td></td>
<td>&gt;100,000</td>
<td>24,600 (4x)</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>13b</td>
<td></td>
<td>66,900</td>
<td>2,060 (32x)</td>
<td>650 (100x)</td>
<td>100% at 2.8</td>
</tr>
<tr>
<td>14b</td>
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<td>3,100</td>
<td>114 (27x)</td>
<td>264 (12x)</td>
<td>11</td>
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<tr>
<td>15b</td>
<td></td>
<td>1,658</td>
<td>248 (6.7x)</td>
<td>173 (9.6x)</td>
<td>95% lethal at 56</td>
</tr>
<tr>
<td>16b</td>
<td></td>
<td>1,583</td>
<td>156 (10x)</td>
<td>36 (44x)</td>
<td>5.6</td>
</tr>
</tbody>
</table>
### TABLE 5-continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁₂</th>
<th>IC₅₀ (nM)</th>
<th>IC₅₀ (nM)</th>
<th>MC (μg/cm²)</th>
<th>IC₅₀ (nM)</th>
<th>MC (μg/cm²)</th>
<th>IC₅₀ (nM)</th>
<th>MC (μg/cm²)</th>
<th>IC₅₀ (nM)</th>
<th>MC (μg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17b</td>
<td>S</td>
<td>494</td>
<td>57 (8.7x)</td>
<td>68 (7.3x)</td>
<td>93% lethal at 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18b</td>
<td>S</td>
<td>2,703</td>
<td>1,177 (2.3x)</td>
<td>411 (6.6x)</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19b</td>
<td>S</td>
<td>15,660</td>
<td>6,903 (2.3x)</td>
<td>3,842 (4.1x)</td>
<td>None at 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20b</td>
<td>O</td>
<td>68,730</td>
<td>1,510 (46x)</td>
<td>nd</td>
<td>95% lethality at 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21b</td>
<td>O</td>
<td>31,850</td>
<td>1,068 (30x)</td>
<td>741 (43x)</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22b (328)</td>
<td>i-Pr</td>
<td>4,542</td>
<td>507 (8.8x)</td>
<td>426 (11x)</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23b (330)</td>
<td>t-Bu</td>
<td>&gt;100,000</td>
<td>79,000 (&gt;1.3x)</td>
<td>51,700 (1.9x)</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Enzyme source is WT *Anopheles gambiae* homogenate; values in parenthesis are IC₅₀ ratios (hAChE/Ag hmg).

bEnzyme source is recombinant full-length *Anopheles gambiae* AChE, WT (susceptible) strain; values in parenthesis are IC₅₀ ratios (hAChE/Ag ace-1 S).

cMinimum concentration (μg/cm²) to cause 100% lethality of *Anopheles gambiae* at 24 h under standard WHO contact toxicity conditions (1 hr exposure to treated filter paper). If all the mosquitoes do not die within 24 h, the % lethality at 24 h is given.
As shown in Table 5, Ag hmg IC50 values are quite similar to those obtained with the recombinant Ag ace-1S. FIG. 2 provides a plot of log [Ag ace-1S IC50] vs log [Ag hmg AChE IC50] for all the compounds in Tables 1 and 5. The r^2 value of 0.954 provides further confirmation that the major ACh-hydrolyzing enzyme in the Ag hmg is ace-1S.

The most striking feature to emerge in Table 5, however, is the highly potent and selective AgAChE inhibition obtained with carbamates 1b, 2b, 4b, 6b, 8b, and 13b. Because two sources of AgAChE are used, two independent measures of the selectivity are available for most compounds. Human/Ag IC50 ratios of these highly selective carbamates range as follows: 58-to 77-fold for 8b; 74-fold for 6b; 32-to 100-fold for 13b; to 32-to 131-fold for 4b; 1200-fold for 1b; and 1,400-9,900-fold for 2b. Full dose-response curves for the two most selective inhibitors are shown in FIG. 3. As can be seen in FIG. 3, carbamates 1b and 2b achieve >90% inhibition of AgAChE at concentrations where hAChE undergoes no measurable inhibition.

To assess the effect of variation of the N-alkyl group on inhibition potency and selectivity, 3 analogues of 8b were prepared (Table 6). As can be seen, only the N-methyl derivative 8b possesses selectivity for AgAChE inhibition.

The present invention has been described with reference to particular embodiments having various features. It will be apparent to those skilled in the art that various modifications and variations can be made in the practice of the present invention without departing from the scope or spirit of the invention. One skilled in the art will recognize that these features may be used singularly or in any combination based on the requirements and specifications of a given application or design. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention. The description of the invention provided is merely exemplary in nature and, thus, variations that do not depart from the essence of the invention are intended to be within the scope of the invention.

The invention claimed is:

1. A compound of Formula (I):

   \[
   \text{Formula (I)}
   \]

   wherein said compound is chosen from at least one of 3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1-trifluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate; 3-(3,3,4,4,4-pentafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate; and 3-(1,1,1,3,3,4,4,4-octafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate.

2. A method of making a compound of Formula (I) comprising:

   deprotonating a phenol with KOt-Bu or NaH in THF to obtain a deprotonated phenol;

   carbamoylating said deprotonated phenol by reacting said deprotonated phenol with N-methyl carbamoyl chloride; and

   isolating the resultant compound to obtain a compound of Formula (I):

   \[
   \text{Formula (I)}
   \]

   wherein said compound is chosen from at least one of 3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1-trifluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate; 3-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate; 3-(3,3,4,4,4-pentafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate; and 3-(1,1,1,3,3,4,4,4-octafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate.
3. A method of controlling mosquitoes comprising applying a compound lethal to mosquitoes to a substrate and exposing said substrate to mosquitoes for a time sufficient to kill said mosquitoes, wherein said compound is a compound of Formula (I):

![Formula (I)](image)

wherein said compound is chosen from at least one of

- 3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3-hexafluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3,6-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1-trifluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate;
- 3-(3,3,4,4,4-pentafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3,4,4,4-octafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
and 3-(1,1,1,3,3,4,4,4-octafluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate.

4. An insecticidal composition comprising a compound of Formula (I):

![Formula (I)](image)

wherein said compound is chosen from at least one of

- 3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3-hexafluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3,6-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1-trifluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate;
- 3-(3,3,4,4,4-pentafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3,4,4,4-octafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
and 3-(1,1,1,3,3,4,4,4-octafluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate.

5. A net for controlling mosquitoes comprising a compound of Formula (I):

![Formula (I)](image)

wherein said compound is chosen from at least one of

- 3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3-hexafluoro-2-methylpropan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3,6-hexafluoro-2-(trifluoromethyl)propan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1-trifluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1-trifluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate;
- 3-(3,3,4,4,4-pentafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
- 3-(1,1,1,3,3,4,4,4-octafluoro-2-methylbutan-2-yl)phenyl N-methylcarbamate;
and 3-(1,1,1,3,3,4,4,4-octafluoro-2-(trifluoromethyl)butan-2-yl)phenyl N-methylcarbamate.

6. The method according to claim 3, wherein said applying comprises applying said compound of Formula (I) to agricultural substrates.

7. The method according to claim 3, wherein said applying comprises indoor residual spraying of said compound of Formula (I) or treating nets to obtain a net treated with an insecticide of Formula (I).

8. The insecticidal composition according to claim 4 further comprising a synergist for increasing lethality of said compound of Formula (I).

9. The net according to claim 5 further comprising a synergist for increasing lethality of said compound of Formula (I).

10. The insecticidal composition according to claim 8, wherein said synergist is piperonyl butoxide.

11. The net according to claim 9, wherein said synergist is piperonyl butoxide.

12. The compound according to claim 1 which exhibits selectivity for AgAChE over hAChE inhibition.