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Article

Potential for *Aedes aegypti* Larval Control and Environmental Friendliness of the Compounds Containing 2-Methyl-3,4-dihydroquinazolin-4-one Heterocycle

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Simple Summary: The *Aedes aegypti* mosquito is the principal vector of dengue, Zika, yellow fever and chikungunya viruses. Factors such as global warming, rapid urbanization, and inter-country traffic are favorable factors for *Ae. aegypti* to expand its distribution. Synthetic pesticides have played an important role in controlling mosquito species for decades, but they have many negative impacts on ecosystems and human health. In addition, frequent repeated use has resulted in drug resistance in mosquito populations. Therefore, the search for new pesticides that are safe for humans and friendly to the environment is of particular interest at present. In this study, we synthesized and evaluated the larvicidal activities of 2-methylquinazolin-4(3*H*)-one derivatives against *Ae. aegypti*. These compounds exhibited excellent larvicidal activity, in addition all of them demonstrated safety for a natural predator of mosquitos, *Diplonychus rusticus*. Larger-scale trials should be performed to consider 2-methylquinazolin-4(3*H*)-one derivatives as an alternative to pesticides in use today.

Abstract: 2-Methylquinazolin-4(3*H*)-one was prepared by reaction of anthranilic acid, acetic anhydride and ammonium acetate. The reaction of 2-methylquinazolin-4(3*H*)-one with *N*-aryl-2-chloroacetamides in acetone in the presence of potassium carbonate gave nine *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide compounds. The structures of these compounds were elucidated on the basis of their IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS spectral data. These synthesized compounds containing the 2-methyl-3,4-dihydroquinazolin-4-one moiety exhibited excellent activity against *Aedes aegypti* mosquito larvae with LC_{50} values in the range of 2.085-4.201 μg/mL after 72 h exposure. Interestingly, these compounds did not exhibit toxicity to the non-target organism *Diplonychus rusticus*. In silico molecular docking revealed acetylcholine binding protein (AChBP) and acetylcholinesterase (AChE) to be potential molecular targets. These data indicated the larvicidal potential and environmental friendliness of these *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide derivatives.

Keywords: acetylcholine binding protein; acetylcholinesterase; green pesticide; molecular docking

1. Introduction

Quinazolin-4(3*H*)-one is the basic skeleton found in many compounds having biological activity. Studies have shown that some compounds containing 2-methylquinazolin-4(3*H*)-one heterocycle possess a variety of biological effects such as antimicrobial, antifungal [1,2], anti-inflammatory [3,4], analgesic [5] and anticancer [6] activities. Along with the quinazolin-4(3*H*)-one nucleus, the acetamide component is also present in the structure of many biologically

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active compounds. A wide range of biological activities such as antimicrobial, antifungal [7,8], antioxidant, anti-inflammatory [9], and enzyme-inhibiting [10] has been attributed to the compounds containing the acetamide component. The combination of quinazolin-4(3*H*)-one nucleus and acetamide group thus promises to produce organic molecules with effective biological activity.

The *Aedes aegypti* mosquito is the principal vector of dengue, Zika, yellow fever and chikungunya viruses and it has spread to most tropical and sub-tropical towns and cities [11]. According to WHO, dengue incidence has been rising, the number of cases reported annually is 96 million cases, including 1.9 million critical cases and 9,110 deaths. Urbanization [12] and global warming [13] are facilitating the territorial expansion of *Ae. aegypti*. Regular and repeated use over many years of insecticides such as carbamates, pyrethroids, organophosphates and organochlorides has resulted in reduced susceptibility or resistance in *Ae. aegypti* populations in most countries in which it is distributed [14]. Furthermore, these insecticides present disadvantages such as toxicity to humans and other non-target species, degradation of the aquatic environment, high annual costs, and the development of target-resistant populations. In response to the challenges of controlling *Ae. aegypti* as well as other mosquito species, it is clear and urgent to find new insecticides that overcome the adverse problems of currently used insecticides. So, the present study reports the synthesis of some *N*-aryl 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide compounds, evaluates their *Ae. aegypti* mosquito larvicidal activity, and investigates their toxicity to non-target organisms.

2. Materials and Methods

2.1. Materials

All starting materials were sourced from Acros Organics or Xilong (distributed by Thinh Phat Scientific Equipment Co., Ltd, Hanoi City, Vietnam.) and used without purification. Melting points were measured in open capillary tubes on a Gallenkamp melting point apparatus without calibration. The structures of all compounds were confirmed by their IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS spectral data. IR spectra (ν, cm^{-1}) were recorded on a FTIR-8400S-SHIMADZU spectrometer using KBr pellets. The NMR spectra were recorded on a Bruker Avance III spectrometer (500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR) using residual solvent DMSO-d_6 signals (δ_H 2.50, δ_C 39.52) as internal references. The spin-spin coupling constants (*J*) are given in Hz. Peak multiplicity is reported as b (broad), s (singlet), d (doublet), dd (doublet-doublet), ddd (doublet-doublet-doublet), and *m* (multiplet), respectively. The HR-ESI-MS spectra were recorded on an Agilent 6200 Q-TOF B.06.01 spectrometer in positive mode.

2.2. Synthesis of derivatives of 2-methylquinazolin-4(3H)-one

The target compounds were synthesized according to the synthetic route in Scheme 1

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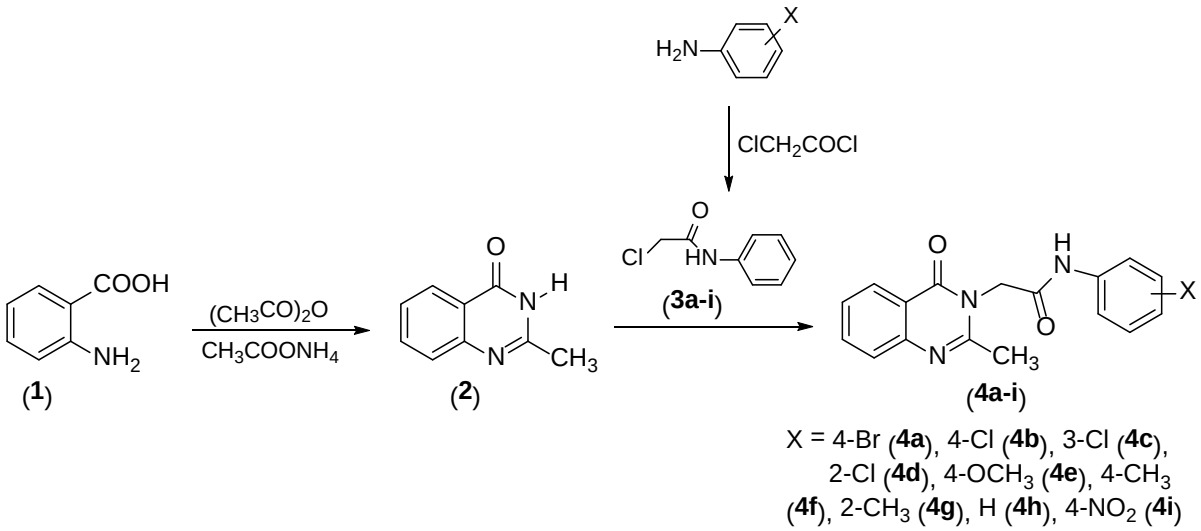

Scheme 1: Synthetic pathway of the acetamides containing 2-methyl-3,4-dihydroquinazolin-4-one heterocycle

2-Methylquinazolin-4(3*H*)-one (2): The mixture of anthranilic acid (13.7 g, 0.1 mol) and anhydride acetic (5 mL) was refluxed for 1.0 h. After cooling, ammonium acetate (7.7 g, 0.1 mol) was added and then, the reaction mixture was refluxed with stirring for 3.0 h. Finally, the mixture was cooled to room temperature and poured into ice-cold water. The precipitate was filtered and recrystallized from a mixture of ethanol and water to give white needle crystals. Yield: 60.0 %. Mp. 239-241 °C (lit. [11]); ^{1}H-NMR (DMSO-d_6) δ: 12.19 (1H, b), 8.07 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.75 (1H, ddd, J_1 = J_2 = 7.5 Hz, J_3 = 1.5 Hz), 7.56 (1H, d, J = 8.0 Hz), 7.44 (1H, d, J = 8.0 Hz); IR (KBr) cm^{-1}: 3404, 3034, 2868, 1655, 1607, 1468. HR-ESI-MS m/z: 161.0722 ([M+H]$^+$, Calcd for $C_9H_9N_2O$: 161.0714).

General procedure for synthesis of *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide compounds (4a-i): An equimolar mixture of 2-methylquinazolin-4(3*H*)-one (0.16 g, 1 mmol) and anhydrous potassium carbonate (0.138 g, 1 mmol) in acetone (20 mL) was stirred for 30 minutes, then 1 mmol of a definite *N*-aryl-2-chloroacetamide compound (**3a-i**) was added. The reaction mixture was refluxed for 2 h with stirring then cooled to room temperature and poured into ice-cold water. The white precipitate was filtered off and purified by crystallization from ethanol to afford pure product **4a-i**, respectively.

N-(4-bromophenyl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (***4a***): Yield: 82.0 %. Mp. 288-289 °C; ^{1}H-NMR (DMSO) δ: 10.60 (1H, s), 8.10 (1H, dd, J_1=8.0Hz, J_2=1.5Hz), 7.83 (1H, dd, J_1=J_2=7.5Hz), 7.64 (1H, d, J=8.5Hz), 7.58 (2H, d, J=9.0Hz), 7.52 (2H, d, J=8.5Hz), 7.51 (1H, dd, J_1=J_2=8.0Hz), 4.98 (2H, s), 2.56 (3H, s); ^{13}C-NMR (DMSO) δ: 166.2 (s), 161.7 (s), 155.8 (s), 147.6 (s), 138.4 (s), 135.0 (s), 132.2 (s), 127.1 (s), 126.9 (s), 126.6 (s), 121.6 (s), 120.1 (s), 115.7 (s), 47.5 (s), 23.5 (s); IR (KBr) cm^{-1}: 3310, 3281, 3065, 2918, 1686, 1647, 1595, 1543, 656; HR-ESI-MS m/z: 372.0353 ([M+H]$^+$, Calcd for $C_{17}H_{15}BrN_3O_2$: 372.0348).

N-(4-chlorophenyl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (***4b***): Yield: 78.0 %. Mp. 256-257 °C; ^{1}H-NMR (DMSO) δ: 10.61 (1H, s), 8.11 (1H, d, J=8.0Hz), 7.83 (1H, dd, J_1=J_2=7.5Hz), 7.64 (3H, d, J=9.0Hz), 7.51 (1H, dd, J_1=J_2=7.5Hz), 7.39 (2H, d, J=9.0Hz), 4.98 (2H, s), 2.56 (3H, s); ^{13}C-NMR (DMSO) δ: 166.2 (s), 161.7 (s), 155.8 (s), 147.6 (s), 138.0 (s), 135.0 (s), 129.2 (s), 127.7 (s), 127.1 (s), 126.8 (s), 126.6 (s), 121.2 (s), 120.1 (s), 47.5 (s), 23.5 (s); IR (KBr) cm^{-1}: 3312, 3283, 3067, 2972, 1686, 1647, 1591, 1547, 1470, 818; HR-ESI-MS m/z: 328.0865 ([M+H]$^+$, Calcd for $C_{17}H_{15}ClN_3O_2$: 328.0853).

N-(3-chlorophenyl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (***4c***): Yield: 69.0 %. Mp. 258-259 °C; ^{1}H-NMR (DMSO) δ: 10.67 (1H, s), 8.09 (1H, dd, J_1=7.5Hz, J_2=1.5Hz), 7.83 (1H, ddd, J_1=J_2=7.0Hz, J=1.5Hz), 7.80 (1H, dd, J_1=J_2=1.5Hz), 7.63 (1H, d, J=8.0Hz), 7.51 (1H, dd, J_1=J_2=7.5Hz), 7.45 (1H, d, J=8.0Hz), 7.37 (1H, dd, J_1=J_2=8.0Hz), 7.15 (1H,

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dd, J_1=8.0Hz, J_2=1.0Hz), 4.97 (2H, s), 2.55 (3H, s); ^{13}C-NMR (DMSO) δ: 166.5 (s), 161.7 (s), 155.8 (s), 147.6 (s), 140.5 (s), 135.1 (s), 133.6 (s), 131.1 (s), 127.1 (s), 126.9 (s), 126.6 (s), 123.8 (s), 120.1 (s), 119.2 (s), 118.0 (s), 47.6 (s), 23.5 (s); IR (KBr) cm^{-1}: 3318, 3285, 3007, 2916, 1692, 1647, 1593, 1553, 772; HR-ESI-MS *m*/*z*: 328.0866 ([M+H]$^+$, Calcd for $C_{17}H_{15}ClN_3O_2$: 328.0853).

N-(2-chlorophenyl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (***4d***): Yield: 75.0 %. Mp. 266-267 °C; ^{1}H-NMR (DMSO) δ: 10.11 (1H, s), 8.12 (1H, dd, J_1=8.0Hz, J_2=1.0Hz), 7.83 (1H, ddd, J_1=J_2=7.5Hz, J_3=1.5Hz), 7.71 (1H, dd, J_1=8.0Hz, J_2=1.5Hz), 7.63 (1H, d, *J*=8.0Hz), 7.53 (1H, d, *J*=7.5Hz), 7.51 (1H, dd, J_1=J_2=7.5Hz), 7.34 (1H, dd, J_1=J_2=7.5Hz), 7.23 (1H, dd, J_1=J_2=7.5Hz), 5.08 (2H, s), 2.57 (3H, s); ^{13}C-NMR (DMSO) δ: 166.7 (s), 161.7 (s), 155.8 (s), 147.6 (s), 135.0 (s), 134.8 (s), 130.1 (s), 128.0 (s), 127.2 (s), 127.1 (s), 126.9 (s), 126.8 (s), 126.7 (s), 120.2 (s), 47.0 (s), 23.4 (s); IR (KBr) cm^{-1}: 3204, 3038, 1682, 1665, 1605, 1541, 781; HR-ESI-MS *m*/*z*: 328.0867 ([M+H]$^+$, Calcd for $C_{17}H_{15}ClN_3O_2$: 328.0853).

N-(4-methoxyphenyl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (***4e***): Yield: 78 %. Mp: 234-235 °C; ^{1}H-NMR (DMSO) δ: 10.31 (1H, s), 8.10 (1H, d, *J*=8.0Hz), 7.83 (1H, dd, J_1=J_2=7.5Hz), 7.63 (1H, d, *J*=8.0Hz), 7.51 (1H, dd, J_1=J_2=7.5Hz), 7.50 (2H, d, *J*=8.0Hz), 6.90 (2H, d, *J*=9.0Hz), 4.95 (2H, s), 3.73 (3H, s), 2.55 (3H, s); ^{13}C-NMR (DMSO) δ: 165.4 (s), 161.7 (s), 160.0 (s), 155.9 (s), 147.6 (s), 135.0 (s), 132.2 (s), 127.1 (s), 126.8 (s), 126.6 (s), 121.2 (s), 120.1 (s), 114.4 (s), 55.7 (s), 47.3 (s), 23.4 (s); IR (KBr) cm^{-1}: 3277, 3017, 2957, 1676, 1643, 1597, 1533; HR-ESI-MS *m*/*z*: 324.1361 ([M+H]$^+$, Calcd for $C_{18}H_{18}N_3O_3$: 324.1348).

2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-(p-tolyl)acetamide (***4f***): Yield: 83 %. Mp: 252-253 °C; ^{1}H-NMR (DMSO) δ: 10.38 (1H, s), 8.10 (1H, d, *J*=8.0Hz), 7.83 (1H, dd, J_1=J_2=7.5Hz), 7.63 (1H, d, *J*=8.5Hz), 7.51 (1H, dd, J_1=J_2=7.0Hz), 7.48 (2H, d, *J*=8.5Hz), 7.13 (2H, d, *J*=8.5Hz), 4.96 (2H, s), 2.55 (3H, s), 2.26 (3H, s); ^{13}C-NMR (DMSO) δ: 165.7 (s), 161.7 (s), 155.9 (s), 147.6 (s), 136.6 (s), 135.0 (s), 133.0 (s), 129.7 (s), 127.1 (s), 126.8 (s), 126.6 (s), 120.1 (s), 119.6 (s), 47.4 (s), 23.5 (s), 20.9 (s); IR (KBr) cm^{-1}: 3312, 3061, 2918, 1667, 1595, 1537; HR-ESI-MS *m*/*z*: 308.1412 ([M+H]$^+$, Calcd for $C_{18}H_{18}N_3O_2$: 308.1399).

2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-(o-tolyl)acetamide (***4g***): Yield: 77 %. Mp: 258-259 °C; ^{1}H-NMR (DMSO) δ: 9.83 (1H, s), 8.12 (1H, d, *J*=7.5Hz), 7.83 (1H, dd, J_1=J_2=8.0Hz), 7.63 (1H, d, *J*=8.5Hz), 7.51 (1H, dd, J_1=J_2=8.0Hz), 7.40 (1H, d, *J*=7.5Hz), 7.24 (1H, d, *J*=7.5Hz), 7.18 (1H, dd, J_1=J_2=7.5Hz), 7.11 (1H, dd, J_1=J_2=7.5Hz), 5.03 (2H, s), 2.57 (3H, s), 2.26 (3H, s); ^{13}C-NMR (DMSO) δ: 166.1 (s), 161.7 (s), 155.9 (s), 147.6 (s), 136.2 (s), 135.0 (s), 132.4 (s), 130.9 (s), 127.1 (s), 126.8 (s), 126.7 (s), 126.5 (s), 126.0 (s), 125.5 (s), 120.2 (s), 47.0 (s), 23.4 (s), 18.3 (s); IR (ν, cm^{-1}): 3246 (NH), 3059 (C-H aromatic), 2947 (C-H aliphatic), 1682, 1653 (C=O), 1599, 1539 (C=N, C=C aromatic); HR-ESI-MS *m*/*z*: 330.1218 ([M+Na]$^+$, Calcd for $C_{18}H_{17}N_3NaO_2$: 330.1218).

2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-phenylacetamide (***4h***): Yield: 80 %. Mp: 261-262 °C; ^{1}H-NMR (DMSO) δ: 10.48 (1H, s), 8.10 (1H, d, *J*=8.0Hz), 7.83 (1H, dd, J_1=J_2=8.0Hz), 7.64 (1H, d, *J*=8.0Hz), 7.60 (2H, d, *J*=7.5Hz), 7.51 (1H, dd, J_1=J_2=7.5Hz), 7.33 (2H, dd, J_1=J_2=7.0Hz), 7.08 (1H, dd, J_1=J_2=8.0Hz), 4.98 (2H, s), 2.56 (3H, s); ^{13}C-NMR (DMSO) δ: 166.0 (s), 161.7 (s), 155.9 (s), 147.6 (s), 139.1 (s), 135.0 (s), 129.3 (s), 127.1 (s), 126.9 (s), 126.6 (s), 124.1 (s), 120.1 (s), 119.6 (s), 47.4 (s), 23.4 (s); IR (ν, cm^{-1}): 3279 (NH), 2970 (C-H aliphatic), 1684, 1651 (C=O), 1595, 1549 (C=N, C=C aromatic); HR-ESI-MS *m*/*z*: 294.1269 ([M+H]$^+$, Calcd for $C_{17}H_{16}N_3O_2$: 294.1243).

2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-(4-nitrophenyl)acetamide (***4i***): Yield: 76 %. Mp: 297-298 °C. ^{1}H-NMR (DMSO) δ: 11.09 (1H, s), 8.25 (2H, d, *J*=9.0Hz), 8.10 (1H, d, *J*=9.0Hz), 7.85 (2H, d, *J*=9.0Hz), 7.84 (1H, dd, J_1=J_2=9.0Hz), 7.64 (1H, d, *J*=8.5Hz), 7.52 (1H, dd, J_1=J_2=7.5Hz), 5.04 (2H, s), 2.57 (3H, s); ^{13}C-NMR (DMSO) δ: 167.2 (s), 161.7 (s), 155.8 (s), 147.6 (s), 145.2 (s), 143.0 (s), 135.1 (s), 127.1 (s), 126.9 (s), 126.6 (s), 125.6 (s), 120.0 (s), 119.5 (s), 47.8 (s), 23.5 (s); IR (ν, cm^{-1}): 3283 (NH), 3092 (C-H aromatic), 1694, 1641 (C=O), 1589, 1570 (C=N, C=C aromatic), 1497, 1470 (NO_2); HR-ESI-MS *m*/*z*: 339.1107 ([M+H]$^+$, Calcd for $C_{17}H_{15}N_4O_4$: 339.1093).

2.3. Biological evaluation

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2.3.1. Mosquito larvicidal assay

Adults from wild *Ae. aegypti* larvae were maintained under laboratory conditions (at 25 ± 2 °C, 65–75% relative humidity and a 12:12 h light:dark cycle) at Duy Tan University. The larvae of the following generations were used to evaluate larvicidal activity. The larvicidal activities were performed according to our previous descriptions [15,16]. Twenty larvae were transferred into 250-mL beakers containing 150 mL of test solution at concentrations of 100, 75, 50, 25, 12.5, 6.25, 3.125 and 1.5625 µg/mL, each concentration was repeated four times. DMSO (Merck) was used to dissolve the pure compounds, permethrin was used as a positive control, a 150-mL solution containing 1 mL of DMSO was used as a negative control. Mortality was recorded after 24 h, 48 h, 72 h and 96 h of exposure.

2.3.2. *Diplonychus rusticus* insecticidal ass**ay**

Adults of *D. rusticus* were collected in the field and identified by Dr. Nguyen Huy Hung which maintained as previously described [17]. Common water hyacinth plants (*Eichhornia crassipes* (Mart.) Solms) were released into tanks to provide shelter for *D. rusticus*. The twenty insects were screened against pure compounds at concentration of 25 µg/mL, four replicates, and mortality recorded after 24 h and 48 h exposure.

2.3.3. Acetylcholinesterase (AChE) inhibition assay

Acetylcholinesterase (AChE) inhibitory activity of essential oil was performed according to the method described by Ellman and our previous study [18,19]. The stock solution was obtained by dissolving the essential oil in DMSO (Merck), which was then diluted with H_2O (deionized distilled water) to obtain different experimental concentrations. Each solution mixture consisted of 140 µL of phosphate buffer solution (pH: 8), 20 µL of test compound solutions at concentrations of 500, 100, 20, and 4 µg/mL) and 20 µL of the electric eel (Electrophorus electricus) AChE (0.25 IU/mL). The reaction mixtures were transferred to the test wells of a 96-well microtiter plate and incubated at 25 °C for 15 min. Then, solutions of 10 µL dithiobisnitrobenzoic acid (DTNB, 2.5 mM) and 10 µL acetylthiocholine iodide (ACTI, 2.5 mM) were added to each of the test wells and incubation continued for 10 min at 25 °C. At the end of the experiment, the absorbance of each solution was measured at 405 nm. Galantamine was used as a positive control. The negative control well did not contain the test sample. Each test was carried out in triplicate.

2.3.4. Molecular docking

Molecular docking of the *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide compounds was carried out as previously described [18]. The structures of the compounds were assembled using Spartan '18 for Windows, v 1.4.4 (Wavefunction, Inc.). Molecular docking was carried out using Molegro Virtual Docker v 6.0.1 (Molegro ApS). A total of 17 relevant *Ae. Aegytpi* protein targets were used for the molecular docking. Twelve protein targets were obtained from the Protein Data Bank (PDB): arylalkylamine *N*-acetyltransferase, 4FD4, 4FD5, and 4FD6; carboxylesterase, 5W1U; D7 salivary protein, 3BKS and 3DXL; glutathione *S*-transferase, 5FT3; odorant binding protein, 3K1E, 3OGN, 6OII, 6OMW, 6OPB, and 6P2E; and sterol carrier protein-2, 2QZT. Five *Ae. aegypti* target proteins were prepared by homology modeling (see below): acetylcholinesterase (AChE, based on PDB structures 1DX4 and 1QO9), acetylcholine receptor (AChR, based on 7EKP), angiotensin converting enzyme 2 (ACE2, based on 6S1Y), and carboxylesterase 5A (CBEB5A, based on 4FNM). The orientations of the ligands with the target proteins were ranked based on the MolDock "rerank" energy values (E_{dock}) and then corrected to account for the bias due to molecular weight to give normalized docking scores (DS_{norm}).[19)]

2.3.5. Homology Modeling

Homology models of the *Ae. aegypti* proteins AChE, AChR, ACE2, and CBEB5A were created using the SWISS MODEL server (https://swissmodel.expasy.org/). Appropriate protein target sequences were obtained from UniProt

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Knowledgebase (UniProtKB, https://beta.uniprot.org/). Three-dimensional structural models were obtained based on multiple-threading alignments; the global model quality estimation was used to rank models (Table 1).

Table 1. *Aedes aegypti* protein target structures from homology modeling.

Ae. aegypti protein target	Target sequence (UniProt ID)	Template PDB structure	Sequence identity	Global Model Quality Estimation (GMQE)
Acetylcholinesterase (AChE)	Q9TX11	1QO9	68.96%	0.78
	Q9TX11	1DX4	69.96%	0.79
Acetylcholine receptor (AChR)	A0A6I8T9N7	7EKP	42.17%	0.60
Angiotensin converting enzyme 2 (ACE2)	A0A1S4G6D0	6S1Y	71.43%	0.93
Carboxylesterase 5A (CBEB5A)	Q17G39	4FNM	31.26%	0.64

2.3.6. Data analysis

Lethality data were subjected to log-probit analysis [20] to obtain LC_{50} values, LC_{90} values and 95 % confidence limits using Minitab® version 19.2020.1 (Minitab, LLC, State College, PA, USA).

3. Results and Discussion

3.1. Chemistry

2-Methylquinazolin-4(3*H*)-one (**2**) was prepared according to reported methods [21]. The affording products showed similarity in both melting point and spectral characteristics including IR [21] and ^{1}HNMR [22] with those reported for the corresponding compounds in the literature (**Table S1**).

The procedure described in the literature was applied to the synthesis of *N*-aryl-2-chloroacetamide compounds (**3a-i**) [23]. Accordingly, a defined aromatic amine reacted with chloroacetyl chloride in the presence of sodium acetate to obtain the corresponding acetamides. The structures of the products produced were confirmed by comparing their melting point with those reported for the corresponding *N*-aryl-2-chloroacetamides in the literature [23].

In alkaline media, (**2**) in the role of a nucleophilic agent, attacks the 2-chloroacetamide molecules (**3a-i**), substitutes to the chlorine atom to form the corresponding *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide compounds (**4a-i**). Acetone is used as an aprotic solvent to facilitate these S_N2 reactions. The HR-MS spectra of the products (**4a-i**) showed pseudomolecular ion peaks $[M+H]^+$ ($[M+Na]^+$ for compound **4g**) in agreement with their molecular formulas. In the IR spectra of compounds (**4a-i**), in addition to the absorption peak of the C=O group in the quinazolin-4-one ring around 1641-1667 cm^{-1}, the appearance of a new band around 1670-1694 cm^{-1} indicated the presence of the C=O group in the acetamide group. The N-H bond in the acetamide group absorbs at a lower frequency (3204-3318 cm^{-1}) than that of the N-H bond in the original 2-methylquinazolin-4(3*H*)-one molecule (3404 cm^{-1}). In the ^{1}H-NMR spectra, the signal of the N-H proton in the acetamide group of the compounds (**4a-i**) is also upfield shifted (9.83-11.09 ppm) in comparison to the signal of the N-H proton in the molecule of the original compound (**2**) (12.19 ppm). Compared with the ^{1}H-NMR spectrum and the ^{13}C-NMR spectrum of compound (**2**), the remarkableness in the ^{1}H-NMR and ^{13}C-NMR spectra of compounds (**4a-i**) is an appearance of a signal in the aliphatic region (around 4.95-5.08 ppm in the ^{1}H-NMR spectra and around 47.0-47.8 ppm in the ^{13}C-NMR spectra). These

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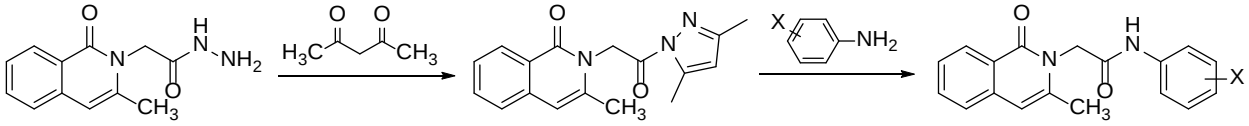
signals correspond to those of protons and carbon in the methylene group. Moreover, additional signals corresponding to the protons and carbons in the *N*-aryl groups also appear in the aromatic region of the spectra.

N-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide compounds were synthesized by Zotta et al. [24,25] according to the synthetic pathway below:



(X = H, 4-Br, 2-Cl, 2-CH_3, 3-CH_3, 4-CH_3, 2-OCH_3, 3-OCH_3, 4-OCH_3, 2-OC_2H_5, 3-OC_2H_5, 4-OC_2H_5, 2-NO_2, 3-NO_2, 4-NO_2).

Obviously, this method is more complicated than the one we introduce in this work because hydrazide (the starting material for this process) also needs to be synthesized from 2-methylquinazolin-4(3*H*)-one (**2**) by hydrazination of the ester obtained in the reaction of (**2**) and ethyl chloroacetate. Therefore, a four-step process is required to synthesize the products from 2-methylquinazolin-4(3*H*)-one. Besides that, the characteristic of NMR and MS spectra of the *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamides have not been fully described in the work of Zotta et al.

3.2. Biological activity

All the acetamide compounds (**4a-i**) containing 2-methyl-3,4-dihydroquinazolin-4-one heterocycle were evaluated for their potential activity against *Ae. aegypti* mosquito larvae and adults of *D. rusticus*. Except for the two compounds **4g** and **4i** which were insoluble, compound **4h** showed weak activity, meanwhile, all other compounds showed excellent larvicidal activities with LC_{50} values at 72 h of exposure varying between 2.085-4.201 µg/mL. (Table 2).

Table 2. *Aedes aegypti* larvicidal activity of oxoquinazolines.

Compound	LC_{50}	LC_{90}	χ^2	*p*
4a	24-h			
	5.819 (5.358-6.391)	8.528 (7.729-9.730)	1.57	0.456
	48-h			
	3.663 (3.271-4.078)	6.396 (5.755-7.334)	0.00144	0.999
	72-h			
	2.261 (1.723-2.693)	5.273 (4.620-6.340)	4.02	0.134
	96-h			
	1.486 (0.704-1.984)	4.470 (3.864-5.530)	0.953	0.621
4b	24-h			
	12.68 (11.32-14.16)	31.11 (26.90-37.20)	19.71	0.001
	48-h			
	3.642 (3.270-4.042)	7.610 (6.607-9.160)	5.76	0.218
	72-h			
	3.476 (3.134-3.846)	6.945 (6.055-8.327)	4.21	0.379
	96-h			
	a	a		
4c	24-h			

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	15.06 (12.70-18.02)	b	10.20	0.017
	48-h			
	10.11 (8.10-12.38)	b	7.37	0.061
	72-h			
	4.423 (2.770-6.030)	b	3.78	0.286
	96-h			
	1.799 (0.574-3.188)	b	2.59	0.459
4d	24-h			
	52.38 (36.87-88.24)	b	14.79	0.005
	48-h			
	22.73 (16.39-35.22)	b	11.40	0.022
	72-h			
	4.201 (1.867-6.900)	b	5.59	0.232
	96-h			
	c	c		
4e	24-h			
	9.252 (8.156-10.562)	25.81 (21.16-33.50)	5.66	0.129
	48-h			
	4.274 (3.643-4.966)	16.26 (12.95-22.06)	7.96	0.047
	72-h			
	2.756 (2.219-3.294)	12.27 (9.67-17.09)	7.77	0.051
	96-h			
	1.280 (0.801-1.729)	7.414 (5.780-10.598)	1.83	0.609
4f	24-h			
	8.671 (7.863-9.617)	14.67 (13.22-16.69)	4.22	0.239
	48-h			
	5.921 (4.944-6.924)	14.33 (12.51-17.09)	1.03	0.795
	72-h			
	2.085 (0.418-3.258)	11.29 (9.56-14.17)	0.816	0.846
	96-h			
	a	a		
4g	Not Soluble			
4h	> 50 (96-h)	> 50 (96-h)	d	d
4i	Not Soluble			
Permethrin	24-h 0.000643 (0.000551–0.000753)	24-h 0.00246 (0.00192–0.00344)	4.64	0.031

[a] LC_{50} and LC_{90} not reliable; > 50% lethality at the lowest concentration.

[b] LC_{90} values not reliable; < 90% lethality at the highest concentration.

[c] Lethality too flat across the different concentrations; not dose-dependent.

[d] Not defined.

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Table 3. AChE inhibitory activities of oxoquinazolines

Concentration (μg/mL)	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**
250	48.46	72.94	97.84	70.27	nt	98.92	73.11	nt	75.60
100	28.64	34.72	56.54	36.55	nt	62.78	34.64	nt	35.55
20	13.99	26.64	29.31	19.23	nt	34.22	13.41	nt	6.08
4	3.75	18.15	15.40	7.58	nt	17.65	-1.33	nt	2.50
IC_{50}	265.77	163.89	75.64	151.50	nt	57.03	150.14	nt	153.64

nt: Not tested.

Several previous studies have shown that quinazolin-4(3*H*)-one derivatives exhibit potent insecticide activity. The 3-[(2-chloroquinolin-3-yl)methyl]quinazolin-4(3*H*)-ones have shown promising larvicidal activity against *Chironomus tentans* with LC_{50} values between 60 and 90 μg/mL [24]. All quinazolin4(3*H*)-one derivatives synthesized by Anil exhibited potent insecticidal activity against *Periplanata americana* with knockdown time in range of 6.5-22 h at 5 g/L [25]. Four 3-[4(3*H*)-quinazolinone-2-yl)thiomethyl]-1,2,4-triazole-5-thiol compounds were active against adults of *Chrysornyia albiceps* equivalent to malathion with LD_{50} from 2.20 to 4.20 μg/mL for males and from 4.20 to 5.20 μg/mL for females, but they did show weak activity against the larval state [26]. The 2-(substituted phenyl)-2,3-dihydroquinazolin-4(1*H*)-ones derivatives showed larvicidal activity comparable to temephos against *Anopheles arabiensis*, mortality rates ranged from 43 to 93% at 4 μg/mL after 48 h of exposure [27]. Most of the 2,3-dihydroquinazolin-4(1*H*)-one derivatives demonstrated moderate to high insecticidal activity against *Mythimna separata*, particularly 2-(3-bromo-1-(3-chloropyridine-)-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3,8-dimethyl-2,3-dihydroquinazolin-4(1*H*)-one showed 80% mortality at 5 μg/mL concentration [28]. A series of 6,8-dichloroquinazoline derivatives bearing a sulfide group showed good insecticidal activities against *Plutella xylostella*, among them, compound 6,8-dichloro-4-(((6-chloropyridine-3-yl)methyl)thio)quinazoline has shown a mortality rate of 85% at 500 μg/mL [29]. The quinazoline derivatives containing 1,1-dichloropropene moiety displayed good insecticidal activities against *Prodenia litura* equivalent to positive control pyridalyl [30]. The compound methyl 4-(4-chlorophenyl)-8-iodo-2-methyl-6-oxo-1,6-dihydro-4*H*-pyrimido[2,1-*b*]quinazoline-3-carboxylate exhibited larvicidal activity against *An. arabiensis* was significantly stronger than temephos [31].

The mechanism of the mosquito larvicidal activities of 2-methylquinazolin-4(3*H*)-one derivatives may be due to their effects on the central nervous system. Quinazolinone derivatives have been reported to exhibit anticonvulsant property [32–35]. Several thiadiazolyl and thiazolidinonyl quinazolin-4(3*H*)-ones derivatives exhibited anticonvulsant activity when compared with positive controls [33]. Several 3-substituted-2-(substituted-phenoxymethyl) quinazolin-4(3*H*)-one derivatives have demonstrated significant anticonvulsant activity [37]. Previously 2-methyl-3-(*o*-tolyl)-4(3*H*)-quinazolone (methaqualone) was used for sedation and sleep induction [38]. Derivatives bearing a substituted 1,3,4-thiadiazole may showed inhibitory activity on AChE enzyme [38]. However, screening of compounds **4a-i** for inhibition of electric eel (*Electrophorus electricus*) AChE only displayed the median inhibitory activities (IC_{50}) ranged from 57 to 266 μg/mL. It may be that *Ae. aegypti* AchE will show better inhbition, but this enzyme was not available to us.

3.3. Molecular docking

In order to provide some insight into the possible mechanism of activity of the 2-methylquinazolin-4(3*H*)-one derivatives, an *in silico* molecular docking analysis was carried out using relevant *Aedes aegypti* protein targets available from the Protein Data Bank (PDB) or prepared by homology modeling. These protein targets include acetylcholinesterase (AChE, homology models based on *Drosophila melanogaster* AChE, PDB 1DX4 and 1QO9);

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acetylcholine receptor (AChR, homology model based on human alpha 7 nicotinic acetylcholine receptor PDB 7EKP); angiotensin-converting enzyme (ACE2, homology model based on *Anopheles gambiae* ACE2, PDB 6S1Y); arylalkylamine *N*-acetyltransferase (aaNAT, PDB 4FD4, 4FD5, and 4FD6); carboxylesterase (CBEB5A, homology model based on *Lucilia cuprina* alpha esterase 7, PDB 4FNM); D7 salivary protein (D7SP, PDB 3BKS and 3DXL); glutathione *S*-transferase (GSTe2, PDB 5FT3); odorant binding protein (OBP, PDB 3K1E, 6OII, 6OMW, 6OPB, and 6P2E); and sterol carrier protein-2 (SCP2, PDB 2QZT). The docking scores are listed in supplementary (**Table S2**).

There were three protein targets that showed preferential docking scores, acetylcholine receptor (AChR), acetylcholinesterase (AChE), and odorant binding protein (OBP). The lowest docking scores (most exothermic) and key intermolecular contacts are summarized in Table 3. In the acetylcholine receptor, the ligands preferentially dock into a binding site formed between two adjacent monomeric proteins of the pentameric structure. The binding site is a hydrophobic pocket flanked by Tyr200, Trp75, and Asp198 of one monomer and Glu149, Phe163, Phe147, and Cys148 of the adjacent monomer. Additional hydrogen-bonding is provided by Gln59 of one monomer and Asn114 and Lys165 of the adjacent monomer (see Table 3).

Table 4. Lowest-energy docking scores and key intermolecular contacts of *N*-aryl-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetamide derivatives with *Aedes aegypti* acetylcholine receptor, acetylcholinesterase, and odorant binding protein.

Compound	DS_{norm}	Interacting protein residues
		Ae. aegypti AChR PDB (7EKP)
4a	-109.4	Tyr200 (face-to-face π-π), Phe147 (hydrophobic), Asn114 (hydrophobic), Glu149 (hydrophobic), Phe163 (hydrophobic), Gln59 (H-bond), Cys148 (hydrophobic), Tyr113 (edge-to-face π-π)
4b	-113.0	Tyr200 (face-to-face π-π), Asn114 (H-bond), Phe147 (hydrophobic), Trp75 (face-to-face π-π), Asp198 (hydrophobic), Gln59 (H-bond)
4c	-112.2	Tyr200 (face-to-face π-π), Asn114 (H-bond), Trp75 (face-to-face π-π), Phe147 (hydrophobic), Asp198 (hydrophobic), Gln59 (H-bond)
4d	-115.9	Tyr200 (face-to-face π-π), Trp75 (face-to-face π-π), Asp198 (hydrophobic), Asn114 (hydrophobic), Tyr113 (edge-to-face π-π), Phe147 (hydrophobic), Lys165 (H-bond)
4e	-118.3	Tyr200 (face-to-face π-π), Phe147 (edge-to-face π-π), Trp75 (face-to-face π-π), Asp198 (hydrophobic), Asn114 (hydrophobic), Gln59 (H-bond)
4f	-118.4	Tyr200 (face-to-face π-π), Phe147 (hydrophobic, H-bond), Asn114 (hydrophobic), Glu149 (hydrophobic), Phe163 (hydrophobic), Cys148 (hydrophobic), Gln59 (H-bond)
4g	-115.2	Tyr200 (face-to-face π-π), Phe147 (hydrophobic), Asn114 (hydrophobic), Trp75 (face-to-face π-π), Tyr113 (hydrophobic), Asp198 (hydrophobic), Ser58 (H-bond)
4h	-106.9	Tyr200 (face-to-face π-π), Asn114 (hydrophobic), Glu149 (hydrophobic), Phe147 (hydrophobic), Gln59 (H-bond)
4i	-119.4	Tyr200 (face-to-face π-π), Glu149 (H-bond), Trp75 (face-to-face π-π), Asp198 (hydrophobic), Phe163 (hydrophobic), Tyr113 (hydrophobic), Phe147 (hydrophobic), Cys148 (hydrophobic), Lys165 (H-bond)

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		Ae. aegypti AChE PDB (1DX4)
4a	-106.9	Trp111 (face-to-face π-π), Tyr390 (face-to-face π-π), His501 (hydrophobic), Ser258 (H-bond)
4b	-110.1	Tyr390 (face-to-face π-π), Trp111 (face-to-face π-π), His501 (hydrophobic), Phe391 (edge-to-face π-π), Gly173 (hydrophobic), Trp291 (edge-to-face π-π), Ser258 (H-bond)
4c	-111.1	Tyr390 (face-to-face π-π), Trp111 (face-to-face π-π), His501 (hydrophobic), Trp291 (edge-to-face π-π), Phe391 (edge-to-face π-π), Ser258 (H-bond)
4d	-112.8	Tyr390 (face-to-face π-π), Trp111 (face-to-face π-π), His501 (hydrophobic), Trp291 (edge-to-face π-π), Phe391 (edge-to-face π-π), Ser258 (H-bond)
4e	-116.2	Trp111 (face-to-face π-π), Tyr390 (face-to-face π-π), His501 (hydrophobic, H-bond), Phe391 (edge-to-face π-π), Ser258 (H-bond)
4f	-114.4	Tyr390 (face-to-face π-π), Trp111 (face-to-face π-π), His501 (hydrophobic), Phe391 (edge-to-face π-π), Gly173 (hydrophobic), Ser258 (H-bond)
4g	-117.1	Trp111 (face-to-face π-π), Tyr390 (face-to-face π-π), Gly173 (hydrophobic), Glu108 (hydrophobic), Phe391 (edge-to-face π-π), Ser258 (H-bond)
4h	-114.8	Trp111 (face-to-face π-π), Tyr390 (face-to-face π-π), Gly173 (hydrophobic), Phe391 (edge-to-face π-π), Glu108 (hydrophobic), Ser258 (H-bond)
4i	-121.8	Tyr390 (face-to-face π-π), Trp111 (face-to-face π-π), His501 (hydrophobic), Phe391 (edge-to-face π-π), Gly173 (hydrophobic), Ser258 (H-bond)
		Ae. aegypti OBP PDB 6OMW
4a	-105.4	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Phe51 (hydrophobic), Ile116 (hydrophobic), Gly104 (hydrophobic)
4b	-111.0	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Phe51 (hydrophobic), Ile116 (hydrophobic), Gly104 (hydrophobic)
4c	-110.6	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Gly104 (hydrophobic)
4d	-106.4	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Pro63 (hydrophobic), Phe51 (hydrophobic), Ile116 (hydrophobic)
4e	-113.2	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Phe51 (hydrophobic), Gly104 (hydrophobic), Ile116 (hydrophobic)
4f	-114.8	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Phe51 (hydrophobic), Ile116 (hydrophobic), Gly104 (hydrophobic)
4g	-111.5	Leu68 (hydrophobic), Phe108 (hydrophobic), Gly104 (hydrophobic), Phe105 (hydrophobic)
4h	-116.3	Phe108 (hydrophobic), Leu68 (hydrophobic), Phe105 (hydrophobic), Gly104 (hydrophobic), Phe51 (hydrophobic)

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4i	-116.4	Leu68 (hydrophobic), Phe108 (hydrophobic), Gly104 (hydrophobic), Ile116 (hydrophobic), Phe105 (hydrophobic), Leu72 (hydrophobic)

In the acetylcholinesterase, the ligands dock into the binding site of the enzyme, with the *N*-arylacetamide groups sandwiched in a π-π sandwich formed by Tyr390 and Trp11 and the quinazolinone moiety in a hydrophobic pocket formed by His501, Phe391, and Gly173 (see Figure 1).

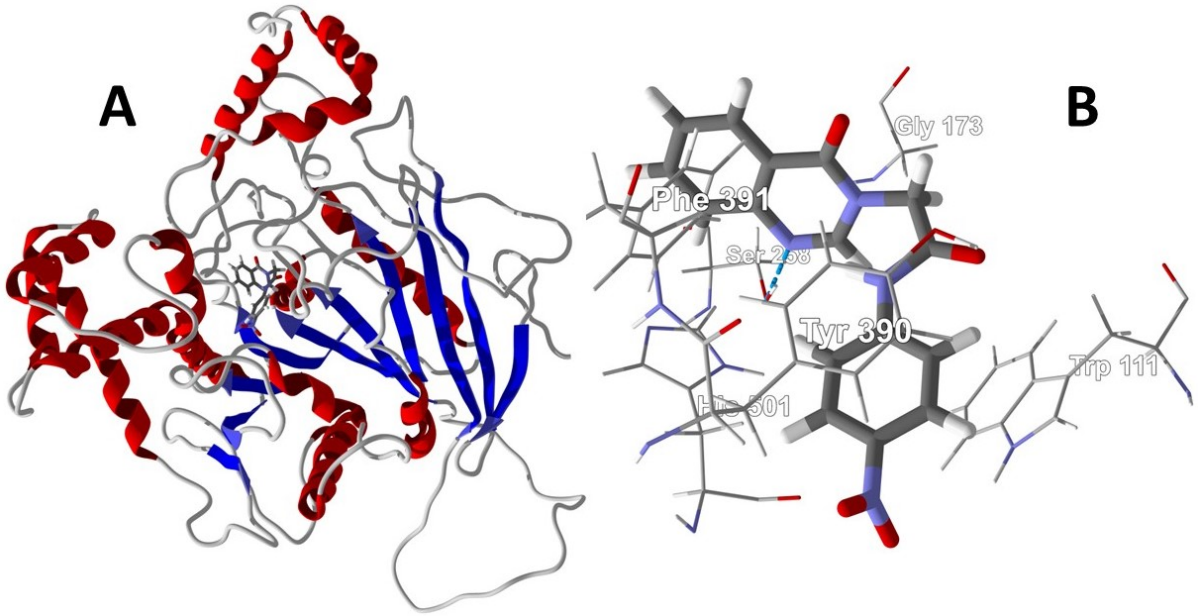

Figure 1. Lowest-energy docked pose of 4i with *Aedes aegypti* acetylcholinesterase (homology model based on *Drosophila melanogaster* AChE, PDB 1DX4). A: Ribbon structure of the protein with the docked ligand (CPK stick figure). B: Key intermolecular interactions between 4i and amino acid residues in the binding site; the hydrogen-bond is shown as a blue dashed line.

The binding pocket of *Ae. aegypti* OBP is surrounded by the hydrophobic residues Phe108, Leu68, Phe105, Phe51, and Ile116, and the *N*-aryl-2-(2-methylquinazolin-4(3*H*)-yl)acetamides all docked in this hydrophobic pocket (see Figure 2).

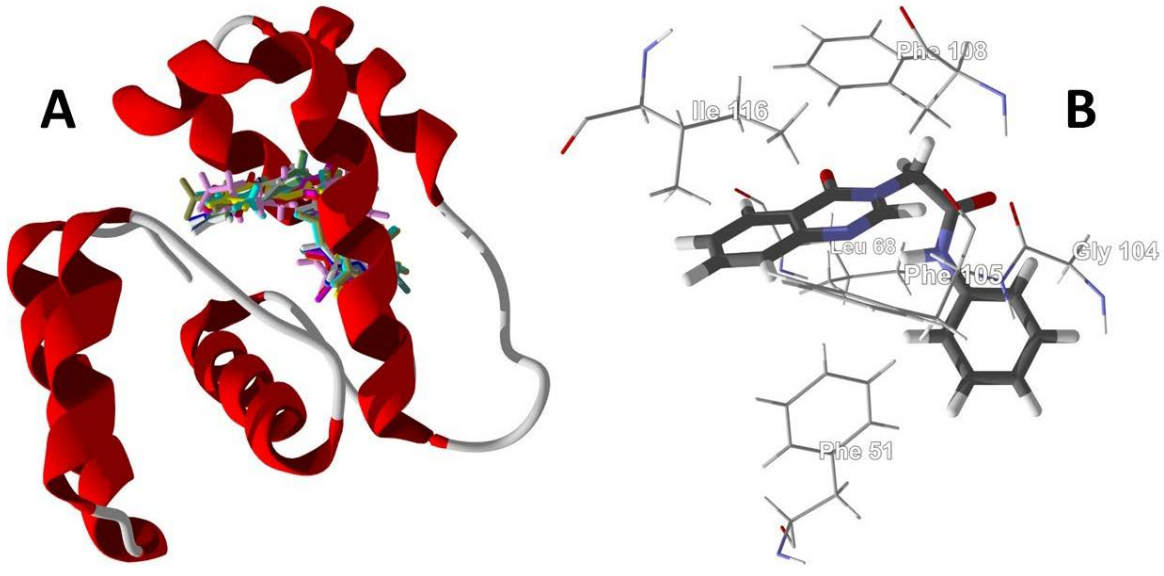

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Figure 2. Lowest-energy docked pose of **4h** with *Aedes aegypti* odorant binding protein (PDB 6OMW). **A:** Ribbon structure of the protein with the docked ligands (colored stick figures). **B:** Key intermolecular interactions between **4h** and amino acid residues in the hydrophobic binding site.

4. Conclusions

In this present work, nine compounds *N*-aryl-2-(2-methylquinazolin-4(3*H*)-yl)acetamides (**4a-i**) were successfully synthesized, and their structure were determined by IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS spectral analysis. This investigation also indicated that the acetamide compounds (**4a-i**) exhibited excellent activities against *Ae. aegypti* mosquito larvae. Furthermore, none of the compounds showed toxicity to the non-target organism *D. rusticus* at 25 μg/mL, with mortality ranging from 0 to 3.75 %. Our results showed that the 2-methyl-3,4-dihydroquinazolin-4-one heterocyclic derivatives exhibited significant activity at 72 h of exposure. Additionally, molecular docking studies suggested that the acetylcholine receptor (AChR), acetylcholinesterase (AChE), and odorant binding protein (OBP) were potential targets of these compounds. However, screening of the compounds for AChE inhibition were not promising. Other, yet-to-be-defined targets may be involved. Nevertheless, based on these promising bioactivity results, follow-up semi-field and field-scale studies are encouraged to be performed to evaluate the residual activity of derivatives and follow-up AChR and OBP binding studies are needed to confirm the mechanism(s) of activity of these compounds.

Supplementary Materials:

The online version of this article contains supplementary materials.

Author Contributions:

Conceptualization, N.T.C. and W.N.S.; methodology, N.T.C., N.H.H., and W.N.S.; software, W.N.S.; validation, N.T.C., W.N.S. and P.C.K.; formal analysis, W.N.S. and P.C.K.; investigation, N.T.C., N.H.H, N.G.H., and N.T.T.G.; resources, N.T.C. and N.H.H.; data curation, N.T.C., W.N.S., and P.C.K.; writing—original draft preparation, N.T.C. and N.H.H.; writing—review and editing, W.N.S. and P.C.K.; visualization, N.H.H. and W.N.S.; supervision, N.T.C.; project administration, N.T.C.; funding acquisition, N.T.C. All authors have read and agreed to the published version of the manuscript.

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The IR, NMR and HR-MS spectral data used to support the findings of this study are included within the supplementary information file.

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Conflicts of Interest:

The authors declare that there is no conflict of interest regarding the publication of this paper.

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