Regiospecific Isomerization of 2-Benzoxazinon-2-yl Benzoic Acid Toward Some Nitrogen Nucleophiles as Environmental Insecticide

Maher A. El-Hashash, Sameh A. Rizk,* Abeer M. El-Naggar, and Mohamed G. El-Bana

Department of Organic Chemistry, Faculty of Science, Ain Shams University, Cairo, Egypt
*E-mail: samehrizk2006@gmail.com

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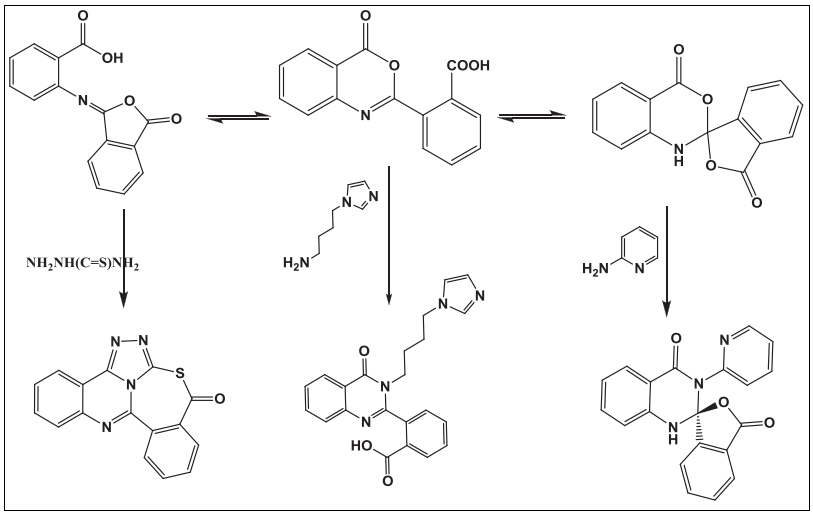

Based on the strategies of receptor structure-guided benzoxazinone design, a series of nitrogen nucleophiles such as benzyl amine, sodium azide, 4,4-bis o-toluidine, 4-butanolamine, glucosamine, 2-amino pyridine, 2-picolinyl amine, hydroxyl amine, and hydrazine derivatives, for example, hydrazine hydrate, semicarbazide, thiosemicarbazide, methylhydrazide, phenylhydrazide, could be reacted with 2-benzoxazine-2-yl benzoic acid **1**. According the basicity of nucleophiles, regiospecific isomerization of benzoxazinone has been considered through formation of the spiro derivatives. Organic reagents can be controlled on the course of reaction of benzoxazinonyl benzoic acid **1**. Preliminary bioassays indicated that the insecticidal spectra of the synthesized compounds were ecofriendly biodegradable materials due to isomerization. Among these analogues, the quinazoline **2**–**4** showed 100% mortality against *Nilaparvata lugens* (LC_{50} = 0.087 mg/L). The insecticidal potency of our designed analogues was dual-controlled by isomerization to quinazolinone and spiro derivatives that observed *in vitro* and shed light on the novel insecticidal mechanism. The chemical structure of the products can be confirmed by microanalytical, spectral data, optimized and stimulated by quantum chemical parameters.

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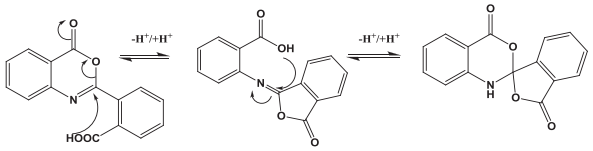
INTRODUCTION

Recently, benzoxazinonyl, benzofuranonyl benzoic acids, and spirobenzoxazinone **1** began to replace organophosphates, carbamates, and several other types of insecticides to control insect pests. Because of their efficient mode of action, they showed little cross-resistance to the conventional long-established insecticides, and they make up approximately one-fourth of the world insecticide market [1,2]. As potent agonists, they selectively act on the insect nicotinic acetylcholine receptors (nAChRs), that is, their molecular target site [3], low mammalian toxicity, broad insecticidal spectra, and good systemic properties [4–6]. However, the new mode of action, frequent applications in the field of pest control, and structural similarity among benzoxazinone isomers **1** have led to the acquisition of resistance and cross-resistance in a range of species such as *Plutella xylostella*, *Tetranychus cinnabarinus*, *Aphis medicaginis*, and *Nilaparvata lugens* [7–13]. Especially, the brown planthopper, *N. lugens*, a major rice pest in many parts of Asia, has developed strong resistance to imidacloprid [14]. As a result, development of new spiroquinazolinone with high insecticidal activities against resistance strains is highly desirable. It is well known that the structure optimization of benzoxazinone is one of the effective strategies to manage tactics [15–17].

These compounds have exhibited good insecticide activities against *N. lugens*. The structure–activity relationships implied that the different insecticidal potency was dual-controlled by the isomerization of benzoxazinone (Scheme 1) and the size of the groups [18]. In addition, the quantum chemical simulations revealed that the insecticidal potency depended greatly on

Scheme 1. Outline the isomerization of the 2-benzoxazinonyl benzoic acid according to attacking nitrogen nucleophiles.



the number of significant hydrogen bonds, which are formed by the benzoxazinonyl benzoic acid **1** and the amino acid residues of insect nAChRs [19,20]. In this context, it is very important to increase the number of significant hydrogen bonds between the benzoic acid analogues and the amino acid residues of insect nAChRs for the purpose of structure optimization or design. In order to increase the number of significant hydrogen bonds between the benzoic acid analogues and the amino acid residues of insect nAChRs, we inserted the peptide bond to the flexible groups arm of the quinazolinone, spiro compounds and their analogues **2**–**17**, designed and synthesized to introduce the organic segment is that it contains more electronegative atoms such as oxygen and nitrogen atoms, which can form more significant hydrogen bonds with the amino acid residues.

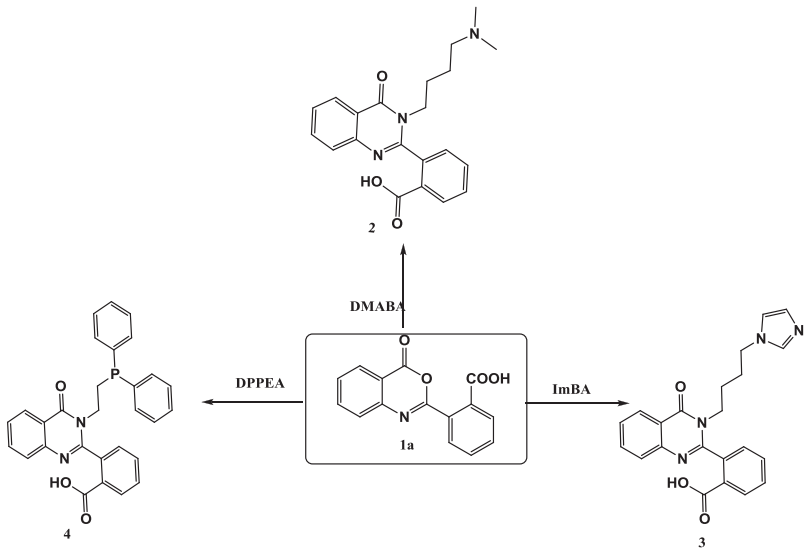
RESULTS AND DISCUSSION

Chemistry. Benzoxazinone **1** was synthesized [21] by the reaction of the anthranilic and/or iodoanthranilic acid with phthalic anhydride and was then converted to the intermediate of benzofuranone and spiro derivative [22] when it was reacted with a variety of substituted amine in ethanol [23] to afford the diverse compounds with regiospecific products. The behavior of benzoxazinone 1 with some nitrogen nucleophiles under microwave assisted method afforded the unexpected products via isomerization differ from the conventional synthetic method (Scheme 1).

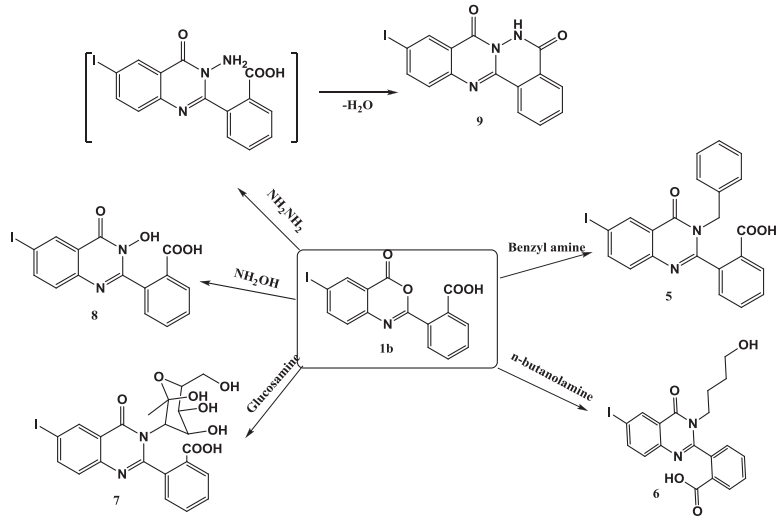
Reaction of the anthranilic and/or 3-iodoanthranilic acid with phthalic anhydride in boiling butanol, it afforded the corresponding anthranil that can be cyclized by using acetic anhydride to afford the 2-benzoxazinonyl benzoic acid **1**. *In situ*, the 2-benzoxazinonyl benzoic acid can be isomerized that depended upon the attacking nucleophiles. The regiospecific reaction of the organic nitrogen nucleophiles with the poly electrophilic sites of benzoxazinone **1** can be allowed to afford the new heterocyclic products. In the present work, reaction of the benzoxazinone and/or iodo-derivative **1** with some important amine derivatives afforded the corresponding quinazolinone derivatives and spiro compounds that rest on attacking position of the benzoxazinone moiety and type of nucleophile.

The behavior of the 2-benzoxazinonyl benzoic acid **1a** with some interesting nitrogen nucleophiles, for example, imidazolopentylamine, diphenylphosphinepentylamine, and dimethylaminopentylamine, afforded quinazolinone derivatives **2**–**4**, respectively, that having good insecticidal properties (Scheme 2). Furthermore, reaction of the 6-iodo-benzoxazinone **1b** with some important aliphatic amine, for example, benzylamine, 4-butanolamine, glucosamine, hydroxyl amine, and hydrazine hydrate, afforded the corresponding quinazolinone derivatives **5**–**9** (Scheme 3).

Scheme 2. Outline some reaction of the 2-benzoxazinonyl benzoic acid isomer 1a with interesting nitrogen nucleophiles.



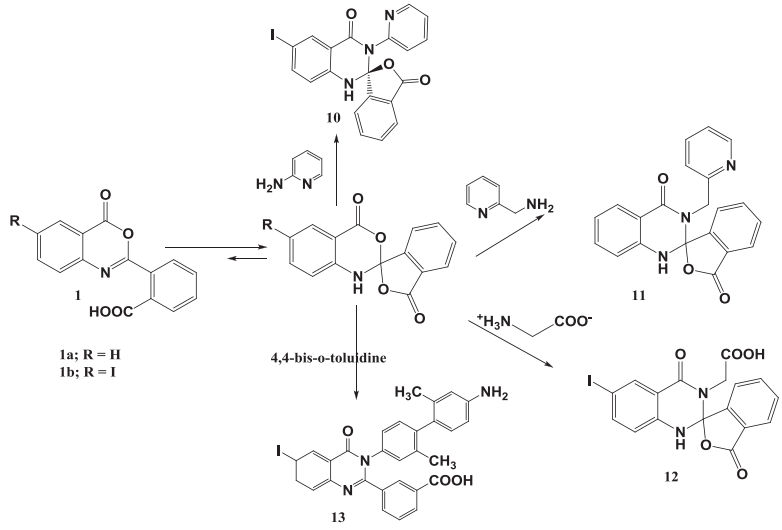
Scheme 3. Reaction of the benzoxazinonyl benzoic acid with aliphatic amine.



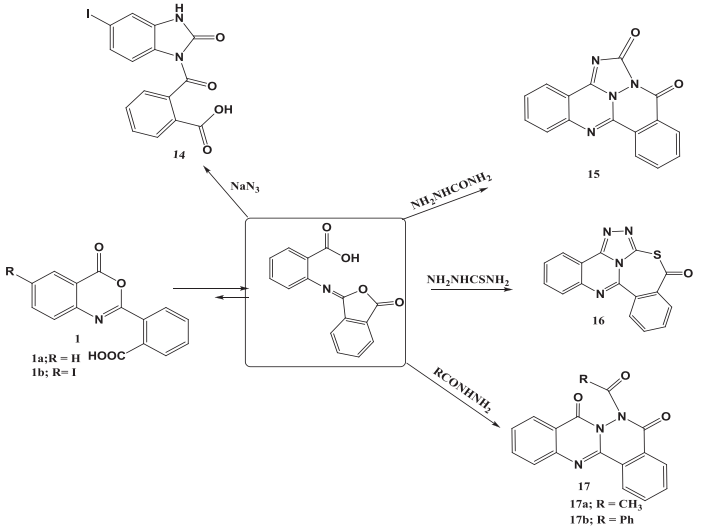
On the reaction of the 2-benzoxazinonyl benzoic acids **1** with 2-aminopyridine, 2-pinacolyl amine, glycine, and *p*-tolidine afforded other products not quinazolinones, IR spectra of the products reveal strong absorption bands at 1782–1794 cm^{-1} corresponding to the carbonyl groups of the furanone ring of the spiro derivatives. Also, quantum chemical parameter see more in Table S1 that indicate the stability of the spiro derivatives ΔE = 1.8 eV more than the corresponding quinazolinone ΔE = 4.2 eV in these case. The authors explained the unpredicted products due to the weak nucleophilicity and higher basicity of glycine and 2-pinacolyl amine, respectively, that enhanced percentage of the spiro isomer. So, when the 2-benzoxazinoyl benzoic acid and iodo derivative **1** were allowed to react with aminopyridine, 2-pinacolyl amine, glycine, and *p*-tolidine (4,4-bis-toliudine) afforded the spiro products **10**–**13** (Scheme 4).

Also, reaction of the benzoxazinonyl benzoic acids **1** with hydrazine hydrate derivatives, for example, semicarbazide, thiosemicarbazide, methylhydrazide, and phenylhydrazide, afforded unexpected heterocyclic products. When the benzoxazinonyl benzoic acid or iodo derivative **1** were allowed to react with sodium azide, methylhydrazide phenylhydrazide, semicarbazide, and thiosemicarbazide, it afforded benzimidazolone **14**, phthalazinoquinazolinone **15**, triazolo-phthalazinoquinazoline **16**, and triazolobenzothiazepinoquinazoline **17**, respectively, (Scheme 5). The mechanism of the carbazide and hydrazide with compound **1** can be illustrated via benzofuranonyl benzoic acid in the following Scheme 6. The low values of

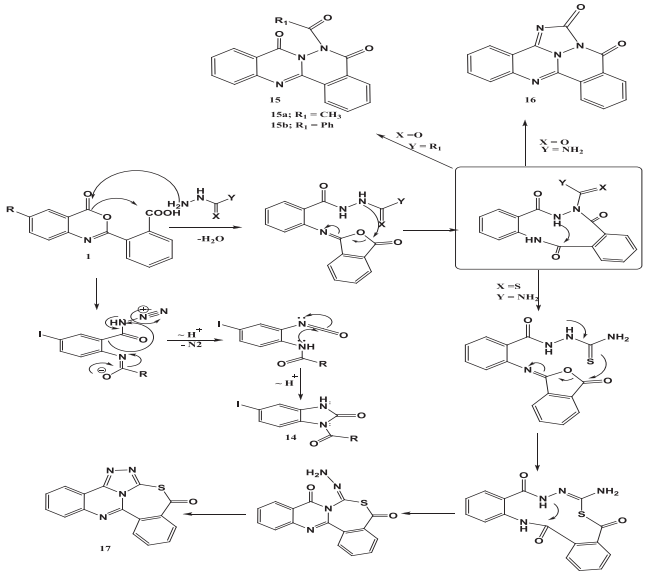
Scheme 4. Reaction of the benzoxazinonyl benzoic acid with glycine and pinacolyl amine via spiro isomer.



Scheme 5. Reaction of the benzoxazinonyl benzoic with hydrazine derivatives via benzofuranonyl benzoic acid.



Scheme 6. Outline the mechanistic equations of the products **14**–**17**.



the energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$) will render the stability of the synthesized compounds that confirmed by microanalytical and spectral data.

Insecticidal activity assay. The quantum chemical computation helped us to explain good inhibition efficiencies of the compounds as insecticidal agents, because the energy needed to remove an electron from the last occupied orbital will be low. The ΔE of a molecule is a measure of the hardness or softness of a molecule. Hard molecules are characterized by larger values of ΔE and vice versa. The linear correlation between E_{HOMO} energy level and the pesticide inhibition efficiency proved that the higher the HOMO energy (less negative values) of the insecticidal compounds, the greater the trend of offering electrons. The order of increasing E_{HOMO}, decreasing E_{LUMO} values, and the energy gap (ΔE) is directly proportional with increasing the inhibition efficiency [24,25]. The insecticidal activities of compounds **2**–**17** were measured against *N. lugens* and *A. medicagini* according to the standard test [26] with a slight modification (Fig. 1). The test analogues were dissolved in dimethylformamide and serially diluted with water containing Triton X-80 (0.1 mg/L) to obtain the required concentrations. The insects were reared at 25 (±1) °C, and groups were transferred to glass Petri dishes and sprayed with the aforementioned solutions using a Potter sprayer.

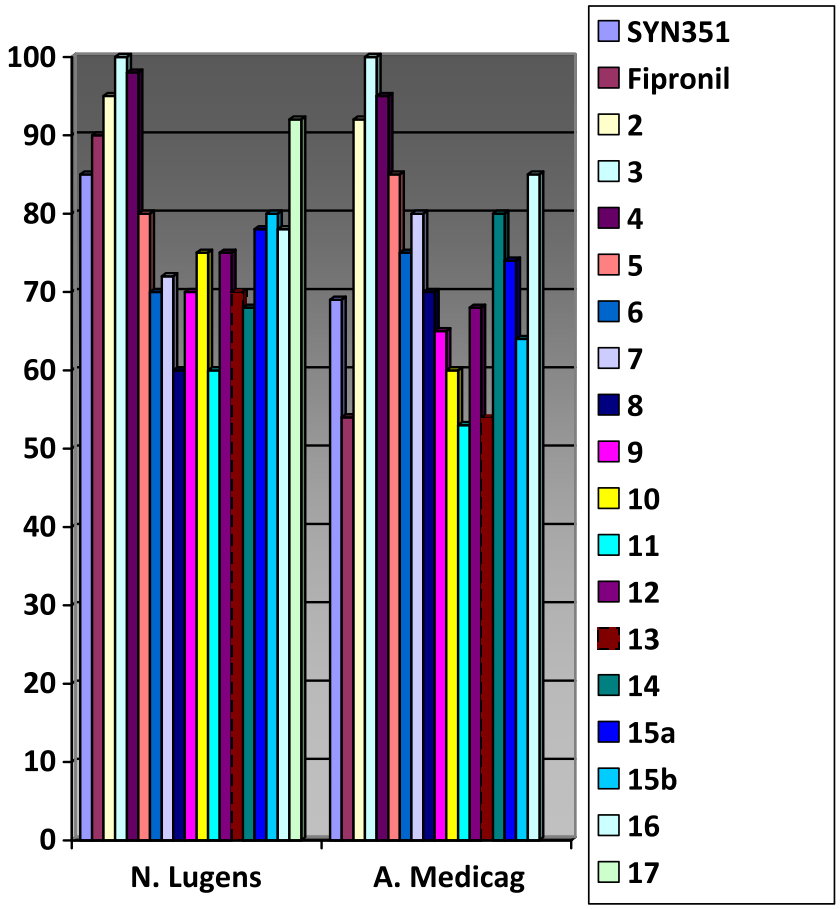


Figure 1. Insecticidal activities of quinazolinone and spiro derivatives (**2**–**17**) against *Nilaparvata lugens* and *Aphis medicagini* (a) LC_{50} = 0.163 mg/L; (b) LC_{50} = 0.129 mg/L. [Color figure can be viewed at wileyonlinelibrary.com]

Assessments were made after 72 h by the number and size of the live insects relative to those in the negative control, and evaluations are based on a percentage scale of 0–100. The mortality rates were subjected to probity analysis [27]. The reference compounds were fipronil and imidacloprid, while water containing Triton X-80 (0.1 mg/L) was used as a negative control. All experiments were carried out in three replicates for the purpose of statistic requirements. As expected, preliminary bioassays indicated that not only the insecticidal spectra of the target compounds were presented excellent insecticidal activities against *N. lugens* and *A. medicagini* at 100 mg/L. Among these analogues, **2**, **3**, and **4** showed approximately 100% mortality against *N. lugens* (LC_{50} = 0.087 mg/L) and 90% against *A. medicagini* at 4 mg/L. Their structure–activity relationships indicated that insecticide activities were dual-controlled by the size and species of the carbamate and thiocarbamate groups. The results showed that the active analogues exhibited significant hydrogen bonding interactions with the amino acid residues of insect nAChRs, where the peptide bonds displayed an important role dues of insect nAChRs, which may result in improving the insecticidal activities. The second reason is that peptides are involved in important physiological and biochemical function such as neuro transmission, neuro modulation, and act as hormones in receptor mediated signal transduction [28].

The increasing interests regarding the manifold actions of the bioactive peptides have made their structural studies an important aspect of research in pharmacology and medical sciences [29]. During drug development, identification of an "active" part of a large peptide is critical for further improving its pharmacology. New analogues, which may provide some useful information for future design of new insecticides to dramatically reduce reaction time, increase product yields and enhance product purities by reducing unwanted side reactions [30]. By analyzing the data, we found that all the designed analogues have better insecticidal performance than fipronil and SYN351 [30,31]. Most of our designed analogues exhibited excellent insecticide activities against *Nilaparvata lugen* and *A. medicagini* at 100 mg/L, while

the synthesized compounds had higher insecticidal activities against *Nilaparvata lugen* than *A. medicagini* at a lower dose. The LC_{50} value of compounds **2**, **3**, and **4** was 0.087 mg/L, which was more comparable with other quinazolinone and spiro compounds **5**–**17** (LC_{50} = 0.145–0.523 mg/L). The insecticidal activities showed significant differences with the change in the size of the groups R, for example, amine, hydroxy, glucoside, hydrazide, carbamate, and thiocarbamate, in the quinazolinone in position 3.

The insecticidal potency was improved because of exhibit significant hydrogen bonding interactions with the amino acid residues of insect nAChRs. Their insecticidal activities increased in the order: quinazolinone (**3**) > quinazolinone (**4**) > hydrazide (**15**) > hydroxide (**7**) > pyridazinone (**8**) > fipronil > spiro derivatives > SYN351.

EXPERIMENTAL

Materials and apparatus. Unless otherwise noted, reagents and solvents were of analytical reagent grade or were chemically pure and used as received without further purification. ^{1}H NMR spectrum ($CDCl_3$) was recorded on a Bruker AVANCE-400 MHz with tetramethylslane as an internal standard. Coupling constants (J values) are in Hertz. The IR spectra were obtained from KBr discs in the range of 4000–400 cm^{-1} on a Nicolet 5DXFT-IR spectrophotometer. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) that used the electron ionization technique at 70 eV. Combustion analyses for elemental composition were conducted on a Perkin-Elmer 2400 instrument. All microwave experiments were performed using a YL8023B1 microwave reactor possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz.

General procedure. ***General synthetic procedures for quinazoline and spiro derivatives 2–17.*** Add the organic base such as benzyl amine, *N*,*N*-dimethylaminopentylamine, imidazolopentylamine, diphenylphosphinopentylamine, n-butanol amine, glucosamine, 2-amino pyridine, 2-picolinyl amine, hydroxyl amine, sodium azide, and hydrazine hydrate derivatives, for example, hydrazine hydrate, semicarbazide, thiosemicarbazide, methylhydrazide, phenylhydrazide (1.2 mmol) was added dropwise to a stirred solution of 2-benzoxazinon-2yl-benzoic acids **1** (1.2 mmol) in EtOH (30 mL of each solvent) at room temperature and the progress of the reaction was tracked by TLC and was heated to 65°C for 15 min in a microwave reactor or stirred for 4 h at the temperature. The reaction mixture was concentrated under reduced pressure, and EtOH was evaporated under vacuum. The resulting crude was used in the next step without further purification. Methanol (10 mL) was added to the reaction mixture that was concentrated under reduced pressure, and the resulting solid products was filter off and recrystallized from proper solvent.

2-(3-(4-(Dimethylamino)butyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (2). Yellow crystal, yield 75%; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.94 (bs, 1H, COOH exchangeable by D_2O), 8.32 (d, *J* = 7.2 Hz, 2H, Ar_1-H), 8 .11 (d, *J* = 9.9 Hz, 2H, Ar_2-H), 7.82 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.68 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.13 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 3.82 (t, *J* = 7.3 Hz, 2H, N^1CH_2), 2.64 (t, *J* = 7.6 Hz, 2H, N^2CH_2), 2.50 (s, 6H, $N2(CH_3)_2$), 1.71–1.64 (m, 4H, CH_2CH_2). FTIR (KBr, cm^{-1}) ν_{max}: 3050 (ArCH), 2951, 2872 (AliCH), 1705, 1681 (C═O), 1251 ($\nu_{a\ (C–O)}$). *Anal*. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.04; H, 6.30; N, 11.50. Found: C, 69.04; H, 6.16; N, 11.10. EIMS ($M^{+\cdot}$) *m*/*z*: 365.

2-(3-(4-(1H-Imidazol-1-yl)butyl)-4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (3). Yellow crystal, yield 71%; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.99 (bs, 1H, COOH exchangeable by D_2O), 8.35 (d, *J* = 7.2 Hz, 2H, Ar_1-H), 8.21 (d, *J* = 9.9 Hz, 2H, Ar_2-H), 7.92 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.84 (d, *J* = 7.9 Hz, 1H, imidazole), 7.71 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.65 (dd, *J* = 7.9, 8.5 Hz, 1H, imidazole), 7.25 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 7.06 (d, *J* = 8.5 Hz, 1H, imidazole), 3.65 (t, *J* = 7.3 Hz, 2H, N^1CH_2), 2.71 (t, *J* = 7.6 Hz, 2H, N^2CH_2), 1.96 (m, 4H, CH_2CH_2). FTIR (KBr, cm^{-1}) ν_{max}: 3078, 2951, 2872, 1704, 1680 (C═O), 1302 ($\nu_{as\ C–O}$). *Anal*. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.04; H, 5.15; N, 14.43, Found: C, 67.88; H, 4.92; N, 14.19. EIMS ($M^{+\cdot}$) *m*/*z*: 388.

2-(3-(2-(Diphenylphosphanyl)ethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (4). Yellow crystal, yield 73%; ^{1}H NMR ($CDCl_3$, 400 MHz) 13.04 (bs, 1H, COOH exchangeable by D_2O), 8.33 (d, *J* = 7.2 Hz, 2H, Ar_1-H), 8.17 (d, *J* = 9.9 Hz, 2H, Ar_2-H), 7.90 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.84 (d, *J* = 7.7 Hz, 4H, P-Ar_3), 7.71 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.65 (d, *J* = 7.7 Hz, 2H, P-Ar_3), 7.25 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 7.06 (d, *J* = 7.7 Hz, 4H, P-Ar_3), 3.25 (t, *J* = 7.3 Hz, 2H, NCH_2), 1.71 (t, *J* = 7.6 Hz, 2H, PCH_2). FTIR (KBr, cm^{-1}) ν_{max}: 3072 (ArCH), 2952, 2873 (AliCH), 1709, 1671 (C═O), 1255 ($\nu_{a\ (C–O}$). *Anal*. Calcd for $C_{29}H_{23}N_2O_3P$: C, 72.95; H, 4.82; N, 5.87. Found: C, 72.60; H, 4.55; N, 5.56. EIMS ($M^{+\cdot}$) *m*/*z*: 477.

2-(3-Benzyl-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (5). Yellow crystal, yield 76.4%; ^{1}H NMR ($CDCl_3$, 400 MHz) 13.12 (bs, 1H, COOH exchangeable by D_2O), 8.34 (d, *J* = 2.2 Hz, 1H, Ar_1-H), 7.99 (d, *J* = 9.9 Hz, 2H, Ar_2-H), 7.71 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.51 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_3-H), 7.41 (d, *J* = 9.9 Hz, 2H, Ar_2-H), 7.22 (dd, *J* = 7.9, 3.2 Hz, 3H, Ar_3-H), 7.09 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 4.14 (q, *J* = 5.1 Hz, 2H, CH_2Ph). FTIR (KBr, cm^{-1}) ν_{max}: 3050 (Ar, CH), 2951, 2872 (Ali, CH), 1701, 1678 (C═O), 1251 ($\nu_{a\ (C–O)}$). *Anal*. Calcd for

$C_{22}H_{15}IN_2O_3$: C, 54.79; H, 3.14; N, 5.81. Found: C, 54.21; H, 2.88; N, 5.10. EIMS ($M^{+\cdot}$) *m*/*z*: 482.

2-(3-(4-Hydroxybutyl)-6-iodo-4-oxo-3,4-dihydro quinazolin-2-yl) benzoic acid (6). Colorless crystals, yield 65% yield as m. p. 106─108°C; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.94 (bs, 1H, COOH exchangeable by D_2O), 8.12 (d, *J* = 2.2 Hz, 1H, Ar_1-H), 8 .11 (d, *J* = 9.9 Hz, 2H, Ar_2-H), 7.80 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.58 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.23 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 5.50 (s, 1H, OH exchangeable by D_2O), 3.82 (t, *J* = 7.3 Hz, 2H, OCH_2), 2.64 (t, *J* = 7.6 Hz, 2H, NCH_2), 1.71–1.64 (m, 4H, CH_2CH_2). FTIR (KBr, cm^{-1}) ν_{max}: 3225 (broad), 3017, 2920, 1671, 1621 cm^{-1}; Calculated *Anal*. Calcd for $C_{19}H_{17}IN_2O_4$: C, 49.16; H, 3.69; I, 27.33; N, 6.03; found C, 49.21; H, 3.55; I, 27.12; N, 6.24. EIMS ($M^{+\cdot}$) *m*/*z*: 464.

2-(6-Iodo-4-oxo-3-(2,4,5-trihydroxy-6-(hydroxymethyl)-2-methyltetrahydro-2H-pyran-3-yl)-3,4-dihydro quinazolin-2-yl) benzoic acid (7). Yellow crystal, yield 78.8%; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.92 (bs, 1H, COOH, exchangeable by D_2O), 8.28 (d, *J* = 2.2 Hz, 1H, Ar_1-H), 7.91 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.73 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.51 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.39 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 4.37–4.12 (m, 4H, gluOH, exchangeable by D_2O), 3.81–3.62 (m, 5H, gluCH), 3.55 (s, 2H, $gluCH_2$), 3.32–1.33 (d, 1H, gluCH). FTIR (KBr, cm^{-1}) ν_{max}: 3210 (N─H), 2952, 2870, 1751, 1542 (C═O), 1312 ($\nu_{as\ (C–O–C)}$), 1252 ($\nu_{a\ (C–O–C)}$). *Anal*. Calcd for $C_{22}H_{21}IN_2O_8$: C, 46.50; H, 3.72; N, 4.93. Found: C, 46.25; H, 3.49; N, 4.48. EIMS ($M^{+\cdot}$) *m*/*z*: 568.

2-(3-Hydroxy-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl) benzoic acid (8). Yellow crystal, yield 75.3%; ^{1}H NMR ($CDCl_3$, 400 MHz) 13.32 (bs, 1H, COOH, exchangeable by D_2O), 10.52 (bs, 1H, OH, exchangeable by D_2O), 8.28 (d, *J* = 2.5 Hz, 1H, Ar_1-H), 8.03 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.93 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.51 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.39 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), FTIR (KBr, cm^{-1}) ν_{max}: 3410 (O─H), 3213 (N─H), 2950, 2874 (AliCH), 1690 (C═O), 1256 ($\nu_{(C–O)}$). *Anal*. Calcd for $C_{15}H_9IN_2O_4$: C, 44.14; H, 2.22; N, 6.68. Found: C, 43.90; H, 1.95; N, 6.25. EIMS ($M^{+\cdot}$) *m*/*z*: 408.

10-Iodo-6H-phthalazino[1,2-b]quinazoline-5,8-dione (9). Yellow crystal, yield 22.8%; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.19 (bs, 1H, N─H, exchangeable by D_2O), 8.32 (d, *J* = 3.1 Hz, 1H, Ar_1-H), 8.05 (dd, *J* = 7.6, 3.2 Hz, 2H, Ar_2-H), 7.86 (dd, *J* = 8.0, 3.1 Hz, 1H, Ar_1-H), 7.63 (dd, *J* = 7.6, 3.2 Hz, 2H, Ar_2-H), 7.39 (d, *J* = 8.0 Hz, 1H, Ar_1-H). FTIR (KBr, cm^{-1}) ν_{max}: 3215 (N─H), 2950, 2871 (AliCH), 1659 (C═O), 1305 ($\nu_{as\ (C–O)}$). *Anal*. Calcd for $C_{15}H_8IN_3O_3$: C, 46.30; H, 2.07; N, 10.80. Found: C, 46.00; H, 1.89; N, 10.23. EIMS ($M^{+\cdot}$) *m*/*z*: 389.

6′-Iodo-3′-(pyridin-2-yl)-1′H,3H–spiro[isobenzofuran-1,2′-quinazoline]-3,4′(3′H)-dione (10). White crystal, yield 75.3%; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.38 (dd, *J* = 11.0, 4.3 Hz, 1H, Ar_3H), 8.32 (d, *J* = 2.2 Hz, 1H, Ar_1-H), 8.25 (bs, 1H, NH, exchangeable by D_2O), 8.15 (dd, *J* = 11.0, 4.3 Hz, 1H, Ar_3H), 7.71 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.67 (d, *J* = 6.8 Hz, 2H, Ar_2-H), 7.51 (d, *J* = 8.3 Hz, 2H, Ar_2H), 7.51 (dd, *J* = 10.9, 4.2 Hz, 2H, Ar_3-H), 7.39 (dd, *J* = 8.2 Hz, 1H, Ar_1-H). FTIR (KBr, cm ^{1}) ν_{max}: 3212 (N─H), 2953, 2872, 1753 (C═O), 1310 ($\nu_{as\ (C–O–C)}$), 1262 ($\nu_{a\ (C–O–C)}$). *Anal*. Calcd for $C_{20}H_{12}IN_3O_3$: C, 51.19; H, 2.58; N, 8.96. Found: C, 50.88; H, 2.25; N, 8.46. EIMS ($M^{+\cdot}$) *m*/*z*: 469.

3′-(Pyridin-2-ylmethyl)-1′H,3H-spiro[isobenzofuran-1,2′-quinazoline]-3,4′(3′H)-dione (11). White crystal, yield 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.29 (bs, 1H, NH, exchangeable by D_2O), 8.24 (d, *J* = 7.2 Hz, 2H, Ar_1-H), 7.71 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.67 (d, *J* = 6.8 Hz, 2H, Ar_2-H), 7.51 (d, *J* = 8.3 Hz, 2H, Ar_2H), 8.15 (dd, *J* = 11.0, 4.3 Hz, 2H, Ar_3H), 7.51 (dd, *J* = 10.9, 4.2 Hz, 2H, Ar_3-H), 7.39 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 4.51 (s, 1H, Py-CH_2). FTIR (KBr, cm^{-1}) ν_{max}: 3210 (N─H), 3052 (ArCH), 2952, 2870 (AliCH), 1750, 1680 (C═O), 1312 ($\nu_{as\ (C–O–C)}$), 1260 ($\nu_{a\ (C–O)}$). *Anal*. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.78; H, 4.21; N, 11.79. Found: C, 70.50; H, 4.05; N, 11.27. EIMS ($M^{+\cdot}$) *m*/*z*: 356.

2-(6′-Iodo-3,4′-dioxo-1′,4′-dihydro-3H,3′H-spiro[isobenzofuran-1,2′-quinazolin]-3′-yl)acetic acid (12). White crystal, yield 76.4%; ^{1}H NMR ($CDCl_3$, 400 MHz) 13.2 (bs, 1H, COOH exchangeable by D_2O), 8.34 (d, *J* = 2.2 Hz, 1H, Ar_1-H), 8.16 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.71 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.51 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.39 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 4.52 (s, 1H, Py-CH_2). FTIR (KBr, cm^{-1}) ν_{max}: 3412 (OH), 3218 (N─H), 2952, 2873 (AliCH), 1749, 1705 (C═O), 1542 (NO_2), 1305 ($\nu_{as(C–O–C)}$), 1250 ($\nu_{a(C–O–C)}$). FTIR (KBr, cm^{-1}) ν_{max}: 3356 (OH), 3213 (NH), 2950, 2874, 1750 (C═O), 1310 ($\nu_{as\ (C–O–C)}$), 1256 ($\nu_{a\ (C–O–C)}$). *Anal*. Calcd for $C_{17}H_{11}IN_2O_5$: C, 45.36; H, 2.46, N, 6.22. Found: C, 45.05; H, 2.21; N, 5.94. EIMS ($M^{+\cdot}$) *m*/*z*: 450.

2-(3-(4′-Amino-2,2′-dimethyl-[1,1′-biphenyl]-4-yl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (13). White crystal, yield 56.3%; ^{1}H NMR (DMSO, 400 MHz) 8.34 (d, *J* = 2.2 Hz, 1H, Ar_1-H), 9.2 (bs, 2H, NH_2 exchangeable by D_2O), 8.22 (bs, 1H, COOH, exchangeable by D_2O), 8.16 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.71 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.51 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_2-H), 7.39 (dd, *J* = 8.2 Hz, 1H, Ar_1-H), 8.16 (dd, *J* = 7.9, 3.2 Hz, 2H, Ar_4-H), 7.21 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar_4-H), 7.11 (dd, *J* = 7.9, 3.2 Hz, 1H, Ar_3-H), 6.69 (dd, *J* = 8.2 Hz, 2H, Ar_3-H), 2.21 (s, 6H, $2CH_3$). FTIR (KBr, cm^{-1}) ν_{max}: 3412, 3218 (N─H), 2952, 2873 (AliCH), 1767 (C═O) 1305 ($\nu_{as(C–O–C)}$), 1250 ($\nu_{a(C–O–C)}$). *Anal*. Calcd for $C_{29}H_{22}IN_3O_3$ C, 59.30; H, 3.78; N, 7.15; found C, 59.16; H, 3.86; N, 7.33. EIMS ($M^{+\cdot}$) *m*/*z*: 587.

2-(5-Iodo-2-oxo-2,3-dihydro-1H-benzo [d]imidazole-1-carbonyl)benzoic acid (14). White crystal, yield 75%; ^{1}H NMR (400 MHz, DMSO) 12.59 (bs, 1H, NH, exchangeable by D_2O),8.29 (bs, 1H, COOH, exchangeable by D_2O), 8.24 (d, J = 2.2 Hz, 1H, Ar_1-H), 7.71 (dd, J = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.67 (d, J = 6.8 Hz, 2H, Ar_2-H), 7.51 (d, J = 8.3 Hz, 2H, Ar_2H), 7.39 (dd, J = 8.2 Hz, 1H, Ar_1-H). FTIR (KBr, cm ^{1}) ν_{max}: 3214 (N—H), 2953, 2870, 1754 (C═O), 1684, 1582, 1508 (C═C), 1313 ($\nu_{as\ (C–O–C)}$), 1261 ($\nu_{a\ (C–O–C)}$). *Anal*. Calcd for $C_{14}H_9IN_2O_3$: C, 44.23; H, 2.39; N, 7.37; found C, 44.36; H, 2.39; N, 7.24. EIMS ($M^{+\cdot}$) m/z: 380.

6-Acetyl-10-iodo-6H-phthalazino[1,2-b]quinazoline-5,8-dione (15a). Yellow crystal, yield 72.3%; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.32 (d, J = 3.1 Hz, 1H, Ar_1-H), 8.05 (dd, J = 7.6, 3.2 Hz, 2H, Ar_2-H), 7.86 (dd, J = 8.0, 3.1 Hz, 1H, Ar_1-H), 7.63 (dd, J = 7.6, 3.2 Hz, 2H, Ar_2-H), 7.39 (d, J = 8.0 Hz, 1H, Ar_1-H), 2.75 (s, 3H, CH_3CO). FTIR (KBr, cm^{-1}) ν_{max}: 3092 (Ar–H), 2950, 2870, 1685, 1662 (C═O), 1260 ($\nu_{a\ (C–O)}$). *Anal*. Calcd for $C_{17}H_{10}IN_3O_3$: C, 47.35; H, 2.34; N, 9.75. Found: C, 47.00; H, 2.02; N, 9.46. EIMS ($M^{+\cdot}$) m/z: 431.

6-Benzoyl-10-iodo-6H-phthalazino[1,2-b]quinazoline-5,8-dione (15b). Yellow crystal, yield 72.3%; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.34 (d, J = 2.2 Hz, 1H, Ar_1-H), 7.99 (d, J = 9.9 Hz, 2H, Ar_2-H), 7.71 (dd, J = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.51 (dd, J = 7.9, 3.2 Hz, 2H, Ar_3-H), 7.41 (d, J = 9.9 Hz, 2H, Ar_2-H), 7.22 (dd, J = 7.9, 3.2 Hz, 3H, Ar_3-H), 7.09 (dd, J = 8.2 Hz, 1H, Ar_1-H). FTIR (KBr, cm^{-1}) ν_{max}: 3095 (Ar–H), 2950, 2870, 1685, 1670 (C═O), 1260 ($\nu_{a\ (C–O)}$). *Anal*. Calcd for $C_{22}H_{12}IN_3O_3$: C, 53.57; H, 2.45; N, 8.52. Found: C, 53.17; H, 2.14; N, 8.29. EIMS ($M^{+\cdot}$) m/z: 493.

3-Iodo-4b1,5,6a,12-tetraazacyclopenta[gh]tetraphene-6,7-dione (16). Yellow crystal oil, yield 72.3%; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.15 (dd, J = 7.6, 3.2 Hz, 1H, Ar_2-H), 8.09 (d, J = 3.1 Hz, 1H, Ar_1-H), 8.05 (dd, J = 7.6, 3.2 Hz, 1H, Ar_2-H), 7.86 (dd, J = 8.0, 3.1 Hz, 1H, Ar_1-H), 7.63 (dd, J = 7.6, 3.2 Hz, 2H, Ar_2-H), 7.39 (d, J = 8.0 Hz, 1H, Ar_1-H). FTIR (KBr, cm ^{1}) ν_{max}: 3051 (Ar–H), 2950, 2870, 1689, 1662 (C═O). *Anal*. Calcd for $C_{16}H_7IN_4O_2$: C, 46.40; H, 1.70; N, 13.53. Found: C, 46.11; H, 1.33; N, 13.21. EIMS ($M^{+\cdot}$) m/z: 414.

10-Iodo-5,8-dioxo-5,8-dihydro-6H-phthalazino[1,2-b] quinazoline-6-carbothioamide (17). Yellow crystal, yield 72.3%; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.32 (d, J = 2.2 Hz, 1H, Ar_1-H), 8.19 (dd, J = 8.1, 2.8 Hz, 1H, Ar_2H), 7.71 (dd, J = 8.2, 2.5 Hz, 1H, Ar_1-H), 7.67 (dd, J = 8.1, 2.8 Hz, 1H, Ar_2-H), 7.51 (d, J = 8.3 Hz, 2H, Ar_1H), 7.51 (d, J = 7.2 Hz, 2H, Ar_2-H), 7.39 (dd, J = 8.2 Hz, 1H, Ar_1-H). FTIR (KBr, cm^{-1}) ν_{max}: 3211 (N—H), 2950, 2870, 1672 (C═O), 1160 ($\nu_{(C=S)}$). *Anal*. Calcd for $C_{16}H_8N_4OS$: C, 63.15; H, 2.65; N, 18.41. Found: C, 62.80; H, 2.17; N, 18.18. EIMS ($M^{+\cdot}$) m/z: 304.

CONCLUSIONS

Based on the strategy of receptor structure-guided heterocyclic design, a new series of quinazoline analogues (**2–17**) were designed and synthesized by introducing the benzoxazinone ring bearing diverse carboxylic acid, which inset the peptide bond to the flexible ester arm. The insecticidal spectra of the target compounds presented excellent insecticidal activities against *N. lugens* and *A. medicagini* at 100 mg/L. Among these analogues, the compounds **2**, **3**, and **4** afforded the best activity and had 100% mortality against *N. lugens* (LC_{50} = 0.163 mg/L) and 90% against *A. medicagini* at 4 mg/L. Structure activity relationships (SARs) suggested that the insecticidal potency of our designed quinazolinone and spiro derivatives analogues was dual-controlled by the size and species of the glucoside and thioamide groups. The electronic structures result revealed a unique binding mode other than the previously designed compounds, because introduction of the peptide bond gave rise to more significant hydrogen bonds between the quinazolinone analogues and the amino acid residues of insect nAChRs. Additionally, they were in good agreement with their high insecticidal potential, which suggested that the more significant the hydrogen bonds were, the better the active would become. The study herein has shed a light on the biodegradation of the function of synthesized analogues, that is, ecofriendly environment when interacted with the amino acid residues of insect nAChRs, and may facilitate receptor structure-guided design of novel insecticidal compounds with less resistance and better selectivity.

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