Abstract: In order to identify novel chlorantraniliprole derivatives as potential insecticides or fungicides, 25 analogues of chlorantraniliprole were synthesized. The insecticidal activities against oriental armyworm and the antifungal activities against five typical fungi of these derivatives were tested. Compounds $2u$, $2x$ and $2y$ exhibited good activities against oriental armyworm, especially compounds $2u$ and $2x$ which showed higher larvicidal activities than indoxacarb. Moreover, all of the tested compounds exhibited activities against five typical fungi. The Ki values of all synthesized compounds were calculated using AutoDock4. The relationship between the Ki values and the results of insecticidal activities against oriental armyworm further indicated that the membrane-spanning domain protein of the ryanodine receptor might contain chlorantraniliprole binding sites.

Keywords: anthranilic diamides; chlorantraniliprole; ryanodine receptor; insecticidal activities; antifungal activities; molecular docking
1. Introduction

Lepidopteran pests such as the oriental armyworm (*Mythimna separata*) have become difficult to control because of their emerging resistance to various types of traditional insecticides [1,2]. In order to control the oriental armyworm effectively, there were currently two new types of diamide insecticides with exceptional insecticidal activities on a range of lepidopteran pests, the phthalic diamides, such as flubendiamide [3,4] and the anthranilic diamides, such as chlorantraniliprole [5] and cyantraniliprole (Figure 1) [6].

Chlorantraniliprole, discovered by DuPont, has excellent control of lepidopteran pests, low mammalian toxicity and a favorable environmental profile. The widespread use of chlorantraniliprole on lepidopteran pests in the future may result in pest resistance and residues in the field [7]. Thus, designing novel chlorantraniliprole derivatives as new insecticides has attracted considerable research attention. However, a reasonable design strategy could not be proposed because of the lack of a clear target for chlorantraniliprol. In our previous work [8], we proposed the ryanodine receptor [9] as a possible binding target for chlorantraniliprole and its derivatives using an AutoDock4 analysis, and we initially confirmed that the membrane-spanning domain protein of the ryanodine receptor might have specific binding site(s) for chlorantraniliprole derivatives. Figure 2a shows the relative position relationship between the proposed ryanodine receptor (in white color) and chlorantraniliprole (in blue color). Diamide insecticides activate insect ryanodine (Ry)-sensitive intracellular Ca\textsuperscript{2+} channels by affecting calcium release [10], as seen in Figure 2b. We initially identified the target by comparing the relationship between the insecticidal activities against diamondback moth and the molecular docking results.

![Figure 1. Insecticides acting on the insect ryanodine receptor [8]. Copyright © 2014 Elsevier Ltd.](image)

Both diamondback moth and oriental armyworm are lepidopteran pests [11]. Therefore, in this study, oriental armyworm was selected for the first time for a bioactivity study, which examines the relationship with the Ki values of molecular docking. On the other hand, it was reported [12] that chlorantraniliprole derivatives might also show antifungal effects. Therefore, in this work the *in vitro* antifungal activity of some chlorantraniliprole derivatives was tested too. The chlorantraniliprole derivatives obtained herein were also used as new probes to bind with the proposed acceptor to further confirm that the membrane-spanning domain protein of ryanodine receptor was the special target binding with chlorantraniliprole and its derivatives.
Figure 2. (a) Docking orientation of proposed ryanodine receptor (white color) and the chlorantraniliprole (blue color); (b) ryanodine receptor (RyR) and its Ca^{2+} release channels [8] Copyright © 2014 Elsevier Ltd.

In the previous work [8,13–16], most modifications of chlorantraniliprole were related to three parts: The pyrazole moiety (part A, Figure 3), amide moiety (part B, Figure 3), and anthraniloyl moiety (part C, Figure 3). Herein, new chlorantraniliprole derivatives were synthesized by modifying the amide-moiety.

Figure 3. Modifications of chlorantraniliprole derivatives [8]. Copyright © 2014 Elsevier Ltd.

2. Results and Discussion

2.1. Chemistry

Compound 1 was obtained by literature methods (Scheme 1) [7,17–19]. The nineteen compounds 2b–t were synthesized according to our previous work [8]. Among the new compounds 2a, 2u–y, compound 2u was conveniently obtained by treatment of compound 1 with methyl 2-aminoacetate without any other catalyst or base at room temperature. Due to the insolvability of glycine in the reaction solvents (tetrahydrofuran or dichloromethane), a mixture of pyridine and water was selected as solvent in the preparation of compound 2v. In the case of compounds 2w and 2x, a strong base (NaH) was needed, while triethylamine was employed for compound 2w.
Scheme 1. General synthetic route to the title compounds 2a–y.

2.2. Larvicidal Activities and Structure-Activity Relationships (SARs)

The results in Table 1 indicate that all of the tested compounds 2a–y, except for four compounds (2a, 2q, 2r and 2w) showed the same larvicidal activities (100%) as chlorantraniliprole, indoxacarb and avermectins at the concentrations of 100 and 200 mg/L. These results reveal that most of the chlorantraniliprole derivatives in our study exhibited considerable insecticidal activities against oriental armyworm.

The larvicidal activities of all compounds except for three compounds (2u, 2x and 2y) were lower than those of chlorantraniliprole and avermectins when the concentration was under 50 mg/L, however, compounds 2u and 2x showed obviously better activities (both 100%) than indoxacarb (40%), even when the concentration was lowered to 5 mg/L, while, compound 2y displayed the same
larvicidal activity (40%) as indoxacarb at this concentration. Notably, these two compounds 2u and 2x displayed the same activity (100%) as chlorantraniliprole and avermectins at the concentration of 5 mg/L.

Table 1. Insecticidal activities of title compounds 2a–y, chlorantraniliprole, indoxacarb and avermectins against oriental armyworm.

| Compd. No. | Insecticidal Activities (%) at Different Concentrations | Concentrations (mg/L) |
|------------|--------------------------------------------------------|------------------------|
| 2a         | 60                                                     |                        |
| 2b         | 100 100 100 100 40                                     |                        |
| 2c         | 100 100 100 100 100 100 100 60                         |                        |
| 2d         | 100 100 100 100 100 100 100 60                         |                        |
| 2e         | 100 100 100 100 100 100 100 60                         |                        |
| 2f         | 100 100 100 100 100 100 40                             |                        |
| 2g         | 100 100 60                                             |                        |
| 2h         | 100 100 60                                             |                        |
| 2i         | 100 100 60                                             |                        |
| 2j         | 100 100 100 100 100 100 100 20                         |                        |
| 2k         | 100 100 40                                             |                        |
| 2l         | 100 100 100 60                                         |                        |
| 2m         | 100 100 100 100 100 100 20                             |                        |
| 2n         | 100 100 100 60                                         |                        |
| 2o         | 100 100 60                                             |                        |
| 2p         | 100 100 70                                             |                        |
| 2q         | 100 60                                                 |                        |
| 2r         | 20                                                     |                        |
| 2s         | 100 100 40                                             |                        |
| 2t         | 100 100 60                                             |                        |
| 2u         | 100 100 100 100 100 100 100 100                         |                        |
| 2v         | 100 100 100 40                                         |                        |
| 2w         | 30                                                     |                        |
| 2x         | 100 100 100 100 100 100 100 40                         |                        |
| 2y         | 100 100 100 100 100 100 100 40                         |                        |

In Table 2, the preliminary structure-activity relationship (SAR) data is summarized. All compounds with cyano groups (R₂ = CN) instead of a chloride group commonly had low insecticidal activities against oriental armyworm. For example, compounds 2o, 2p, 2q, 2r, 2s and 2t in Table 1 had no insecticidal activities when the concentration was less than 25 mg/L.

Most of the researchers in previous work [20–22] preserved the anthranilic amide moiety, which suggested that this structure was an important pharmacophore in those compounds [23]. The number of methylene groups in the amide moiety was also an important element for the insecticidal activity and two methylenes was the most favorable number for high activity. For example, compounds 2c, 2d, 2j, 2l and 2n (n = 2) had high insecticidal activities (100%), while compounds 2g and 2h (n = 3 or 4)
showed lower activities (60%). Obviously, when R₄ and R₅ had the same substituent groups (Table 2) as in compounds 2d, 2g and 2h (R₄ = R₅ = ethyl group), the insecticidal activities were dramatically reduced.

**Table 2.** SAR study of typical chlorantraniliprole derivatives.

| Compd. No. | The Number of Methylenes (n) | R₄            | R₅            | Insecticidal Activities * (%) |
|------------|-----------------------------|---------------|---------------|-----------------------------|
| 2c         | 2                           | CH₃           | CH₃           | 100                         |
| 2e         | 3                           | CH₃           | CH₃           | 100                         |
| 2d         | 2                           | CH₃CH₂        | CH₃CH₂        | 100                         |
| 2g         | 3                           | CH₃CH₂        | CH₃CH₂        | 60                          |
| 2h         | 4                           | CH₃CH₂        | CH₃CH₂        | 60                          |
| 2i         | 2                           | (CH₃)₂CH      | (CH₃)₂CH      | 60                          |
| 2j         | 2                           | CH₃CH₂        | H             | 100                         |
| 2k         | 2                           | CH₃CH₂CH₂     | H             | 40                          |
| 2l         | 2                           | (CH₃)₂CH      | H             | 100                         |
| 2n         | 2                           | CH₃           | H             | 100                         |

* The insecticidal activities against oriental armyworm at a concentration of 50 mg/L.

In addition, the substitution of R₄ or R₅ at the tail of the amide moiety was a significant factor affecting the insecticidal activities. When either one of R₄ or R₅ was substituted by hydrogen, most compounds (2j, 2l and 2n) displayed relatively high activities (100%), except compound 2k (40%), while, when both R₄ and R₅ were substituted by alkyl groups, most of compounds (2g, 2h, and 2i) displayed relatively lower activities (60%), except compound 2d (100%), which indicated that the secondary amine at the tail of the amide moiety was an necessary pharmacophore. In conclusion, the substitution at the terminal positions of the amide moiety and the number of methylene groups might be important factors that influence the insecticidal activities, which could be verified when more chlorantraniliprole derivatives are designed to increase the insecticidal activities against oriental armyworm.

2.3. Antifungal Activities

According to the data presented in Table 3, all of the chlorantraniliprole derivatives exhibited certain inhibitory effects against the five tested phytopathogenic fungi: *Fusarium oxysporum* (FO); *Cercospora arachidicola* (CA); *Physalospora piricola* (PP); *Alternaria solani* (AS); and *Fusarium graminearum* (FG).

The activities on FO and CA for all compounds, except 2t and 2f (both were 0%) showed varying inhibitory activities (ranging from 4.2% to 41.7%). Regarding the antifungal activities on PP, all tested compounds showed low to good inhibitory activities (from 5.3% to 78.9%) and two compounds (2h
and 2j) showed higher activities (78.9%, 63%, respectively) than other compounds. The activities on AS for all compounds except for three (2k, 2l and 2t, no activity) showed inhibitory activities ranging from 11.1% to 50.0%.

Table 3. The antifungal activities against five fungi.

| Fungi Compd. No. | Antifungal Activities (%) Against Five Fungi |
|------------------|---------------------------------------------|
|                  | FO  | CA  | PP  | AS  | FG  |
| 2b               | 11.4| 20.8| 31.6| 38.9| 51.9|
| 2c               | 8.7 | 12.5| 10.5| 22.2| 37.5|
| 2d               | 20.0| 20.8| 28.1| 22.2| 29.6|
| 2e               | 14.3| 29.2| 26.3| 11.1| 14.8|
| 2f               | 8.6 | 0.0 | 22.8| 38.9| 37.0|
| 2g               | 40.0| 29.2| 54.4| 33.3| 44.4|
| 2h               | 25.7| 41.7| 78.9| 11.1| 29.6|
| 2i               | 11.4| 20.8| 33.3| 27.8| 25.9|
| 2j               | 20.0| 29.2| 63.2| 22.2| 40.7|
| 2k               | 11.4| 12.5| 22.8| 0   | 40.7|
| 2l               | 11.4| 29.2| 33.3| 0   | 14.8|
| 2o               | 8.7 | 37.5| 5.3 | 22.2| 40.6|
| 2p               | 13.0| 31.3| 7.9 | 16.7| 31.3|
| 2q               | 13.0| 12.5| 7.9 | 16.7| 18.8|
| 2r               | 5.7 | 12.5| 28.1| 27.8| 40.7|
| 2s               | 11.4| 20.8| 31.6| 50.0| 44.4|
| 2t               | 0.0 | 4.2 | 24.6| 0   | 18.5|
| 2u               | 8.7 | 25.0| 10.5| 16.7| 46.9|
| 2y               | 8.7 | 6.3 | 7.9 | 11.1| 25.0|

FO: Fusarium oxysporum; CA: Cercospora arachidicola; PP: Physalospora piricola; AS: Alternaria solani; FG: Fusarium graminearum.

The activities of all tested compounds on FG were commonly higher than those on FO and AS. All compounds showed low to average inhibitory activities (from 14.8% to 51.9%) against FG and the compound 2b showed better activity (51.9%) than the other compounds.

2.4. Molecular Docking Results

The results in Table 4 reveal that ten compounds (2e, 2l, 2m, 2o, 2q, 2r, 2s, 2t, 2w and 2y) with unavailable Ki values except for four of them (2e, 2l, 2m and 2y) displayed low biological activities (≤60%) against oriental armyworm, while the other 15 compounds (2a, 2b, 2c, 2d, 2f, 2g, 2h, 2i, 2j, 2k, 2n, 2p, 2u, 2v and 2x) with available Ki value, except one compound (2a), generally displayed medium to high biological activities (40%–100%). These results further confirm that the membrane-spanning domain protein (GenBank accession no. JF927788) of the ryanodine receptor selected in our previous work [8] might have specific binding site(s) for chlorantraniliprole and its derivatives, and identification of the possible binding site is worthy of further study from a protein molecular level point of view. However, the docking software program might affect the accuracy of the Ki values and the biological diversity of pests plays an important role in the experimental activity.
tests. These reasons could explain why compounds 2e, 2l, 2m and 2y with unavailable Ki values showed high activities (100%) and compound 2a with available Ki values showed relatively no activity.

Table 4. The Ki values and the insecticidal activities against oriental armyworm.

| Compd. No. | Ki Values | Insecticidal Activities* | Compd. No. | Ki values# | Insecticidal Activities* |
|------------|-----------|--------------------------|------------|-----------|--------------------------|
| 2h         | 3.64      | 60                       | 2e         | unavailable | 100                      |
| 2j         | 5.98      | 100                      | 2l         | unavailable | 100                      |
| 2f         | 8.25      | 100                      | 2m         | unavailable | 100                      |
| 2b         | 14.4      | 40                       | 2o         | unavailable | 60                       |
| 2a         | 8.41      | 0                        | 2q         | unavailable | 0                        |
| 2g         | 15.16     | 60                       | 2r         | unavailable | 0                        |
| 2d         | 17.68     | 100                      | 2s         | unavailable | 40                       |
| 2p         | 17.85     | 70                       | 2t         | unavailable | 60                       |
| 2x         | 21.07     | 100                      | 2w         | unavailable | 0                        |
| 2i         | 28.27     | 60                       | 2y         | unavailable | 100                      |
| 2u         | 63.83     | 100                      |            |           |                           |
| 2n         | 64.92     | 100                      |            |           |                           |
| 2k         | 99.57     | 40                       |            |           |                           |
| 2c         | 93.86     | 100                      |            |           |                           |
| 2v         | 916.28    | 40                       |            |           |                           |
| Chlorantraniliprole | 50.12 | 100 |            |           |                           |

* Insecticidal activities of tested compounds against oriental armyworm at 50 mg/L; # Unavailable: The compound couldn’t interact with the selected receptor and the Ki values couldn’t be calculated.

3. Experimental Section

3.1. Chemistry

3.1.1. General

Melting points (mp) of the products were determined in open capillary tubes and are uncorrected. The products were purified by column chromatography by using silica gel (200–300 mesh). 1H-NMR and 13C-NMR spectra were recorded on a Varian-400 instrument at room temperature with TMS as an internal standard and CDCl3 or DMSO-d6 as solvents. Mass spectra were recorded with a JEOL MS-D300 mass spectrometer. The reactions were monitored by analytical thin-layer chromatography TLC with ultraviolet (UV) light and the TLC was carried out on silica gel GF254. All reagents were purchased from Acros (Geel, Belgium) or Alfa Aesar (Deisenhofen, Germany). The anhydrous solvents were dried and purified according to standard techniques before use.

3.1.2. Syntheses

The intermediate compound 1 was obtained in six steps by literature methods [7,17,18]. The nineteen compounds 2b–t were synthesized according to our previous methods [8]. The other six new title compounds 2a, 2u–y were prepared as follows:
3-Bromo-N-(4-chloro-2-methyl-6-((2,4,4-trimethylpentan-2-yl)carbamoyl)phenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (2a). 2,4,4-Trimethylpentan-2-amine (28 mg, 0.22 mmol) was added to compound 1 (50 mg, 0.11 mmol) in tetrahydrofuran (THF, 5 mL). Then the mixture was stirred at room temperature and monitored by TLC. The crude product was recrystallized from a dichloromethane/hexane (1:2) to give the product 2a as a white solid in 55% yield. mp. 202–206 °C

$^1$H-NMR (CDCl$_3$): δ 11.84 (s, 1H, NHCOC), 8.37 (d, $J$ = 4.8 Hz, 1H, 6-H pyridine), 7.78 (d, $J$ = 8 Hz, Ph-H), 7.78 (dd, $J$ = 4.8, 8 Hz, 1H, 5-H pyridine), 7.23 (d, $J$ = 1.6 Hz, 1H, Ph-H), 7.01 (s, 1H, pyrazole-H), 7.31 (dd, $J$ = 4.8, 8 Hz, 1H, 4-H pyridine), 7.23 (d, $J$ = 1.6 Hz, 1H, Ph-H), 7.01 (s, 1H, pyrazole-H), 2.18 (s, 3H, Ph-CH$_3$), 1.56 (s, 2H, CH$_2$), 1.30 (s, 6H, (CH$_3$)$_2$C), 0.89 (s, 9H, (CH$_3$)$_3$C); $^{13}$C-NMR (CDCl$_3$): δ 172.42, 155.66, 148.91, 146.77, 140.10, 139.07, 136.29, 134.78, 133.14, 130.47, 129.06, 128.09, 127.95, 125.79, 110.77, 55.99, 52.97, 31.23, 31.18, 27.26, 19.44; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{25}$H$_{28}$BrCl$_2$N$_5$O$_2$: 602.0701. Found: 602.1055.

3-Bromo-N-(4-chloro-2-((2-(2-(methoxy)oxoethyl))carbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (2u). To a solution of methyl glycinate (29 mg, 0.33 mmol) in dichloromethane (DCM, 2 mL), a solution of 1 (148 mg, 0.33 mmol) in DCM (3 mL) was added dropwise at 0 °C. Then the resulting mixture was stirred at room temperature and monitored by TLC. The reaction mixture was evaporated to remove most of the DCM to give the crude product, which was recrystallized from n-hexane to give 2u as a white solid in 40% yield. mp. 142–146 °C; $^1$H-NMR (CDCl$_3$): δ 9.84 (s, 1H, CONH-Ar), 8.42 (d, $J$ = 7.2 Hz, 1H, pyridyl-H), 7.84 (d, $J$ = 8 Hz, 1H, pyridyl-H), 7.36 (dd, $J$ = 4.8 Hz, 8 Hz, 1H, pyridyl-H), 7.29 (s, 1H, Ph-H), 7.25 (d, $J$ = 5.2 Hz, 1H, Ph-H), 7.05 (s, 1H, pyrazolyl-H), 6.76 (br, s, 1H, NHCO-Ar), 4.12 (d, $J$ = 5.6 Hz, 2H, COCH$_2$NH), 3.77 (s, 3H, CH$_3$O), 2.17 (s, 3H, Ph-CH$_3$); $^{13}$C-NMR (CDCl$_3$): δ 169.55, 167.89, 156.34, 156.18, 148.90, 146.75, 138.98, 138.56, 133.37, 132.20, 131.79, 131.19, 128.94, 128.13, 125.67, 124.78, 110.91, 52.62, 41.69, 18.82; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{20}$H$_{17}$BrCl$_2$N$_5$O$_4$: 553.0521. Found: 553.0526.

Methyl2-(2-(2-(3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamido-5-chloro-3-methyl-benzamido)acetic acid (2v). To a solution of glycine (24 mg, 0.33 mmol) in a mixed solvent of pyridine/water (1:1.5, 5 mL), a solution of 1 (0.11 mmol) in pyridine/water (1:1.5, 2 mL) was added dropwise at 0 °C Then the mixture was stirred at room temperature and monitored by TLC. When the reaction mixture was adjusted to pH 2–3 by addition of 1 mol/L hydrochloric acid, a white solid precipitated, which was collected and dried to give 2v in 52% yield. mp. 212–214 °C; $^1$H-NMR (DMSO-$d_6$): δ 12.67 (s, 1H, COOH), 10.54 (s, 1H, CONH-Ar), 8.83 (s, 1H, Ar-CONH), 8.49 (d, $J$ = 4.4 Hz, 1H, pyridyl-H), 8.17 (s, $J$ = 4 Hz, 1H, pyridyl-H), 7.61 (dd, $J$ = 4.8 Hz, 8 Hz, 1H, pyridyl-H), 7.53 (s, 1H, pyrazolyl-H), 7.50 (s, 1H, Ph-H), 7.39 (s, 1H, Ph-H), 3.82 (d, $J$ = 5.6 Hz, 2H, COCH$_2$NH), 2.16 (s, 3H, Ph-CH$_3$); $^{13}$C-NMR (DMSO-$d_6$): δ 170.55, 165.68, 155.54, 148.34, 146.88, 139.07, 135.57, 131.33, 130.94, 127.74, 126.58, 126.40, 125.63, 110.83, 40.97, 17.60; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{19}$H$_{15}$BrCl$_2$N$_5$O$_4$: 527.9664. Found: 527.9668.

3-Bromo-N-(4-chloro-2-((2-(5-(dimethylamino)naphthalen-1-ylsulfonyl))carbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (2w). To a solution of 5-(dimethylamino)naphthalene-1-sulfonamide (94 mg, 0.4 mmol) and NaH (14 mg, 0.6 mmol) in THF (5 mL), a solution of 1 (180 mg, 0.4 mmol) in THF (3 mL) was added dropwise at 0 °C. Then the resulting mixture was
stirred for 10 min at room temperature. The reaction mixture was washed with 1 mol/L hydrochloric acid to pH 5. The aqueous phase was extracted with DCM (20 mL) and then dried to give the crude residue that was recrystallized from a DCM/hexane (1:1.5) mixture to give the product 2w as a yellow solid in 77% yield. mp. 142–146 °C; 1H-NMR (DMSO-d6): δ 10.23 (s, 1H, CONH-Ar), 8.53 (dd, J = 1.6, 4.8 Hz, 1H, pyridyl-H), 8.17 (dd, J = 1.6, 8Hz, 1H, pyridyl-H), 8.32 (s, 1H, Ph-H), 8.30 (s, 1H, Ph-H), 8.10 (dd, J = 4.8Hz, 8 Hz, 1H, pyridyl-H), 7.252–7.690 (m, 6H, pyridine-H), 6.95 (s, 1H, pyrazolyl-H), 3.84 (s, 6H, 2NCH3), 2.11 (s, 3H, Ph-CH3); 13C-NMR (DMSO-d6): δ 163.90, 155.66, 151.34, 148.00, 146.93, 139.20, 139.15, 132.86, 132.67, 131.93, 130.77, 128.89, 128.18, 127.44, 126.58, 126.32, 126.01, 123.24, 118.06, 115.06, 110.52, 109.19, 44.93, 17.37; HRMS (ESI): m/z [M+H]+ calcd for C29H24BrCl2N6O4S: 701.0140. Found: 701.0092.

3-Bromo-N-(4-chloro-2-((2-cyanoacetyl)carbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (2x). To a solution of 2-cyanoacetamide (11 mg, 0.13 mmol) and NaH (1 mg, 0.17 mmol) in THF (3 mL), a solution of 1 (0.11 mmol) in THF (1 mL) was added dropwise at room temperature. Then the mixture was stirred for 30 min and monitored by TLC. The reaction mixture was evaporated to give the product 2x as a white solid in 50% yield. mp. 163–166 °C; 1H-NMR (DMSO-d6): δ 10.31 (s, 1H, CONH-Ar), 8.49 (d, J = 4.4 Hz, 1H, pyridyl-H), 8.16 (d, J = 4 Hz, 1H, pyr idyl-H), 7.60 (dd, J = 4.8 Hz, 8 Hz, 1H, pyridyl-H), 7.57 (s, 1H, pyrazolyl-H), 7.48 (s, 1H, Ph-H), 7.33 (s, 1H, Ph-H), 3.58(d, J = 5.6 Hz, 2H, COCH2NH), 2.23 (s, 3H, Ph-CH3); 13C-NMR (DMSO-d6): δ 182.92, 169.50, 152.51, 145.12, 143.97, 143.97, 136.17, 135.92, 131.92, 129.07, 127.88, 124.62, 123.57, 123.40, 122.90, 107.58, 36.50, 14.46; HRMS (ESI): m/z [M+H]+ calcd for C20H14BrCl2N6O3: 553.9610. Found: 554.9688.

3-Bromo-N-(4-chloro-2-((2-heptyl)carbamoyl)-6-methylphenyl)-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (2y). n-Heptylamine (25 mg, 0.22 mmol) was added to a solution of compound 1 (50 mg, 0.11 mmol) in THF (5 mL) at 50 °C. After 5 h, TLC showed the complete consumption of compound 1. The mixed solution was evaporated to remove the THF. The residue was dissolved in DCM (20 mL). The organic layer was washed with H2O, and dried to give a crude product that was then recrystallized from DCM/hexane (1:1.5) to give the product 2y as a white solid in 58% yield; mp. 162–168 °C; 1H-NMR (CDCl3): δ 10.12 (s, 1H, NHCOCH2), 8.44 (dd, J = 4.8 Hz, 1H, 6-H pyridine), 7.83 (dd, J = 4.8 Hz, 1H, 4-H pyridine), 7.36 (dd, J = 4.8 Hz, 8 Hz, 1H, 5-H pyridine), 7.21 (s, 1H, Ph-H), 7.17 (d, J = 6.4 Hz, 1H, NHCO), 7.15 (s, 1H, Ph-H), 6.14 (s, 1H, pyrazole-H), 3.35 (m, J = 7.2 Hz, 2H, CH2NH), 2.16 (s, 3H, Ph-CH3), 1.52 (m, J = 7.2 Hz, 2H, CH2CH3), 1.28 (m, J = 14 Hz, 8H, (CH2)4), 0.89 (t, J = 7.2 Hz, 3H, CH3); 13C-NMR (CDCl3): δ 167.84, 156.56, 149.09, 146.79, 138.81, 138.72, 133.22, 132.65, 132.26, 131.27, 129.00, 128.21, 125.63, 124.35, 111.03, 40.34, 31.68, 29.37, 28.91, 26.92, 22.59, 18.70, 14.06; HRMS (ESI): m/z [M+H]+ calcd for C25H26BrCl2N5O2: 566.0725. Found: 566.0740.

3.2. Biological Tests

3.2.1. Biological Assay Methods

All of the tested compounds had the purity of more than 95%, and all bioassays were performed on representative test organisms reared in the laboratory. Evaluations were based on a percentage scale of
0–100, in which 0 = no activity and 100 = total kill. The standard deviations of the tested biological values were ±5%.

3.2.2. Larvicidal Activities against Oriental Armyworm (*Mythimna separata* Walker)

The larvicidal activities against oriental armyworm were tested by foliar application [7]. The test was repeated at 25 °C ± 1 °C according to statistical requirements. The tested compounds were dissolved in acetone and diluted with water to the required concentrations from 200 to 5 mg/L for bioassay. Individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then dipped in the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 24 h after treatment. Each treatment was replicated for three times. For comparative purposes, chlorantraniliprole, indoxacarb and avermectins were selected as the controls under the same conditions.

3.2.3. Antifungal Bioassay: Inhibitory Effects on Phytopathogenic Fungi

The five phytopathogenic fungi chosen included *Fusarium oxysporum* (FO), *Cercospora arachidicola* (CA), *Physalospora piricola* (PP), *Alternaria solani* (AS), and *Fusarium graminearum* (FG). All the fungi are typical and often occur in the Chinese agro-ecosystem. The antifungal activities of nineteen chlorantraniliprole derivatives (2b–l, 2o–u and 2x) were tested in vitro by the poisoned food technique at the concentration of 50 µg/mL by dissolving the compounds in DMSO and sterilized water (containing 1% Tween) and diluting with PDA in a Petri dish [24–26].

3.3. Molecular Docking Methods

In our study, the membrane-spanning domain protein of the ryanodine receptor was selected from GenBank (accession No. JF927788) [8] as the possible specific receptor, which was proposed to bind with small molecules to give the Ki values using AutoDock4. For the AutoDock4 docking methods readers can refer to our previous work [8]. The Ki values were used to evaluate the binding energy between the small molecules and their possible receptor. The analysis of the relationship between the Ki values and the insecticidal activities against oriental armyworm could thus afford further information about the specific receptor.

4. Conclusions

A series of novel chlorantraniliprole derivatives containing different amide groups and anthraniloyl moieties were designed and synthesized. Their insecticidal activities against oriental armyworm and the antifungal activities against five typical fungi were evaluated. The results indicated that all tested compounds except three (2a, 2r and 2w) exhibited favorable insecticidal activities against oriental armyworm. In particular, compounds 2u and 2x showed obviously better activities than indoxacarb even when the concentration was lowered to 5 mg/L. The preliminary structure-activity relationship of the title compounds indicated that compounds with a cyano group (R2 = CN) had low insecticidal activities. Two methylene groups and a secondary amine in the amide moiety were necessary factors for increasing the insecticidal activities. Moreover, all of the tested compounds exhibited activities
against five typical fungi. The molecular docking results revealed that most of the compounds with available Ki values exhibited moderate to high activities against oriental armyworm. The relationship between the Ki values and the insecticidal activities suggested that the proposed membrane-spanning domain protein (GenBank accession no. JF927788) of the ryanodine receptor has special binding site(s) and might be the receptor of chlorantraniliprole and its analogs. Confirmation of this is a worthy topic for further study.

**Supplementary Materials**

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/03/3854/s1.

**Acknowledgments**

The project was supported by the National High-Tech Program of China (863 Project No. 2012AA020306).

**Author Contributions**

Conceived, designed the synthesis: Dequn Sun. Performed the chemical experiments and spectroscopic analysis: Qichao Chen, Min Luo, Jin Wang and Changyan Hu. Designed, performed and analysed the biological experiments: Lixia Xiong, Xiao Zhang, Shujing Yu and Yonghong Li. Performed the molecular docking part: Qichao Chen. Wrote the paper: Qichao Chen and Dequn Sun. All authors contributed to the paper and approved the manuscript.

**Conflicts of Interest**

The authors declare no conflict of interest.

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*Sample Availability:* Samples of the compounds 2a–y are available from the authors.

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