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Communication

Synthesis, insecticidal activities, and SAR studies of novel piperazine-containing heterocyclic mono-/di-/tri-amide derivatives

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ABSTRACT

Diamide compounds such as chlorantraniliprole, a famous anthranilic diamide insecticide targeting the insect ryanodine receptor (RyR), have received continuous attention in pesticide research during the past 15 years owing to their excellent insecticidal potentials. With the aim of discovering new heterocyclic pesticides used for crop protection, based on the structural information of compound **M** from the reported pharmacophore-based virtual screening for RyR insecticides and diamide compound, a series of new heterocyclic mono-, di-, and tri-amide derivatives containing piperazine moiety have been synthesized in this paper. The new compounds were identified and confirmed by melting point, ^{1}H NMR, ^{13}C NMR and HRMS. Compound **M** was firstly validated for insecticidal activities, and the new synthesized compounds were all made comprehensive insecticidal evaluations against diamondback moth and oriental armyworm. The bioassay results showed that some of the compounds exhibit favorable insecticidal potentials, particularly some novel piperazine-containing heterocyclic mono-/di-/tri-amide derivatives such as **8g**, **14a**, **15a**, **15g**, **15i**, **15j**, **15k**, **15l**, and **15m** could be used as new insecticidal leading structures for further study (*e.g.*, towards diamondback moth, **15i-15m** LC_{50}: 0.0022−0.0081 mg/L). The structure-activity relationships of the compounds discussed in detail provide useful guidance for further design and development of new insecticides.

Pesticides, particularly organosynthetic pesticides play a very important role in crop protection and ultimately bring numerous benefits to our life. Among the commercial organosynthetic pesticides produced in the last twenty years, there are about 70% structures of them containing the heterocyclic characteristics, which may be owing to the versatile physicochemical and biological properties of heterocyclic compounds [1–3]. Therefore, all kinds of new synthesized structures with different heterocycles are rich potential resources for the discovery and development of novel pesticides.

It is well known in pesticide chemistry area that the ryanodine receptor (RyR) has become one of the most attractive targets for the discovery of novel insecticides since the natural ryanodine was found have high insecticidal activity [4]. In the past 15 years, some new insecticides targeting at RyR have been successfully developed and marketed. As representatives of these insecticides, flubendiamide (discovered by Nippon Kayaku Co., Ltd., Fig. 1), chlorantraniliprole and cyantraniliprole (discovered by DuPont, Fig. 1) show potent and selective activating effect towards insect RyR, and possess exceptional activities upon a broad range of Lepidoptera, Diptera, Isoptera, and Coleoptera insects [5–7]. However, due to the overuse or misuse of these insecticides, resistance issue has been developed in some pests, such as *Tuta absoluta*, *Plutellidae Plutella*, and *Spodoptera exigua* [8–10]. Therefore, there is an urgent need to develop new insecticides to address the resistance and safety issues associated with this kind of insecticides. From the viewpoint of molecular structures of them, there are two amide bonds being composed of two carbonyl groups and two active NH groups that may have essential H-bond receptor and/or donor functions, especially there are pyridine and pyrazole heterocyclic motifs both in chlorantraniliprole and cyantraniliprole. Furthermore, cyclaniliprole, another recently developed insecticide by Ishihara Sangyo Kaisha (Fig. 1) [11], also has such two amide bonds and heterocyclic features.

Since the discovery of RyR insecticides, structural modifications related to them have received considerable attention. Although a variety of new compounds have been designed and synthesized based on their structures during the past 15 years, most of the synthesized compounds with favorable insecticidal activities still have such main diamide structural features [12]. Recently, Sindhu *et al.* carried out the pharmacophore-based virtual screening study to identify potential insect RyR modulators; as a result, five

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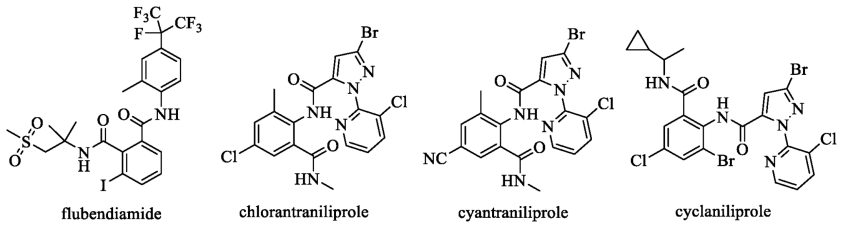


Fig. 1. Commercial diamide insecticides.

top-ranked compounds, code-named as ChemBridge_9217967, ChemBridge_7904959, ChemBridge_5913730, ChemBridge_7903714, and ChemBridge_6652261 (chemical structures shown in Supporting information), were obtained from a virtual screening of ChemBridge chemical database which contains 5,20,000 compounds using the pharmacophore model they developed [13]. Although Sindhu *et al.* did not report the further insecticidal bioassay for those "hit" compounds, that is, the experimental validation of their computational model and results [13], those hit structure information have already provided potential resource for the design and development of new insecticides. Inspired by this, one heterocyclic compound among the fives (4-(4-chloro-2-nitrophenyl)piperazin-1-yl)(5-methyl-2-phenylfuran-3-yl)methanone (ChemBridge_7903714, compound **M** in Fig. 2) raised our interest in viewing of its special skeleton of furanoyl piperazine and relatively convenient procedure for synthesis, and was selected to carry out the synthesis and bioactivity investigations of itself and some derivative new compounds based on its structural motifs in this paper. In addition, there are also other two reasons that compound **M** was considered as a structural precursor in this research. For one thing this compound is quite different in structure from the diamide RyR insecticides available, which would lead to new findings for RyR modulator research; for another, piperazine-containing compounds deserve being studied and developed for insecticidal agents since they are relatively rarely reported in the field of pesticides (especially insecticides), in spite of their wide applications in pharmaceutical area such as antifungal [14], anticancer [15], antituberculous [16], and antimicrobial [17] agents.

Based on the apparent insecticidal activity of the compound **M** from the preliminary evaluation, some new analogues **8a-8i** were thus designed for an extension with 2-nitro-4-chlorophenyl group in piperazine ring of precursor **M** being replaced by some other groups including alkyl, substitutedphenyl, and pyrimidyl groups. Furthermore, in view of the heterocyclic amide structure of the anthranilic diamide insecticide, *e.g.* chlorantraniliprole, some new piperazine-containing compounds (series of **14** and **15**) were designed by means of introducing various substitutedpiperazine moiety into the skeleton of pyridylpyrazole amide and synthesized for insecticidal activity evaluation. In addition, the anthranilamide moiety of chlorantraniliprole structure was also taken into account for the structure-activity relationship (SAR) exploration; a combination of it with the phenylfuran acyl motif (a partial group of compound **M**) could lead to new compound **16** (Fig. 2). Based on these strategies, in this study a series of new heterocyclic mono-, or di-, or tri-amide derivatives containing piperazine moiety mentioned above have been obtained under different reaction conditions, by taking into account of the structures of compound **M** along with that of RyR insecticide chlorantraniliprole. The insecticidal activities of the synthesized compounds were evaluated on diamondback moth and oriental armyworm and the SAR were also analyzed in detail.

Due to space constraints, the specific synthetic procedures of the intermediates and title compounds were included in the Supporting information. As shown in Scheme 1, compound 1-(4-chloro-2-nitrophenyl)piperazine (intermediate **2**) was successfully prepared in 41.2% yield from a nucleophilic substitution reaction of 1,4-dichloro-2-nitrobenzene and piperazine in DMF at 100 °C. Using ethyl 3-oxo-3-phenylpropanoate **3** as starting material, the key intermediate 5-methyl-2-phenylfuran-3-carboxylic acid **6** was prepared *via* multi-step reactions of carbon anion nuleophilic substitution, Paal-Knorr furan synthesis [18], and ester hydrolysis, successively. Treating phenylfuran acid **6** with oxalyl chloride gave the acyl chloride **7**, which was further reacted with piperazine **2** led to the compound **M** in 68.2% yield; using the similar procedure

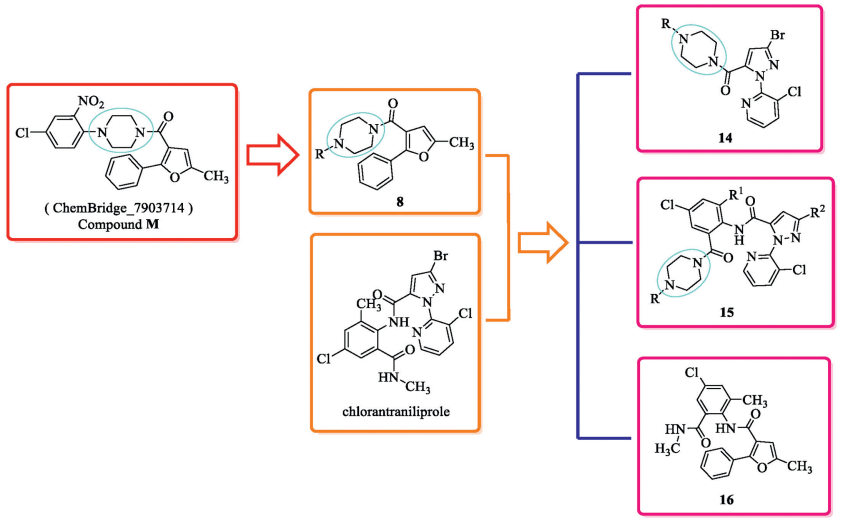
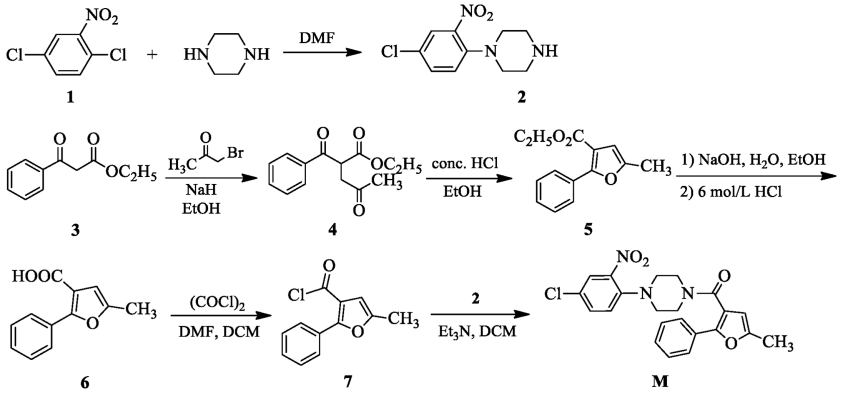
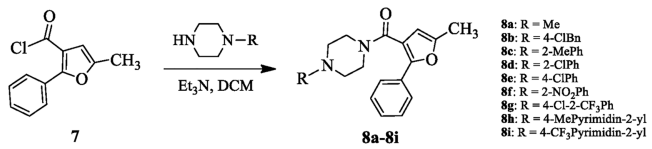


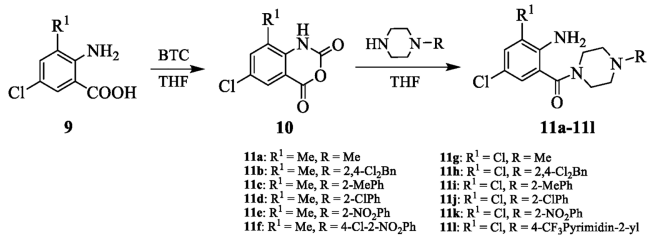
Fig. 2. Design of the title compounds.



Scheme 1. Synthesis of compound **M**.



Scheme 2. Synthesis of the title compounds **8**.



Scheme 3. Synthesis of the intermediates **11**.

with various 1-substitutedpiperazine as material, the title new compounds **8a-8i** were successfully synthesized (Scheme 2).

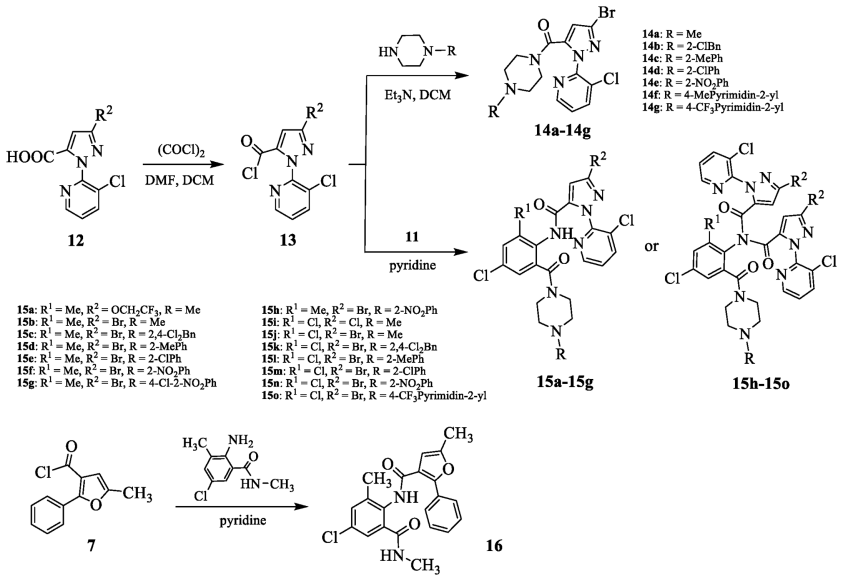
Adopting a similar procedure [19,20] a reaction of substituted 2-aminobenzoic acid **9** with bis(trichloromethyl)carbonate (BTC), followed by the treatment of the generated substituted-benzo[*d*]-[1,3]oxazine dione **10** with excess 1-substitutedpiperazine (1.5 equiv.) in boiling THF, afforded new intermediates **11** in moderate to high yield (48%– 88%) (Scheme 3).

As shown in Scheme 4, the nucleophilic addition-condensation reaction of *N*-pyridylpyrazole acyl chloride **13** and various 1-substitutedpiperazine also smoothly gave rise to the new title compounds **14a-14g**.

For the synthesis of the title compounds **15** by means of the mono-acylation reaction between *N*-pyridylpyrazole acyl chloride **13** and the piperazine-containing arylamine **11**, when initially using triethylamine as acid binding agent it was found that the reaction mainly led to the di-acylated product (for R^1 = Cl in most of cases); the desired mono-acylated product was also included, but the amount was little, and the work-up process to get pure product was difficult. The relatively weaker base pyridine was further tried for such reaction. The experiments showed that the reaction is comparatively clean under conditions of pyridine (both as acid binding agent and solvent) and room temperature to reflux, leading to an easier purification process. As a result, when using arylamine intermediates **11** with R^1 group as Me to conduct the reaction by the pyridine-protocol, the new mono-acylated products **15a-15g** can be successfully obtained in good yield; when using **11e** (R^1 = Me, R = 2-NO_2Ph) as arylamine reactant, both mono- and di-acylated products (**15f** and **15h**) were obtained; when using arylamine intermediates **11g-11l** which all contain Cl group for R^1 group to carry out this reaction, unexceptionally, the di-acylated products **15i-15o** were achieved in moderate yield. These results indicated that after the first acylation of compounds **13** and **11g-11l**, the activity of H atom in the generated —CONH— group (mono-acylated product) may be increased by its neighbouring Cl (R^1) and carbonyl (—(C=O)—) groups due to the electron-withdrawing conjugative/inductive effect, the second acylation therefore would be easier to occur to give the di-acylated products. Whereas, in the case of arylamine **11e**, besides mono-acylated product **15f**, a certain amount of di-acylated product **15h** was also formed, which may be derived from the electronic effect influence of both carbonyl group (—(C=O)—) generated in mono-acylation step and the *o*-NO_2Ph group of piperazine part (amide N—H activated). In addition, using a similar procedure, phenylfuran acyl chloride **7** and 2-amino-5-chloro-*N*,3-dimethylbenzamide reacted in pyridine at 0 °C to reflux, new compound **16** was obtained in 52.6% yield.

The novel structures of the related intermediates and title compounds were confirmed by ^{1}H NMR, and ^{13}C NMR. The measured high-resolution mass spectroscopy (HRMS) data were also consistent with the corresponding calculated values (presented in Suppoting information). In the ^{1}H NMR of the new piperazine-containing arylamines **11a-11L**, the active proton (NH_2) signal was observed at highfield with the chemical shift of 4.25–4.77 ppm. However, the active proton (NH) signals of the di-amide compounds **15a-15g** showed up one group of peak at very downfield with the chemical shift of 10.06–10.41 ppm, due to the deshielding effects of its neighbouring carbonyl and phenyl groups. In the cases of the piperazine-containing intermediates and title compounds (*i.e.*, **11**, **8**, **14** and **15**), the proton signals in the piperazine ring (CH_2) mostly appeared at chemical shift of 2.04–4.11 ppm as some groups of "brs" peaks with partial overlaps. Especially, in the ^{1}H NMR of tri-amide compounds **15h-15m**, there were eight groups of "brs" peaks for the corresponding piperazine—CH_2 protons being observed. This result indicated that each of protons in four piperzine—CH_2 groups of these compounds may be probably in different chemical surroundings, owing to a chair conformation of the existing six-membered piperazine ring [21,22]. Moreover, in the ^{13}C NMR of these piperazine compounds, the carbon signals of the piperazine ring were observed as four groups of peaks at different chemical shift from 41 ppm to 55 ppm, further indicating the "difference" of four piperzine—CH_2 groups.

Initially, compound **M** was successfully synthesized in our lab, and was then investigated on its insecticidal effect for the first time. It was found that **M** exhibited obvious larvicidal activity at a test concentration of 200 mg/L, with modest lethality rate of 35.0%



Scheme 4. Synthesis of the title compounds **14**, **15**, and **16**.

and 30.0% (100% means total kill) against oriental armyworm (*Mythimna separata* Walker) and diamondback moth (*Plutella xylostella* L.), respectively (Table 1). This result could not only provide a good validation for Sindhu's pharmacophore model to a certain extent, but also give us an useful clue for further structural modifications based on this interesting structure that contains piperazine and furan heterocycles, and mono-amide (non-NH type) motif. Subsequently, new derivatives **8a-8i**, **14a-14g**, **15a-15o** and **16** were further synthesized for insecticidal activity evaluation.

As a result, these novel compounds synthesized with mono-, or di-, or tri- amide structural characteristics showed good, even remarkable insecticidal activities towards diamondback moth and oriental armyworm on the whole. It should be noted that the compound may not be determined further at lower concentrations in most of the cases when the tested compound does not exhibit better insecticidal potentials at higher concentration of 200 mg/L or 100 mg/L (generally lower than 80%), since this is based on an unified bioassay pattern for a preliminary activity evaluation (Tables 1, 2 and 4). While partial compounds with a promising activity trend may be carried out further determination for LC_{50} values (Table 3). The detailed bioactivity and SAR analysis are discussed as follows.

As shown in Table 1, the mono-amide derivatives **8a-8i**, as the new analogues of compound **M**, were found to have better insecticidal activity against diamondback moth than that of compound **M**, *e.g.*, compound **8c** possessed lethality rate of 80.0% and 40.0% at the concentration of 100 mg/L and 10 mg/L, respectively; compound **8g** that bears a 4-Cl-2-CF_3Ph group in the piperazine ring particularly showed the best insecticidal activity in this series of compounds – 50.0% lethality rate at 1 mg/L. The R substituent corresponding to the insecticidal activity of compounds **8a-8i** generally displayed a trend of substituted phenyl ≥ methyl > substituted pyrimidyl > 4-chlorobenzyl. For the substituted phenyl groups, the activity trend was 4-Cl-2-CF_3Ph > 2-MePh > 2-NO_2Ph > 2-ClPh > 4-ClPh. Interestingly, a structural modification from 4-Cl-2-NO_2Ph (**M**) to 4-Cl-2-CF_3Ph (**8g**) led to a great improvement of insecticidal activity against diamondback moth, indicating that the substituents at phenyl *ortho*- and *para*- positions of piperazine group would result in great influence on the insecticidal activity of the corresponding compounds, possibly *via* their electronic/steric effect. Compared with the conventional structures of anthranilic diamide insecticides, these piperazine- and phenylfuran- containing mono-amide compounds have novel and simple structures, and favorable insecticidal potentials, especially **8g** could be taken as a new lead compound for further study.

Table 1
Larvicidal activities of compounds **M**, **8a-8i** and chlorantraniliprole against oriental armyworm *(Mythimna separata* Walker*)* and diamondback moth (*Plutella xylostella* L.).

Compd.	Activity against oriental armyworm (%) at 200 mg/L	Activity against diamondback moth (%) at a concentration of (mg/L)			
		200	100	10	1
M	35.0	30.0	n.t.*	n.t.	n.t.
8a	0	100	70.0	n.t.	n.t.
8b	0	70.0	n.t.	n.t.	n.t.
8c	25.0	97.0	80.0	40.0	n.t.
8d	70.0	80.0	50.0	n.t.	n.t.
8e	30.0	60.0	n.t.	n.t.	n.t.
8f	40.0	90.0	65.0	n.t.	n.t.
8 g	70.0	100	100	83.0	50.0
8h	10.0	80.0	n.t.	n.t.	n.t.
8i	25.0	80.0	n.t.	n.t.	n.t.
Chlorantraniliprole	100	100	100	100	100

* n.t. – not test.

Table 2
Larvicidal activities of the title compounds **14a-14g**, **15a-15o**, **16** and chlorantraniliprole against diamondback moth (*Plutella xylostella* L.).

Compd.	Activity (%) at a concentration of (mg/L)					
	200	100	10	1	0.1	0.01
14a	100	100	67.0	n.t.*	n.t.	n.t.
14b	75.0	n.t.	n.t.	n.t.	n.t.	n.t.
14c	0	n.t.	n.t.	n.t.	n.t.	n.t.
14d	70.0	n.t.	n.t.	n.t.	n.t.	n.t.
14e	40.0	n.t.	n.t.	n.t.	n.t.	n.t.
14f	80.0	n.t.	n.t.	n.t.	n.t.	n.t.
14g	100	70.0	n.t.	n.t.	n.t.	n.t.
15a	100	100	100	90.0	75.0	40.0
15b	100	100	100	80.0	50.0	n.t.
15c	75.0	60.0	n.t.	n.t.	n.t.	n.t.
15d	100	100	100	88.0	65.0	27.0
15e	100	100	100	93.0	78.0	45.0
15f	90.0	77.0	45.0	n.t.	n.t.	n.t.
15g	100	100	85.0	n.t.	n.t.	n.t.
15h	100	100	100	90.0	70.0	30.0
15i	100	100	100	100	85.0	60.0
15j	100	100	100	100	100	83.0
15k	100	100	100	100	90.0	70.0
15l	100	100	100	100	87.0	60.0
15m	100	100	100	100	100	75.0
15n	100	100	100	70.0	37.0	n.t.
15o	100	100	100	75.0	44.0	n.t.
16	100	100	100	90.0	61.0	n.t.
Chlorantraniliprole	100	100	100	100	100	80.0 (0.001 mg/L)

* n.t. – not test.

Table 3
LC_{50} values of compounds **15a**, **15e**, **15i**, **15j**, **15k**, **15l**, **15m** and chlorantraniliprole against diamondback moth (*Plutella xylostella* L.).

Compd.	$y = a + bx$	LC_{50} (mg/L)	R
15a	$y = 6.43 + 0.88x$	0.0237	0.9609
15e	$y = 6.78 + 0.93x$	0.0122	0.9643
15i	$y = 10.14 + 2.17x$	0.0042	0.9920
15j	$y = 9.91 + 2.21x$	0.0059	0.9916
15k	$y = 10.20 + 2.48x$	0.0081	0.9952
15l	$y = 10.25 + 1.97x$	0.0022	0.9846
15m	$y = 10.05 + 2.06x$	0.0035	0.9859
Chlorantraniliprole	$y = 10.64 + 2.25x$	0.0031	0.9812

As shown in Table 2, mono-amide derivatives **14a-14g** which were derived from a structural modification of compounds **8** by a substitution of phenylfuran group with *N*-pyridylpyrazole group mostly exhibited good larvicidal activity against diamondback moth at 200 mg/L (70.0%– 100%). At lower test concentrations, most of compounds **14** generally exhibited lower insecticidal potential than that of compounds **8** except that **14a** had a lethality rate of 67.0% towards diamondback moth at 10 mg/L.

From the data listed in Table 2, we can see that almost all the compounds **15** showed excellent insecticidal activity against diamondback moth at 200 mg/L and 100 mg/L. At lower concentrations, compounds **15a**, **15b**, **15d**, **15e**, and **15h-15o** held 70.0%–100% lethality rate at 1 mg/L; especially, compounds **15i-15m** still possessed 60.0%–83.0% activity at 0.1 mg/L, close to that of chlorantraniliprole.

An overall structure-activity relationship based on the diamondback moth bioassay data of compounds **15** could be concluded as follows. For one thing, a combination of piperazine-containing arylamine and pyridylpyrazole groups would generate very high insecticidal effect. For another, the tri-amide-like derivatives (di-acylated compounds) were more effective than the di-amide derivatives (mono-acylated compounds) in general. For example, under situation of bearing the same substituents (R^1 = Me, R^2 = Br, R = 2-NO_2Ph), tri-amide compound **15h** had much higher insecticidal activity than that of di-amide compound **15f** (70.0% at 0.1 mg/L (**15h**) *vs.* 45.0% at 10 mg/L (**15f**)). For the di-amide compounds **15a-15g**, when R^2 was fixed as Br, the R group in the piperazine of the corresponding compounds exhibited an activity trend: 2-ClPh > 2-MePh > Me > 4-Cl-2-NO_2Ph > 2-NO_2Ph > 2,4-Cl_2Bn (**15e** > **15d** > **15b** > **15g** > **15f** > **15c**); when R = Me, the activity trend for R^2 group is CF_3CH_2O > Br (**15a** > **15b**). For the tri-amide compounds **15h-15o**, when R^1 = Cl and R^2 = Br, the R group indicated an activity sequence: Me > 2-ClPh > 2,4-Cl_2Bn > 2-MePh > 4-CF_3Pyrimidyl > 2-NO_2Ph (**15j** > **15m** > **15k** > **15l** > **15o** > **15n**); when R^1 and R were fixed as Cl and Me, respectively, the R^2 group in corresponding compounds showed an activity trend of Br > Cl (**15j** > **15i**); when R^2 and R were fixed as Br and 2-NO_2Ph, respectively, the R^1 group displayed an activity sequence of Me > Cl (**15h** > **15n**). The results indicated that the piperazine moiety containing various groups have significant influence on the insecticidal activity of such novel di- and tri-amide compounds; a possible synergistic effect of substituted piperazine moiety with other groups such as pyridylpyrazole, two amide bonds (one "NH" and one "non-NH") and three amide bonds (three "non-NH") may contribute to the favorable insecticidal activity of this type of compounds.

From the same Table 2, it was found that compound **16** also show high insecticidal activity and can even possess 61.0% lethality rate at a lower test concentration of 0.1 mg/L towards diamondback moth. As mentioned above, compound **16** is derived from both compound **M** (from pharmacophore-based virtual screening [13]) and chlorantraniliprole. Based on the common anthranilic diamide skeleton, the structural difference of compound **16** and chlorantraniliprole is that the former has a phenylfuran group and the latter has a pyridylpyrazole group. Although less effective than chlorantraniliprole, compound **16** might provide an useful reference for further design and development of new insecticidal agents, owing to its novel heterocyclic structure of phenylfuran.

In addition, some compounds with high insecticidal activity against diamondback moth were made further investigation on LC_{50} values. As shown in Table 3, compounds **15a**, **15e**, and **15i-15m** displayed favourable larvicidal activity against diamondback moth with LC_{50} value of 0.0022−0.0237 mg/L. Among which, **15i-15m** whose LC_{50} values were 0.0022−0.0081 mg/L, were comparable with that of chlorantraniliprole (0.0031 mg/L). Particularly, **15i**, **15m**, and **15l** held LC_{50} values of 0.0042 mg/L, 0.0035 mg/L, and 0.0022 mg/L, respectively, close to even superior to chlorantraniliprole (0.0031 mg/L) under the same bioassay conditions.

As shown in Tables 1 and 4, most of the title compounds **8**, **14**, **15** and **16** mainly exhibited apparent insecticidal activity against oriental armyworm at 200 mg/L. Partial compounds were found to retain good activity at lower dosages, better than that of compound **M**. For examples, **14a**, **14c**, **15f**, **15g**, **15k**, and **15l** possessed lethality rate of 40.0%–100% at 100 mg/L; **14a**, **15g**, and **15l** at 50 mg/L showed larvicidal activity of 60.0%, 70.0%, and 40.0%, respectively. The substituent (R) in the piperazine ring also had an impact on the insecticidal activity of the corresponding compounds in some extent. Take the situation in compounds **15** as an example, the structure-activity relationship indicated that the R substituent showed an activity sequence of 4-Cl-2-NO_2Ph > 2-NO_2Ph > 2-ClPh > 2-MePh, 2,4-Cl_2Bn > Me for the di-amide compounds **15b-15g** (R^1 = Me, R^2 = Br), and 2-MePh > 2,4-Cl_2Bn > 2-NO_2Ph > 2-ClPh, 4-CF_3Pyrimidyl > Me for the tri-amide compounds **15j-15o** (R^1 = Cl, R^2 = Br), respectively.

According to the bioassay results of these synthesized compounds towards diamondback moth and oriental armyworm, some novel piperazine-containing mono-/di-/tri-amide compounds such as **8g**, **14a**, **15a**, **15g**, **15i**, **15j**, **15k**, **15l**, and **15m** could be used as new insecticidal leading compounds for further

Table 4
Larvicidal activities of the title compounds **14a-14g**, **15a-15o**, **16** and chlorantraniliprole against oriental armyworm (*Mythimna separata* Walker).

Compd.	Activity (%) at a concentration of (mg/L)		
	200	100	50
14a	100	100	60.0
14b	15.0	n.t.*	n.t.
14c	100	65.0	n.t.
14d	25.0	n.t.	n.t.
14e	80.0	n.t.	n.t.
14f	15.0	n.t.	n.t.
14g	20.0	n.t.	n.t.
15a	80.0	n.t.	n.t.
15b	30.0	n.t.	n.t.
15c	50.0	n.t.	n.t.
15d	50.0	n.t.	n.t.
15e	70.0	n.t.	n.t.
15f	100	40.0	n.t.
15g	100	100	70.0
15h	30.0	n.t.	n.t.
15i	30.0	n.t.	n.t.
15j	40.0	n.t.	n.t.
15k	100	40.0	n.t.
15l	100	100	40.0
15m	50.0	n.t.	n.t.
15n	60.0	n.t.	n.t.
15o	50.0	n.t.	n.t.
16	55.0	n.t.	n.t.
Chlorantraniliprole	100	100	100

* n.t. – not test.

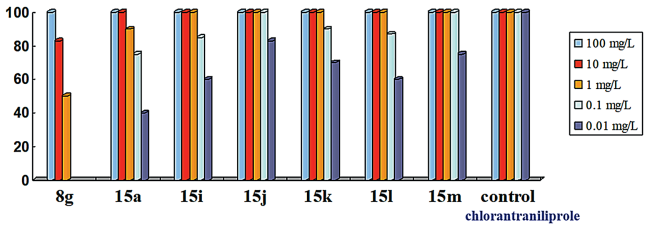


Fig. 3. The larvicidal activity diagram of new piperazine-containing compounds **8g**, **15a**, and **15i-15m** against diamondback moth (*Plutella xylostella* L.) at different test concentrations.

development of novel insecticides (partial structures corresponding to their activity data were illustrated in Fig. 3).

In summary, on referring to the structural information of one of the "hit" compounds (**M**) from the reported pharmacophore-based virtual screening for RyR insecticides by Sindhu *et al*., a series of new heterocyclic mono-, di-, and tri-amide derivatives containing piperazine moiety have been synthesized under different reaction conditions in this paper. The new compounds were identified and confirmed by melting point, ^{1}H NMR, ^{13}C NMR and HRMS. Besides that compound **M** was firstly validated for insecticidal activities, the new synthesized compounds were all made comprehensive bioactivity evaluations on diamondback moth and oriental armyworm. The bioassay results showed that some of the compounds exhibit favorable insecticidal potentials, particularly some novel piperazine-containing heterocyclic mono-/di-/tri-amide derivatives such as **8g**, **14a**, **15a**, **15g**, **15i**, **15j**, **15k**, **15l**, and **15m** could be used as new insecticidal leading structures for further study (*e.g.*, towards diamondback moth, **15i-15m** LC_{50}: 0.0022−0.0081 mg/L). The structure-activity relationships of these compounds discussed in detail provide useful guidance for further design and development of new insecticides.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2021.02.002.

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