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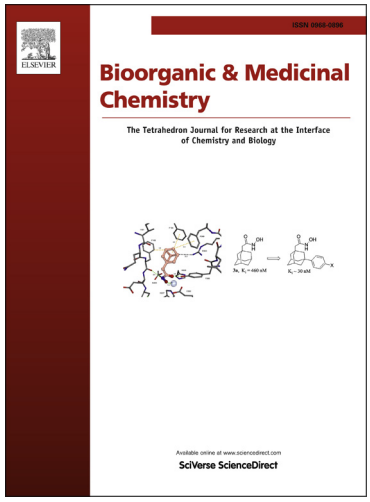

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Synthesis and insecticidal activities of 2,3-dihydroquinazolin-4(1*H*)-one derivatives targeting calcium channel

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ABSTRACT

A series of compounds containing dihydroquinazolinone moiety was designed and synthesized. Amine bridge part was changed in comparison with known anthranilic diamides insecticides. Their insecticidal activities against oriental armyworm (*Mythimna separata*) indicated that most of the compounds showed moderate to high activities at the tested concentrations. In particular, compound **5a** and **5k** showed 80 % larvicidal activities against oriental armyworm at the concentration of 5 mg/L. The present study also explored the possible effects of target compounds on the high voltage-gated calcium channel and the calcium channels in the endoplasmic reticulumn in the central neurons isolated from the third instar larvae of *Spodoptera exigua* using whole-cell patch clamp and calcium imaging technique. The results showed that compound **5a** activated the high voltage-gated calcium channel in the central neurons of *S. exigua* weakly. The peak currents only increased by 6 % of the initial value at the end of the 10-min recording after treated with 0.22 μM **5a,** while chlorantraniliprole has an opposite effect. The effects of **5a** on the intracellular calcium ion concentration ($[Ca^{2+}]_i$) in neurons were well investigated. The experimental results indicated that these novel compounds have different mechanism compared with chlorantraniliprole.

1. Introduction

The majority of insecticides currently available on the market is affecting signal transmission in the central nervous system.[1] Recently, two anthranilic diamide insecticides were discovered by Dupon,[2] namely chlorantraniliprole (**Fig. 1**, **A**) and cyantraniliprole (**B**),[4,5] have been introduced into the market. They have a novel mode of action targeting at ryanodine receptors-disrupting calcium homeostasis.[3]

So far, these two compounds exhibit exceptional broad-spectrum activity,[2] high potency and low mammalian toxicity. In addition, both are selective activators of insect ryanodine receptor, causing uncontrolled release of internal calcium and ultimately leading to death.[6] Since the discovery of anthranilic diamides, most of the modifications were categorized to *N*-pyridylpyrazole moiety (**a**)[7-11] and benzamide moiety (**b**),[12-17] while few changes of amine bridge moiety were reported (**c**).[18, 19] In our previous work, we found the amine bridge part has a great impact on the insecticidal activity.[20, 21]

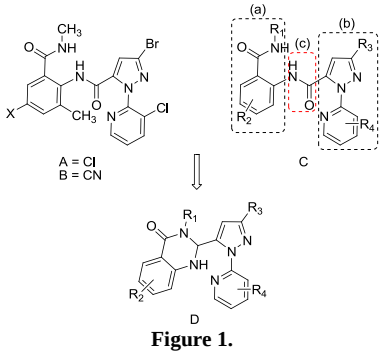

Figure 1.

Dihydroquinazolinone moiety as an efficient pharmacophore was extensively used in pesticide and drug molecule design.[22, 23] Until now, anthranilic diamides containing 2,3-dihydroquinazoline structure have not been reported. To further study the role of the amine bridge moiety played in the biological activities, a series of compounds which have dihydroquinazolinone moiety were synthesized.

Their synthetic routes were shown in **Scheme 1-5**, and the insecticidal activity against oriental armyworms was tested accordingly. The preliminary structure-activity relationship

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(SAR) was also discussed. In order to increase understanding of the mechanisms of the compounds, the whole-cell patch-clamp and calcium imaging techniques were used to investigate the effects of compounds on calcium channels in the central neurons of *S. exigua*.

2. Results and discussion

2.1. Chemistry

The synthetic route of compounds **4a-p** were shown in **Schemes 1, 2** and **3**. Compounds **4a-n** were prepared according to the reported method [24-29] with minor improvements. 2-Aminobenzoic acid with different substituents were treated with thionyl chloride and then coupled with excessive amine to provide amides **4a-n**. Nevertheless, a reaction in milder conditions and satisfactory yields to synthesize **4o** and **4p** was reported in this paper. 2-Aminobenzoic acid was reacted with triphosgene or *N*, *N*'-carbonyldiimidazole (CDI) to generate the isatoic anhydride, subsequently reacted with excessive amine to yield compounds **4o** and **4p** in excellent yields after filtration.

Compound **1** was achieved by referring to the known procedure, further reduction to give alcohol **2** by using one equivalent of lithium aluminum hydride as reductant. When more than twice of the reducing agent were used, dechlorination in the 3-position of the pyridine ring was found, which was confirmed by ^{1}H NMR. The compound **2** was oxidized to **3** with PCC in high yields and purity.

As shown in **Scheme 4**, compounds **5a-r** were synthesized from compounds **4a-p** and **3a-b** using *p*-toluenesulfonic acid monohydrate as a catalyst, and this kind of reaction can be carried out smoothly in toluene.

Compound **6** was obtained from compound **4a** reacted with acetone. However, subsequent reaction with **7** failed to afford **8**, probably owing to steric hindrance of two methyl groups in the 2-poistion of compound **6**.

2.2. Crystal structure analysis

Compound **5a** was recrystallized from ethyl acetate to give colorless crystals (0.26 mm × 0.22 mm × 0.20 mm) suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a = 9.369 (2) Å, b = 12.973 (3) Å, c = 15.592 (4) Å, α = 90º , β = 104.521 (4)º, γ = 90º, V = 1834.5 (7) Å^3, D_c = 1.691 g cm^{-3}, μ = 2.552 mm^{-1}, F (000) = 936, R = 0.0287, wR = 0.0690, Z = 4. Compound **5b** was recrystallized from ethyl acetate/petroleum ether (60-90 ℃) to give colorless crystals (0.20 mm × 0.18 mm × 0.10 mm) suitable for X-ray single-crystal diffraction with the following crystallographic parameters: a = 13.089(4) Å, b = 11.032(4) Å, c = 14.270(5) Å, α = 90º, β = 109.241 (4)º, γ = 90º, V = 1945.3 (11) Å^3, D_c = 1.650 g cm^{-3}, μ = 2.413 mm^{-1}, F (000) = 968, R = 0.0335, wR = 0.0725, Z = 4. Their structures are shown in **Fig. 2**. The dihedral angels of **5a** and **5b** are shown in **Table 1**.

Generally, the average bond lengths and bond angles of ring system (pyridine, pyrazole and dihydroquinazolinone ring) are normal ranges.[30-36] As shown in **Fig. 2**, in the compound **5a**, the phenyl ring is vertically with both the pyridine ring and pyrazole ring with the dihedral angles of 79.78º and 81.89º. The pyridine ring is nearly planar with pyrazole ring with a small dihedral angle (θ) of 22.40º. In the compound **5b**, the pyridine ring is oblique with pyrazole ring and phenyl ring with dihedral angle (θ) of 42.88º and 71.55º respectively. From the crystal structure, the dihedral angles are not the same between compound **5a** and **5b**, resulting in a difference in insecticidal activity.

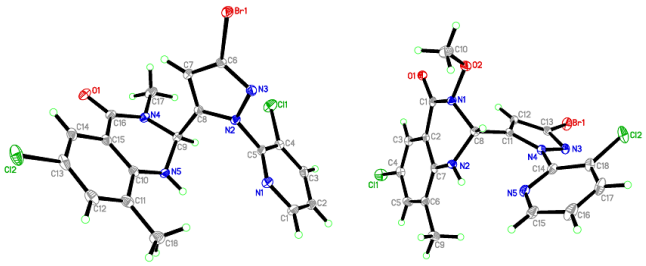


Figure 2. Molecular structure of compound **5a** and **5b**

Table 1. Dihedral angles of **5a** and **5b**

			angle (deg)	
No.	plane1	plane2	**5a**	**5b**
I	pyridine ring	pyrazole ring	79.78	42.88
II	pyridine ring	benzene ring	22.40	71.55
III	pyrazole ring	benzene ring	81.89	87.39

2.3. Structure-activity relationship (SAR).

The larvicidal activities of **5a-s** and commercial chlorantraniliprole against oriental armyworms were summarized in **Table 2**. The bioassay results indicated that most of the compounds showed moderate to good insecticidal activities. Especially compounds **5a** and **5k** showed 80 % larvicidal activities at the concentration of 5 mg/L.

Activities varied significantly depending upon the types of substituents on the 3-position dihydroquinazolinone. Compared with 3-CH_2CH_3 and 3-OCH_3 in dihydroquinazolinone, compounds with 3-H and 3-CH_3 substituents showed higher insecticidal activities against oriental armyworm, with the sequence of **5a** = **5k** > **5b** > **5h** > **5f** > **5e** > **5d**, suggesting that in the 3-position of dihydroquinazolinone, small substituents have a positive effect on the larvicidal activities. When the substituent is *t*-Bu, it shows no activity at 50 mg/L.

Furthermore, different substituents in the benzene ring had diverse influence on activity. When R_1 was fixed as CH_3, the bioactivity of compounds with different R_2 indicated the sequence of 6-Cl, 8-CH_3 (**5a**) > 8-CH_3 (**5j**) >> H (**5i**), and compounds with 3-cyclopropyl showed a similar trend. However, when R_1 was fixed as isopropyl, the compounds with CH_3 group in 8-position of the benzene ring exhibited lower activities, this trend is not consistent with that when R_1 was CH_3. In addition, the dechlorination at the 3-position of the pyridine ring led to a significant decrease in activity, such as **5q** and **5r**. Surprisingly, the bioassay showed that the compound **5a** exhibited significantly higher insecticidal activity than **5s**, indicating that the C-N bond of 1-position in dihydroquinazolinone has significant effect on the activity.

The larvicidal activities of compounds **5a** and **5d** against *S. exigua* was also tested. The results indicate that compound **5a** has 100 % morality at 25 mg/L, and compound **5d** shows 40 % larvicidal activities at the concentration of 50 mg/L. Further studies on SAR are currently underway in our laboratories.

2.4. Electrophysiological recordings

The currents of calcium (I_{Ca}) were recorded using the reported procedure.[37] **Fig. 3** shows the change rate of peak current amplitude versus recording time in neurons treated with 0.22 μM **5a**, 0.1 μM, 0.01 mM chlorantraniliprole and the control neurons. Compared to chlorantraniliprole and control, the peak currents were elevated to 106.3 ± 1.58 % (n = 9) after the neurons were

treated with 0.22 μM **5a**. The peak currents decreased by 20 % of the initial value by the end of 10-min recording. The experimental results obtained from patch-clamp technique indicated that compound **5a** has weak effect on the voltage-gated calcium channel. **Fig. 4** shows the maximal value of calcium currents (I_{Ca}) did not shift after the neurons were treated with **5a**. It is concluded that the voltage dependency of calcium do not affact by **5a**. The recorded peak currents of calcium channels and *I-V* relationship curves of whole-cell calcium channels recorded in 0.22 μM **5a**-treated the third larvae neurons of *S. exigua* indicated that the activation of voltage-gated channel by compound **5a** is weak.

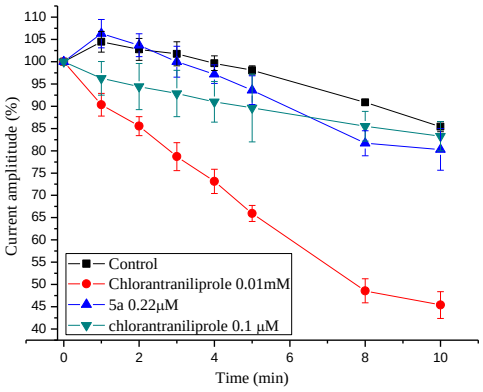


Figure 3. The change rates of peak current amplitude versus recording time in the **5a**, chlorantraniliprole treated and control neurons.

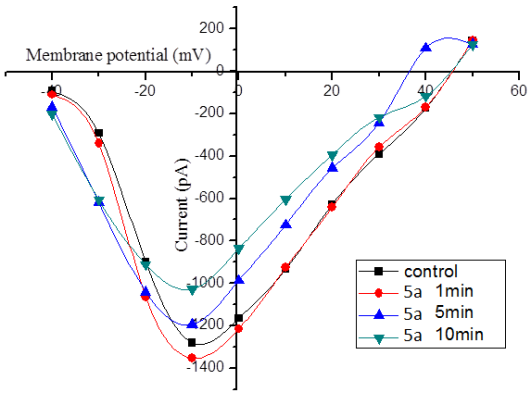


Figure 4. The current–voltage relationship curves of whole-cell calcium channels recorded in 0.22 μM **5a**-treated the third larvae neurons of *S. exigua* at different times.

2.5. Calcium imaging

Fig. 5 shows the change of $[Ca^{2+}]_i$ vs. recording time when the neurons were treated with 2.2 μM, 1.1 μM, 0.54 μM **5a** in the presence or absence of extracellular calcium. Application of **5a** to isolated *S. exigua* neurons caused an increase in the cytosolic calcium concentration. The peaks of $[Ca^{2+}]_i$ were 104.68 ± 2.26 % (n = 12), 111.91 ± 4.47 % (n = 6) 107.2 ± 2.6 % (n = 12) of the initial value after the neurons were treated with **5a** shorter than 20 seconds respectively. In the absence of extracellular calcium, the elevation of calcium ion concentration in the neurons is due to release from internal stores. Our experimental results also indicated that the elevation of calcium concentration by **5a** is concentration independent.

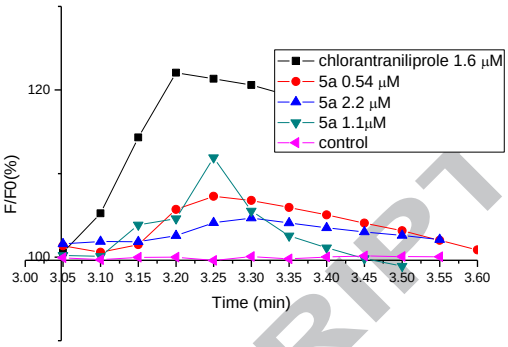


Figure 5. **5a** induced calcium elevation in isolated *S. exigua* in the presence or absence of extracellular calcium. The central neurons of *S. exigua* third larvae were dyed by loading with fluo-3 AM.

After the incubation of the primary cultured neurons with 2-aminoethoxydiphenyl borate (2-APB, 50 μM, a chemical that acts to inhibit both IP_3R and TRP), there is no difference in the elevation of calcium ion concentration.

Though the calcium imaging technique experiments demonstrated that RyRs would be the possible action target of this series of novel compounds, the whole-cell patch clamp also indicated that these novel compounds have different effect on the voltage-gated calcium channel compared with chlorantraniliprole. In view of the complexity of calcium-signaling pathways, a depolarization-induced limited calcium influx *via* voltage-gated calcium channel by compound **5a** may induce calcium release from endoplasmic reticulum.

3. Conclusion

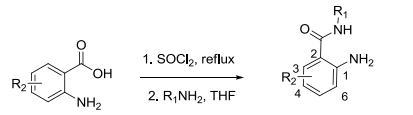
In summary, a series of compounds containing 2, 3-dihydroquinazolinone moiety were synthesized, and their structures were characterized and confirmed by ^{1}H NMR and HRMS. The bioassays showed that some compounds exhibited favorable insecticidal activities against oriental armyworm. In particular, compounds **5a** and **5k** against oriental armyworm were 80 % at 5.0 mg/L. The preliminary structure-activity relationship of the title compounds indicated that the small substituents in dihydroquinazolinone were preferred. The calcium imaging technique experiments demonstrated that RyRs would be the possible action target of this series of novel compounds. To meet the requirements of future insect control, RyRs is a promising targets for designing novel insecticides.

4. Experimental section

4.1. Chemistry

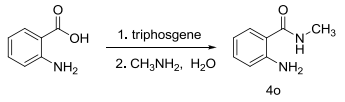
^{1}H NMR spectra were recorded at 300 MHz using a Bruker AC-P300 spectrometer or 400 MHz using a Bruker AV 400 spectrometer (Bruker Co., Switzerland) in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard, and chemical shift values (δ) were given in ppm. High-resolution mass spectrometry (HRMS) data were obtained on a Varian QFT-ESI instrument. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and uncorrected. Flash chromatography was performed with silica gel (200-300 mesh). The whole-cell patch-clamp was performed using patch-clamp amplifier (EPC-10, HEKA Electronik, Lambrecht, Germany).

Reagents were all analytically or chemically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. Chlorantraniliprole used in this work was synthesized according to the literature[38] as the control.



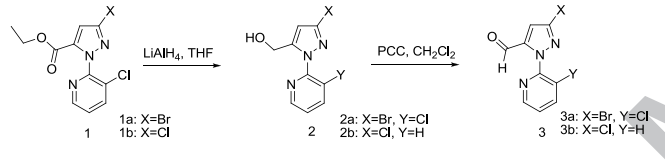
4a: R_1=CH_3, R_2=4-Cl, 6-CH_3; 4b: R_1=OCH_3, R_2=4-Cl, 6-CH_3
4c: R_1=i-Pr, R_2=4-Cl, 6-CH_3; 4d: R_1=t-Bu, R_2=4-Cl, 6-CH_3
4e: R_1=cyclopropyl, R_2=4-Cl, 6-CH_3; 4f: R_1=n-Pr, R_2=4-Cl, 6-CH_3
4g: R_1=2-thiazole , R_2=4-Cl, 6-CH_3; 4h: R_1=Et, R_2=4-Cl, 6-CH_3
4i: R_1=CH_3, R_2= 6-CH_3; 4j: R_1=i-Pr, R_2=4-Cl
4k: R_1=n-Pr, R_2=4-Cl; 4l: R_1=cyclohexyl, R_2=4-Cl
4m: R_1=cyclopropyl, R_2=4-Br, 6-CH_3; 4n: R_1=cyclopropyl, R_2= 6-CH_3

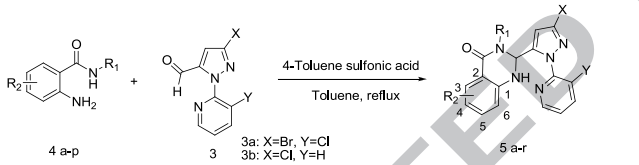
Scheme 1



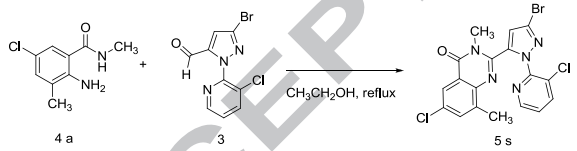
Scheme 2

Scheme 3

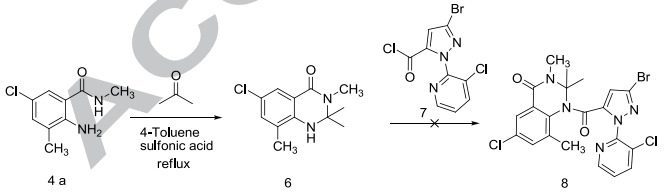




Scheme 4



Scheme 5



Scheme 6

4.1.1. General synthetic procedure for compounds 4a-n, 4o and 4p

Compounds **4a-f**, **4i** and **4n** were prepared in moderate yield by the method reported[9, 24-29, 38] respectively. Compounds **4o** and **4p** were prepared according to Hanusek[39] and Cheng[40] respectively. The ^{1}H NMR and melting point data were consistent with the literature.

2-Amino-5-chloro-3-methyl-*N*-(thiazol-2-yl)benzamide (4g) Yellow solid; yield, 45 %; mp 250-252 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.05 (s, 1H, CONH), 7.48 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.31 (d, 1H, ^3J = 4.4 Hz, Ar-H), 7.22 (s, 1H, Ar-H), 6.99 (d, 1H, ^3J = 4.8 Hz, Ar-H), 5.77 (s, 2H, NH_2), 2.20 (s, 3H, CH_3).

2-Amino-5-chloro-*N*-ethyl-3-methylbenzamide (4h) White solid; yield, 52 %; mp 109-110 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.10 (d, 1H, ^4J = 1.8 Hz, Ar-H), 5.95 (br s, 1H, NH), 5.53 (s, 2H, NH_2), 3.49-3.40 (m, 2H, CH_2), 2.14 (s, 3H, Ar-CH_3), 1.25 (t, 3H, ^3J = 7.5 Hz, CH_3).

2-Amino-5-chloro-*N*-isopropylbenzamide (4j) White solid; yield, 40 %; mp 165-166 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.14 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.7 Hz, Ar-H), 6.62 (d, 1H, ^3J = 8.7 Hz, Ar-H), 5.78 (br s, 1H, NH), 5.47 (s, 2H, NH_2), 4.28-4.16 (m,1H, CH), 1.26 (d, 6H, ^3J = 6.3 Hz, CH_3).

2-Amino-5-chloro-*N*-propylbenzamide (4k) White solid; yield, 55 %; mp 120-122 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (in $CDCl_3$, 1H, Ar-H), 7.15 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.7 Hz, Ar-H), 6.62 (d, 1H, ^3J = 8.7 Hz, Ar-H), 6.01 (br s, 1H, NH), 5.47 (s, 2H, NH_2), 3.37 (q, 2H, ^3J = 6.9 Hz, NH$\underline{CH_2}$), 1.69-1.57 (m, 2H, CH_2), 0.99 (t, 3H, ^3J = 7.5 Hz, CH_3).

2-Amino-5-chloro-*N*-cyclohexylbenzamide (4l) White solid; yield, 60 %; mp 176-177 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.14 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.7 Hz, Ar-H), 6.62 (d, 1H, ^3J = 8.7 Hz, Ar-H), 5.82 (br s, 1H, NH), 5.47 (s, 2H, NH_2), 3.97-3.84 (m, 1H, CH), 2.04-1.99 (m, 2H, cyclohexyl), 1.80-1.74 (m, 2H, cyclohexyl), 1.68-1.61 (m, 1H, cyclohexyl), 1.50-1.35 (m, 2H, cyclohexyl),1.29-1.15 (m, 3H, cyclohexyl).

2-Amino-5-bromo-*N*-cyclopropyl-3-methylbenzamide (4m) White solid; yield, 65 %; mp 150-151 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (s, 2H, Ar-H), 6.10 (s, 1H, NH), 5.63 (s, 2H, NH_2), 2.88-2.79 (m,1H, CH), 2.14 (s, 3H, Ar-CH_3), 0.90-0.84 (m, 2H, cyclopropyl), 0.64-0.58 (m, 2H, cyclopropyl).

4.1.2. General synthetic procedure for compounds 2a-b

To a 0℃ solution of ethyl 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylate (**1a**) (0.33 g, 1.0 mmol) in 15 mL of tetrahydrofuran, lithium aluminum hydride (0.038 g, 1.0 mmol) was added in small portions. The reaction was maintained at 0 ℃ and monitored with TLC. After agitation for 1 h, excessive dosage of sodium sulfate was added with vigorous stirring for 20 min. The precipitation was filtered and the filtrate was evaporated. The residue was applied to a flash column chromatography by eluting with petroleum ether/ethyl acetate (3:1) to give the compound **2a** as a white solid; yield, 89 %; mp 109-111 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, 1H, ^3J = 4.8 Hz, ^4J = 1.6 Hz, Ar-H), 8.01 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.4 Hz, Ar-H), 7.39 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 6.49 (s, 1H, Ar-H), 4.51 (d, 2H, ^3J = 6.8 Hz, CH_2), 4.29 (t, 2H, ^3J = 6.8 Hz, OH).

Compound **2b** was synthesized according to the procedure of **2a**, except for duplation of the amount of lithium aluminum hydride. White solid; yield, 70 %; mp 72-73 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (dd, ^3J = 5.0, ^4J = 1.0 Hz, 1H, Ar-H), 8.00 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.94 - 7.88 (m, 1H, Ar-H), 7.33 - 7.27 (m, 1H, Ar-H), 6.34 (s, 1H, Ar-H), 5.82 (t, ^3J = 7.5 Hz, 1H, OH), 4.68 (d, ^3J = 7.4 Hz, 2H, CH_2).

4.1.3. General synthetic procedure for compounds 3a-b

To the suspension of PCC (0.43 g, 2 mmol) in 15 mL of dichloromethane, a solution of (3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)methanol (**2a**) (0.287 g, 1.0 mmol) in 15 mL of dichloromethane was added in one portion at room temperature. The reaction was monitored with TLC. After agitation for 10 h, 1 g of silica gel was added and stirred for another 30 min. The solvent was evaporated, and the residue

was applied to a flash column chromatography by eluting with ethyl acetate to give the compound **3a** as a yellow solid; yield, 78 %; mp 104-105 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H, CHO), 8.53 (dd, 1H, ^4J = 2.0 Hz, ^3J = 6.0 Hz, Ar-H), 7.99 (dd, 1H, ^4J = 2.0 Hz, ^3J = 10.8 Hz, Ar-H), 7.49 (dd, 1H, ^3J = 6.0 Hz, ^3J = 10.8 Hz, Ar-H), 7.12 (s, 1H, Ar-H).

(3-Chloro-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)methanol (3b) yellow solid; yield, 80 %; mp 70-71 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.71 (s, 1H, CHO), 8.46 (d, ^3J = 4.3 Hz, 1H, Ar-H), 7.92 (q, 2H, Ar-H), 7.33 (t, 1H, Ar-H), 6.97 (s, 1H, Ar-H).

4.1.4. General synthetic procedure for compounds 5a-r

2-Amino-5-chloro-*N*, 3-dimethylbenzamide (**4a**) (0.099 g, 0.5 mmol) and 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbaldehyde (**3a**) (0.143 g, 0.5 mmol) were dissolved in 20 mL of toluene, followed by a catalytic amount of *p*-toluenesulfonic acid monohydrate. The resulting mixture was refluxed for 1 h and then evaporated. The residue was dissolved in ethyl acetate (40 mL), and washed with saturated sodium bicarbonate solution (2 × 20 mL). The organic layer was dried over with sodium sulfate and evaporated to obtain the crude product, which was further purified with flash column chromatography by eluting with petroleum ether/ethyl acetate (2:1) to afford the compound **5a** as a white solid; yield, 92 %; mp 247-249 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, 1H, ^4J = 1.4 Hz, ^3J = 4.6 Hz, Ar-H), 8.05 (dd, 1H, ^4J = 1.6 Hz, ^3J = 8.0 Hz, Ar-H), 7.82 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.46 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.14 (d, 1H, ^4J = 2.4 Hz, Ar-H), 6.26 (s, 1H, Ar-H), 5.95 (d, 1H, ^3J = 1.6 Hz, NH), 5.71 (d, 1H, ^3J = 3.6 Hz, CH), 3.07 (s, 3H, NCH_3), 2.09 (s, 3H, Ar-CH_3). HRMS calcd for $C_{18}H_{14}BrC_{l2}N_5O$ ([M-H]$^-$): 463.9686, found: 463.9682.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-methoxy-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5b) White solid; yield, 89 %; mp 200-202 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, 1H, ^4J = 1.6 Hz, ^3J = 4.8 Hz, Ar-H), 8.04 (dd, 1H, ^4J = 1.4 Hz, ^3J = 8.2 Hz, Ar-H), 7.84 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.45 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.18 (d, 1H, ^4J = 2.0 Hz, Ar-H), 6.44 (s, 1H, Ar-H), 6.07 (br s, 1H, NH), 6.03 (d, 1H, ^3J = 2.4, CH), 3.83 (s, 3H, OCH_3), 2.11 (s, 3H, Ar-CH_3). HRMS calcd for $C_{18}H_{14}BrCl_2N_5O_2$ ([M+H]$^+$): 481.9781, found: 481.9785.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-isopropyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5c) White solid; yield, 88 %; mp 222-224 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (dd, 1H, ^4J = 1.4 Hz, ^3J = 4.6 Hz, Ar-H), 8.08 (dd, 1H, ^4J = 1.6 Hz, ^3J = 8.2 Hz, Ar-H), 7.84 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.51 (dd, 1H, ^3J = 4.4 Hz, ^3J = 8.0 Hz, Ar-H), 7.13 (d, 1H, ^4J = 2.0 Hz, Ar-H), 6.27 (s, 1H, Ar-H), 5.88 (d, 1H, ^3J = 2.0, NH), 5.67 (d, 1H, ^3J = 2.4 Hz, CH), 4.97 (m, 1H, NCH), 2.09 (s, 3H, Ar-CH_3), 1.18 (d, 3H, ^3J = 6.8 Hz, CH_3), 1.01 (d, 3H, ^3J = 6.8 Hz, CH_3). HRMS calcd for $C_{20}H_{18}BrCl_2N_5O$ ([M+H]$^+$): 494.0145, found: 494.0146.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-3-tert-butyl-6-chloro-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5d) White solid; yield, 85 %; mp 168-170 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, 1H, ^4J = 1.2 Hz, ^3J = 4.8 Hz, Ar-H), 8.06 (dd, 1H, ^4J = 1.0 Hz, ^3J = 8.0 Hz, Ar-H), 7.83 (d, 1H, ^4J = 1.6 Hz, Ar-H), 7.49 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.11 (s, 1H, Ar-H), 6.32 (s, 1H, Ar-H), 6.00 (d, 1H, ^3J = 3.2, NH), 5.74 (d, 1H, ^3J = 2.0 Hz, CH), 2.06 (s, 3H, Ar-CH_3), 1.47 (s, 9H, CH_3). HRMS calcd for $C_{21}H_{20}BrCl_2N_5O$ ([M+H]$^+$): 508.0301, found: 508.0302.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-cyclopropyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5e) White solid; yield, 91 %; mp 267-269 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, 1H, ^4J = 1.4 Hz, ^3J = 4.6 Hz, Ar-H), 8.06 (dd, 1H, ^4J = 1.2 Hz, ^3J = 4.6 Hz, Ar-H), 7.84 (d, 1H, ^4J = 2.0 Hz, Ar-H), 7.49 (dd, 1H, ^3J = 4.6 Hz, ^3J = 8.2 Hz, Ar-H), 7.14 (d, 1H, ^4J = 2.0 Hz, Ar-H), 6.32 (s, 1H, Ar-H), 5.98 (d, 1H, ^3J = 2.0, NH), 5.71 (d, 1H, ^3J = 2.4 Hz, CH), 2.70-2.65 (m, 1H, NCH), 2.08 (s, 3H, Ar-CH_3), 1.12-1.04 (m, 1H, CH), 0.89-0.82 (m, 1H, CH), 0.69-0.61 (m, 1H, CH), 0.52-0.45 (m, 1H, CH). HRMS calcd for $C_{20}H_{16}BrCl_2N_5O$ ([M-H]$^-$): 489.9843, found: 489.9835.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methyl-3-propyl-2,3-dihydroquinazolin-4(1*H*)-one (5f) White solid; yield, 87 %; mp 198-200 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, 1H, ^4J = 1.6 Hz, ^3J = 4.6 Hz, Ar-H), 8.06 (dd, 1H, ^4J = 1.4 Hz, ^3J = 8.2 Hz, Ar-H), 7.83 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.48 (dd, 1H, ^3J = 4.6 Hz, ^3J = 8.2 Hz, Ar-H), 7.13 (d, 1H, ^4J = 2.0 Hz, Ar-H), 6.26 (s, 1H, Ar-H), 5.95 (d, 1H, ^3J = 2.0, NH), 5.69 (d, 1H, ^3J = 2.4 Hz, CH), 4.05 (m, 1H, NCH), 2.80 (m, 1H, NCH), 2.07 (s, 3H, Ar-CH_3), 1.58 (m, 2H, $\underline{CH_2}CH_3$), 0.91 (t, 3H, ^3J = 7.2 Hz, CH_3). HRMS calcd for $C_{20}H_{18}BrCl_2N_5O$ ([M+H]$^+$): 494.0145, found: 494.0140.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methyl-3-(thiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (5g) White solid; yield, 80 %; mp 260-262 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, ^3J = 3.6 Hz, Ar-H), 8.08 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.94 (s, 1H, Ar-H), 7.49 (dd, 1H, ^3J = 4.4 Hz, ^3J = 8.2 Hz, Ar-H), 7.41 (d, 1H, ^4J = 2.8 Hz, Ar-H), 7.36 (d, 1H, ^3J = 3.6 Hz, Ar-H), 7.24 (s, 1H, Ar-H), 7.04 (d, 1H, ^3J = 3.6 Hz, Ar-H), 6.14 (s, 1H, NH), 6.10 (s, 1H, CH), 2.14 (s, 3H, Ar-CH_3). HRMS calcd for $C_{20}H_{13}BrCl_2N_6OS$ ([M+H]$^+$): 534.9505, found: 534.9501.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-ethyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5h) White solid; yield, 65 %; mp 222-224 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (dd, 1H, ^4J = 1.7 Hz, ^3J = 4.7 Hz, Ar-H), 8.06 (dd, 1H, ^4J = 1.5 Hz, ^3J = 8.1 Hz, Ar-H), 7.83 (d, 1H, ^4J = 2.1 Hz, Ar-H), 7.48 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.1 Hz, Ar-H), 7.13 (d, 1H, ^4J = 2.4 Hz, Ar-H), 6.26 (s, 1H, Ar-H), 5.99 (d, 1H, ^3J = 1.8 Hz, NH), 5.72 (d, 1H, ^3J = 2.4 Hz, CH), 4.12-4.00 (m, 1H, NCH), 3.07-2.95 (m, 1H, NCH), 2.08 (s, 3H, Ar-CH_3), 1.18 (t, 3H, ^3J = 7.2 Hz, CH_3). HRMS calcd for $C_{19}H_{16}BrCl_2N_5O$ ([M+Na]$^+$): 501.9813, found: 501.9800.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5i) White solid; yield, 70 %; mp 233-235 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, 1H, ^4J = 1.6 Hz, ^3J = 4.4 Hz, Ar-H), 8.04 (dd, 1H, ^4J = 1.2 Hz, ^3J = 8.0 Hz, Ar-H), 7.98 (d, 1H, ^3J = 7.6 Hz, Ar-H), 7.46 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.30 (t, 1H, ^3J = 8.0 Hz, Ar-H), 6.90 (t, 1H, ^3J = 7.6 Hz, Ar-H), 6.62 (d, 1H, ^3J = 7.6 Hz, Ar-H), 6.28 (s, 1H, Ar-H), 5.74 (s, 1H, NH), 5.64 (d, 1H, ^3J = 2.0 Hz, CH), 3.05 (s, 3H, NCH_3). HRMS calcd for $C_{17}H_{13}BrClN_5O$ ([M+Na]$^+$): 439.9890, found: 439.9897.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-3,8-dimethyl-2,3-dihydroquinazolin-4(1*H*)-one (5j) White solid; yield, 80 %; mp 265-267 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (dd, 1H, ^4J = 1.4 Hz, ^3J = 4.7 Hz, Ar-H), 8.05 (dd, 1H, ^4J = 1.2 Hz, ^3J = 8.1 Hz, Ar-H), 7.86 (d, 1H, ^3J = 7.8 Hz, Ar-H), 7.47 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.1 Hz, Ar-H), 7.17 (d, 1H, ^3J = 7.2 Hz, Ar-H), 6.82 (t, 1H, ^3J = 7.7 Hz, Ar-H), 6.28 (s, 1H, Ar-H), 5.92 (s, 1H, NH), 5.72 (d, 1H, ^3J = 2.1 Hz, CH), 3.08 (s, 3H, NCH_3), 2.11 (s, 1H, Ar-CH_3). HRMS calcd for $C_{18}H_{15}BrClN_5O$ ([M+Na]$^+$): 454.0046, found: 454.0047.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5k) White solid; yield, 75 %; mp 222-224 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, 1H, ^4J = 1.0 Hz, ^3J = 4.6 Hz, Ar-H), 8.03 (dd, 1H, ^4J = 1.2 Hz, ^3J = 8.0 Hz, Ar-H), 7.79 (d, 1H, ^4J = 2.0 Hz, Ar-H), 7.45 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.20 (d, 1H, ^4J =

1.6 Hz, Ar-H), 6.57 (s, 1H, Ar-H), 6.41 (s, 1H, CONH), 5.86 (s, 1H, NH), 5.65 (s, 1H, CH), 2.16 (s, 3H, CH_3). HRMS calcd for $C_{17}H_{12}BrCl_2N_5O$ ($[M+Na]^+$): 473.9500, found: 473.9501.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-isopropyl-2,3-dihydroquinazolin-4(1*H*)-one (5l) White solid; yield, 72 %; mp 220-222 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, 1H, ^4J = 1.2 Hz, ^3J = 4.8 Hz, Ar-H), 8.09 (dd, 1H, ^4J = 1.6 Hz, ^3J = 8.0 Hz, Ar-H), 7.99 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.53 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.26 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.4 Hz, Ar-H), 6.61 (d, 1H, ^3J = 8.8 Hz, Ar-H), 6.29 (s, 1H, Ar-H), 5.79 (d, 1H, ^3J = 1.2 Hz, NH), 5.61 (d, 1H, ^3J = 2.0 Hz, CH), 5.01-4.94 (m, 1H, NCH), 1.17 (d, 3H , ^3J = 6.8 Hz, CH_3), 0.99 (d, 3H, ^3J = 6.8 Hz, CH_3). HRMS calcd for $C_{19}H_{16}BrCl_2N_5O$ ($[M+Na]^+$): 501.9813, found: 501.9807.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-propyl-2,3-dihydroquinazolin-4(1*H*)-one (5m) White solid; yield, 86 %; mp 203-205 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (dd, 1H, ^4J = 1.4 Hz, ^3J = 4.6 Hz, Ar-H), 8.07 (dd, 1H, ^4J = 1.2 Hz, ^3J = 8.0 Hz, Ar-H), 7.96 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.50 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.26 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.8 Hz, Ar-H), 6.59 (d, 1H, ^3J = 8.4 Hz, Ar-H), 6.28 (s, 1H, Ar-H), 6.85 (s, 1H, NH), 5.63 (d, 1H, ^3J = 2.0 Hz, CH), 4.04-3.97 (m, 1H, NCH), 2.87-2.80 (m, 1H, NCH), 1.61-1.53 (m, 2H, CH_2), 0.92 (t, 3H, ^3J = 7.4 Hz, CH_3). HRMS calcd for $C_{19}H_{16}BrCl_2N_5O$ ($[M+Na]^+$): 501.9813, found: 501.9806.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-cyclohexyl-2,3-dihydroquinazolin-4(1*H*)-one (5n) White solid; yield, 84 %; mp 293-295 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (dd, 1H, ^4J = 1.5 Hz, ^3J = 4.8 Hz, Ar-H), 8.08 (dd, 1H, ^4J = 1.5 Hz, ^3J = 8.1 Hz, Ar-H), 7.96 (d, 1H, ^4J = 2.4 Hz, Ar-H), 7.51 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.1 Hz, Ar-H), 7.24 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.4 Hz, Ar-H), 6.58 (d, 1H, ^3J = 8.4 Hz, Ar-H), 6.26 (s, 1H, Ar-H), 5.72 (d, 1H, ^3J = 1.8 Hz, NH), 5.61 (d, 1H, ^3J = 2.4 Hz, CH), 4.61-4.51 (m, 1H, NCH), 1.76-1.64 (m, 5H, cyclohexyl), 1.47-1.17 (m, 3H, cyclohexyl), 1.02-0.79 (m, 2H, cyclohexyl). HRMS calcd for $C_{22}H_{20}BrCl_2N_5O$ ($[M+Na]^+$): 542.0126, found: 542.0111.

6-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-3-cyclopropyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5o) White solid; yield, 80 %; mp 272-274 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, ^3J = 3.6 Hz, Ar-H), 8.06 (dd, 1H, ^4J = 0.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.99 (s, 1H, Ar-H), 7.49 (dd, 1H, ^3J = 4.6 Hz, ^3J = 8.2 Hz, Ar-H), 7.28 (s, 1H, Ar-H), 6.32 (s, 1H, Ar-H), 6.03 (s, 1H, NH), 5.70 (d ,1H, ^3J = 2.4 Hz, CH), 2.69-2.64 (m, 1H, NCH), 2.08 (s, 3H, Ar-CH_3), 1.12-1.05 (m, 1H, cyclopropyl), 0.90-0.83 (m, 1H, cyclopropyl), 0.68-0.61 (m, 1H, cyclopropyl), 0.51-0.45 (m, 1H, cyclopropyl). HRMS calcd for $C_{20}H_{16}Br_2ClN_5O$ ($[M+Na]^+$): 557.9308, found: 557.9290.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-3-cyclopropyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5p) White solid; yield, 86 %; mp 217-219 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (dd, 1H, ^4J = 1.4 Hz, ^3J = 3.6 Hz, Ar-H), 8.06 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.89 (d, 1H, ^3J = 7.6 Hz, Ar-H), 7.48 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.0 Hz, Ar-H), 7.18 (d, 1H, ^3J = 7.6 Hz, Ar-H), 6.82 (t, 1H, ^3J = 7.6 Hz, Ar-H), 6.34 (s, 1H, Ar-H), 5.93 (s, 1H, NH), 5.72 (d ,1H, ^3J = 2.4 Hz, CH), 2.70-2.65 (m, 1H, NCH), 2.10 (s, 3H, Ar-CH_3), 1.12-1.04 (m, 1H, cyclopropyl), 0.90-0.83 (m, 1H, cyclopropyl), 0.66-0.59 (m, 1H, cyclopropyl), 0.51-0.45 (m, 1H, cyclopropyl). HRMS calcd for $C_{20}H_{17}BrClN_5O$ ($[M+Na]^+$): 480.0203, found: 480.0201.

6-chloro-2-(3-chloro-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)-3-cyclopropyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5q) White solid; yield, 82 %; mp 208-209 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, ^3J = 4.1 Hz, 1H, Ar-H), 8.01 (d, ^3J = 8.3 Hz, 1H, Ar-H), 7.94 (t, ^3J = 7.6 Hz, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.39-7.31 (m, 1H, Ar-H), 7.08 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 6.20 (s, 1H, NH), 6.16 (s, 1H, CH), 3.14 (s, 3H, NCH_3), 1.96 (s, 3H, Ar-CH_3). HRMS calcd for $C_{18}H_{15}Cl_2N_5O$ ($[M+Na]^+$): 410.0551, found: 410.0616.

2-(3-bromo-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3-cyclopropyl-8-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5r) White solid; yield, 79 %; mp 173-174 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, ^3J = 4.2 Hz, 1H, Ar-H), 8.03 (d, ^3J = 8.3 Hz, 1H, Ar-H), 7.94 (t, ^3J = 7.5 Hz, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.39-7.32 (m, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.28 (s, 1H, CH), 6.18 (s, 1H, NH), 2.69 (s, 1H, cyclopropyl), 1.94 (s, 3H, Ar-CH_3), 0.97-0.82 (m, 2H, cyclopropyl), 0.68 (m, 2H, cyclopropyl). HRMS calcd for $C_{20}H_{17}Cl_2N_5O$ ($[M+Na]^+$): 436.0708, found: 436.0634.

2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-3,8-dimethylquinazolin-4(3*H*)-one (5s) 2-Amino-5-chloro-*N*,3-dimethylbenzamide (**4a**) (0.099 g, 0.5 mmol) and 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carbaldehyde (**3a**) (0.143 g, 0.5 mmol) were added to 20 mL of ethanol, then refluxed and monitored with TLC. After 1 h, the reaction was completed, the solution was evaporated, and the residue was applied to a flash column chromatography by eluting with petroleum ether/ethyl acetate (2:1) to give the compound **5s** as a white solid; yield, 30 %; mp 214-216 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (d, 1H, ^3J = 4.4 Hz, Ar-H), 8.21 (d, 1H, ^3J = 8.0 Hz, Ar-H), 7.90 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.58 (dd, 1H, ^3J = 4.4 Hz, ^3J = 8.0 Hz, Ar-H), 7.48 (s, 1H, Ar-H), 3.71 (s, 3H, NCH_3), 1.91 (s, 3H, Ar-CH_3). HRMS calcd for $C_{18}H_{13}BrCl_2N_5O$ ($[M+H]^+$): 463.9675, found: 463.9672.

4.1.5. 6-chloro-2,2,3,8-tetramethyl-2,3-dihydroquinazolin-4(1*H*)-one 6.

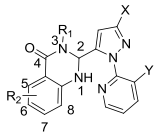
2-Amino-5-chloro-*N*, 3-dimethylbenzamide (**4a**) (0.198 g, 1 mmol) was dissolved in 5 mL of acetone, followed by a catalytic amount of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 1 h and the solvent was evaporated. The 20 mL of ethyl acetate was added and the solution was washed with saturated sodium bicarbonate, and brine. The ethyl acetate solution was dried and evaporated to afford title compound as a white solid; yield, 95 %; mp 154-156 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, 1H, ^4J = 2.0 Hz, Ar-H), 7.15 (s, 1H, Ar-H), 3.88 (s, 1H, NH), 3.07 (s, 3H, NCH_3), 2.14 (s, 3H, Ar-CH_3), 1.56 (s, 6H, $C(CH_3)_2$).

4.2. Biological Assay.

Insecticidal activity against oriental armyworms was performed on test organisms reared in a greenhouse. The bioassay was replicated at 25 ± 1 ℃ according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected applying Abbott's formula.[41] Evaluation was based on a percentage scale of 0-100, where 0 equals no activity, and 100 equals total kill. Error of the experiments was 5 %. For comparative purposes, chlorantraniliprole was tested as reference under the same conditions. The insecticidal activity was summarized in **Table 2**.

The larvicidal activity of compounds **5a-s** and chlorantraniliprole were evaluated using the reported procedure.[23] The insecticidal activity against oriental armyworms was tested by foliar application; individual corn (Tangyu 10, Zeamays L.) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was replicated three times.

Table 2. Insecticidal activities of compounds **5a-s** and chlorantraniliprole against oriental armyworms



					Larvicidal activity (%) at a concentration of (mg/L)			
Comp.	R_1	R_2	X	Y	50	25	10	5
5a	CH_3	6-Cl, 8-CH_3	Br	Cl	100	100	100	80
5b	OCH_3	6-Cl, 8-CH_3	Br	Cl	50	30	20	0
5c	i-Pr	6-Cl, 8-CH_3	Br	Cl	10	0		
5d	t-Bu	6-Cl, 8-CH_3	Br	Cl	0			
5e	Cyclopropyl	6-Cl, 8-CH_3	Br	Cl	40	0		
5f	n-Pr	6-Cl, 8-CH_3	Br	Cl	50	10	0	
5g	2-thiazolyl	6-Cl, 8-CH_3	Br	Cl	20	0	0	
5h	CH_2CH_3	6-Cl, 8-CH_3	Br	Cl	100	50	0	
5i	CH_3	H	Br	Cl	20[a]			
5j	CH_3	8-CH_3	Br	Cl	100	70	20	0
5k	H	6-Cl, 8-CH_3	Br	Cl	100	100	100	80
5l	i-Pr	6-Cl	Br	Cl	100	100	60	0
5m	n-Pr	6-Cl	Br	Cl	70	0		
5n	Cyclohexyl	6-Cl	Br	Cl	20[a]			
5o	Cyclopropyl	6-Br,8-CH_3	Br	Cl	100	60	0	
5p	Cyclopropyl	8-CH_3	Br	Cl	40[b]			
5q	CH_3	8-CH_3	Cl	H	60[a]			
5r	Cyclopropyl	8-CH_3	Cl	H	10[a]			
5s					20[a]			
	Chlorantraniliprole							100

[a] 200 mg/L [b] 100 mg/L

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Graphical Abstract

Synthesis and insecticidal activities of 2,3-dihydroquinazolin-4(1*H*)-one derivatives targeting calcium channel

5a induced calcium elevation in isolated *S. exigua* in the presence or absence of extracellular calcium.

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