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Design, synthesis and biological activity of novel substituted pyrazole amide derivatives targeting EcR/USP receptor

Xi-Le Deng [a], Jin Xie [a], Yong-Qiang Li [b], De-Kai Yuan [a], Xue-Ping Hu [a], Li Zhang [a,*], Qing-Min Wang [b], Ming Chi [a], Xin-Ling Yang [a,*]

[a] Department of Applied Chemistry, College of Science, China Agricultural University, Beijing 100193, China
[b] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

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ABSTRACT

In order to discover highly active ecdysone analogs, a series of new substituted pyrazole amide derivatives were obtained using structure-guided optimization method and further screened for their insecticidal activities, in the basis of the core structures of the two active compounds *N*-(3-methoxyphenyl)-3-(*tert*-butyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**6e**) and *N*-(4-(*tert*-butyl)phenyl)-3-(*tert*-butyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**6i**), previously presented by us. The chemical structures of the title compounds were identified by spectral analyses. The preliminary bioassay results indicated that one among the synthesized pyrazole derivatives, compound **34**, endowed with good activity against *Mythimna Separata* at 10 mg/L, which was equal to that displayed by the positive control tebufenozide. In addition, examples of molecular docking and molecular dynamics studies demonstrated that **34** may be the potential inhibitor to EcR and its docking conformation was similar to that of tebufenozide. In addition, increasing the hydrophobic effect and considering the suitable bulk effect on pyrazole ring are beneficial to the inhibiting activity to EcR and activity *in vivo*.

1. Introduction

Molting hormones, such as 20-hydroxyecdysone (20E), are compounds that regulate the molting of insects [1,2]. Molting or ecdysis is a critical aspect of insect growth. The binding of 20E to the ecdysone (EcR)–ultraspiracle protein (USP) heterodimer during insect development results in ecdysis. One prominent approach toward the development of environmentally benign insect growth regulators has been to design ligands that target the EcR–USP heterodimer. For example, the non-steroidal ecdysone agonists, dibenzoylhydrazines (DBHs), bind to the EcR subunit of the heterodimer and induce insect moulting. These agents, which bear the common dibenzoylhydrazine core structure, display outstanding activity against lepidopteran pests while having no negative effects on mammals and the environment [3–6].

Recently, a series of novel ecdysone agonists with non-steroidal or non-dibenzoylhydrazine structures and displaying highly insecticidal activity have been identified [7,8]. These ecdysone agonists have been rationally designed using target structure-guided approaches. Additional efforts that include structural modifications of previously identified agonists may led to the identification of other highly active and novel ecdysone agonists in recent years [9] (I, Fig. 1). Hence, that modification of the structure designed by target ecdysone receptor is a success way to design new ecdysone agonists for pest controls.

In the course of our research efforts, we had previously identified two compounds, **6e** and **6i** (II, Fig. 1), which displayed high ecdysone agonistic activities, and an active conformer of these compounds was similar to that of tebufenozide [10]. Attribute to the hydrophobic effect of the *t*-butyl and methoxy substituent in phenyl ring and their excellent activity of **6e** and **6i**, so we retained the methoxy and *t*-butyl substituents on aromatic amide at positions 3 and 4, and then modified the substituent groups in the pyrazole ring. Inspired by these facts, we focused on designing and synthesizing novel substituted pyrazole amide derivatives based on the lead compounds **6e** and **6i** in this study to discover highly active ecdysone analogs (Fig. 2) and a range of lepidopteran biological activities was ascribe to this series. Additionally, selected examples of molecular docking and molecular dynamics studies were evaluated to study the mechanisms of these derivatives with active site of the EcR subunit of the heterodimeric receptor.

* Corresponding authors.
E-mail addresses: zhang_li@cau.edu.cn (L. Zhang), yangxl@cau.edu.cn (X.-L. Yang).

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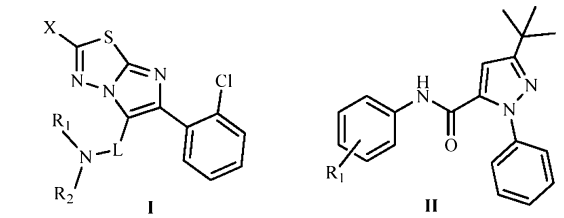


Fig. 1. Chemical structures of known potential ecdysone agonists.

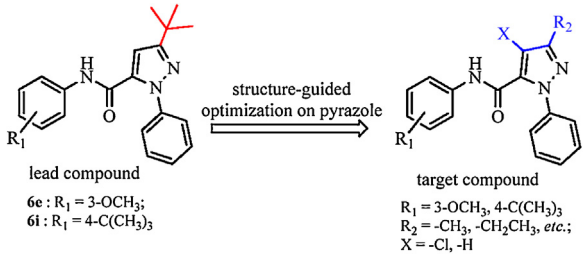


Fig. 2. Design strategy of target compounds **7–8**, **13–14** and **21–38** through modifying the substituent on pyrazole of lead **6e** and **6i**.

2. Experimental

Melting points of all compounds were determined on an X-5 binocular (Fukai Instrument Co., Beijing, China), and were not corrected. ^{1}H NMR spectra and ^{13}C NMR were recorded on a Bruker AM-300 (300 MHz) spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts were reported in δ (parts permillion) values. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometor (KBr presser method). High resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS Varian 7.0 T FTICR-MS instrument. All the reagents were obtained commercially and used after further purification.

2.1. General procedures for synthesis and Insecticidal test of compounds *7–8*, *13–14* and *21–38*

The general procedures for synthesis of compounds **7**–**8**, **13**–**14** and **21**–**38** were listed in the Supporting information. Their biological activities against *Mythimna separate*, *Helicoverpa armigera* and *Pyrausta nubilalis* were evaluated using the reference methods [11,12].

2.2. Molecular docking study

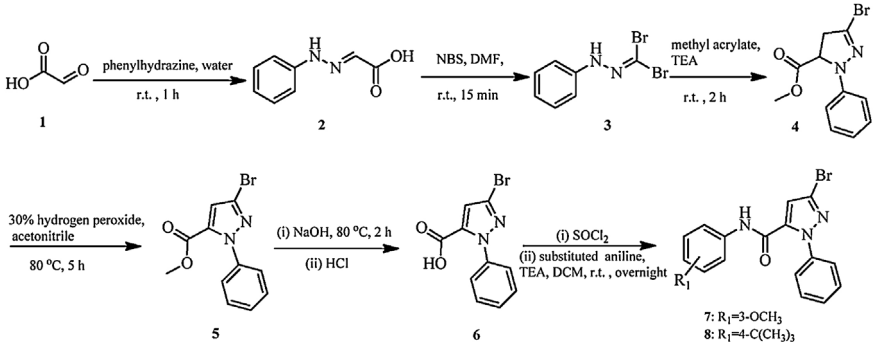
Compounds **6e**, **6i**, **34** and tebufenozide were built and optimized using the MMFF94 force field and charges in Molecular Operating Environment (MOE) software [13]. The first low energy conformation of every compound was selected to dock into the active pocket using the Induced Fit protocol. A crystal structure of ecdysone receptor (EcR) complexed with BYIO8346 (PDB ID: 1R20) was modified and protonated. Waters and phosphatidylethanolamines were deleted. The active site was set by the residues with a radius of 6 Å around BYIO8346. The docked small molecules were placed in the site with the Triangle Matcher method and ranked with the London dG scoring function. Thirty conformations with the docking poses were output and further rescored with the GBVI/WSA dG scoring function. The docking complex with the rational binding mode and higher scoring would be studied further for molecular dynamics simulation.

2.3. Molecular dynamics simulation

The molecular dynamics (MD) simulation were finished using the AMBER 12 software [14]. EcR receptor was solvated using explicit TIP3P water models and the water molecules were filled in the range of 10 Å bound to the protein atom in a cubic periodic box. AMBER ff99SB force field was used for EcR and gaff force field was assigned to the small molecules. Energy minimization was first performed using the steepest descent algorithm for two thousand steps and then the conjugated gradient algorithm for another three thousand steps before the MD simulation. Then three dynamics simulation steps were applied to the whole system. First, only waters and counterions were heated for 10 ps to ensure the solute was entirely solvated; second, the system was slowly heated from 10 to 298 K by a weak-coupling method and equilibrated for 100 ps except the protein backbone; finally, the full system was executed to a constant pressure equilibration for 20 ns. The binding free energies between ligands and EcR were computed, as a sum of the gas-phase molecular mechanics energies, and solvation energies, and conformational entropy, based on the MM-PBSA method.

3. Results and discussion

The synthetic procedures for substituted pyrazole amide derivatives are depicted in Schemes 1–3. Condensation of the phenylhydrazine with malonaldehydic acid **1** yields the compound **2**. Bromination of **2** with NBS gives the compound **3**, which undergoes cyclization with a methyl acrylate to afford the bromopyrazoline **4** [15]. The oxidation of **4** affords the pyrazole ester **5** [16], which is subjected to saponification and amidation to afford the target amides **7** and **8** in moderate overall yields (Scheme 1). A different method is followed to install a trifluoro methyl group on



Scheme 1. Synthetic procedure for title compounds **7–8**.

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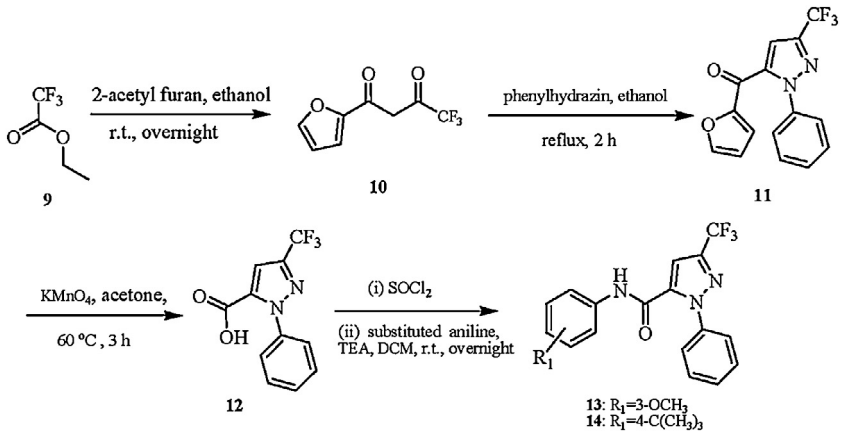


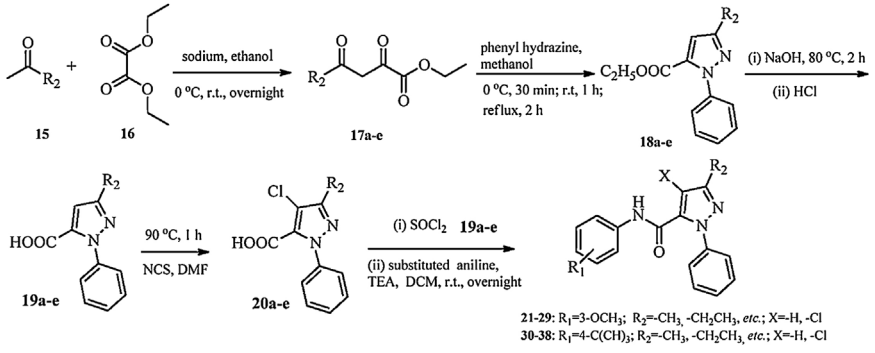
Scheme 2. Synthetic procedure for title compounds **13–14**.

the pyrazole ring (Scheme 2). The 1,3-diketone compound **10** is synthesized from **9** following a previously described protocol [17]. The trifluromethyl-substituted pyrazole core of the key intermediate **11** is prepared by the cyclization of the 1,3-diketone moiety in **10** with phenylhydrazine [17]. Subsequently, oxidation of **11** and the amidations of the resulting carboxylic acid **12** yield the desired trifluromethyl-substituted pyrazole amides **13** and **14** in moderate yields [18]. The synthesis of the alkyl-substituted pyrazoles **21–38** is initiated with the compounds **15** following a previously described protocol [19] (Scheme 3). The pyrazole core of the key intermediate **18a–e** is prepared by the cyclization of the 1,3-diketone moiety in **17a–e** with phenylhydrazine (Scheme 3). The saponification of the ester **18a–e** affords the carboxylic acid **19a–e**, and aromatic halogenation of **19a–e** gives the chlorine substituted compound **20a–e** [20]. Amidations of the carboxylic acids (containing pyrazole and chloro-pyrazole motifs) using appropriately substituted anilines obtain the target compounds **21–38** in moderate yields.

The structures of the targeted compounds are confirmed through the analyses of their melting points, ^{1}H NMR spectra, ^{13}C NMR spectra, IR spectra, and HRMS. These data can be found in the Supporting information. Signals corresponding to the C–H and the N–H protons of the pyrazole ring in target compounds are observed at about $\delta \sim 6.84$–6.68 and $\delta \sim 7.97$–8.71 in the ^{1}H NMR spectra of the compounds, respectively signals as the C–H protons of *t*-butyl substituent and methoxy substituent in phenyl ring are observed at about $\delta \sim 1.33$ and $\delta \sim 3.79$ and signal for the protons on the benzene ring are observed at δ 6.63–7.73. In the IR spectra of target compounds, strong absorptions at 3200–3400 cm^{-1}, functionality, are observed. In addition, other strong absorptions bonds representing the carbonyl and unsaturated pyrazole groups are observed at 1600–1700 cm^{-1} and 1530 cm^{-1}, respectively. The HRMS data of the target compounds are in good agreement with the theoretical data calculated based on the chemical formulae.

The insecticidal activities of all title compounds were evaluated against lepidopteran pests (*M. separata*, *H. armigera*, and *P. nubilalis*) *in vivo* and the corresponding data are shown in Table 1. In this study, we focused on the relative small sizes and suitable hydrophobic effects of the substituents at the modification positions on the pyrazole ring. Therefore, a series of alkyl substitutes, trifluoro methyl group, and bromine atom at position 3 were taken into consideration, as well as hydrogen atom and chlorine atom at position 4. While keeping the methoxy on phenyl ring at positions 3, compounds **7** and **29**, exhibited superior activity against *M. separate*. The compounds **26**, **27** harboring ethyl or *n*-propyl substituents at position 3 and chlorine atom at position 4 on the pyrazole ring displayed promising activity against *H. armigera*, and *P. nubilalis*. Respectively, retaining the substituents as *t*-butyl at position 4 of the phenyl substituent, higher activity was observed with compound **14**, **34**, **36**, and **38** against *M. separate*. Moreover, compound **34** even exhibited excellent activities against *H. armigera*, and *P. nubilalis*, containing 3-methyl and 4-chloro substituent on pyrazole ring. In particular, the superior activity of compound **34** against *M. separata* at lower doses was comparable to that displayed by the positive control tebufenozide (see Table 2). This indicates that different sizes of substituents on the pyrazole ring contribute significantly to the insecticidal activities *in vivo*.

Molecular docking is an effective method used in structure-guided design, due to its ability to elucidate the possible binding conformations for ligands to bind into EcR/USP receptor. Moreover, the characterization of binding process, such as hydrogen bonding interactions and hydrophobic effect, plays a critical role in rational design of ecdysone analogs [7,8]. In order to gain insights into the mode of action of the substituted pyrazole ring, molecular docking



Scheme 3. Synthetic procedure for title compouds **21–38**.

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Table 1
Observed *in vivo* insecticidal activity (mortality) of pyrazole analogs.

Compounds.	R_1	R_2	X	Mortality (%) (Conc. 600 mg/L)		
				Mythimna Separata	*Helico verpa armigera*	*Pyrausta nubilalis*
7	3-OCH_3	–Br	–H	100	50	60
13	3-OCH_3	–CF_3	–H	50	35	45
21	3-OCH_3	–CH_3	–H	15	65	70
22	3-OCH_3	–CH_2CH_3	–H	45	65	70
23	3-OCH_3	–$CH_2CH_2CH_3$	–H	70	40	45
24	3-OCH_3	–$CH(CH_3)_2$	–H	50	35	40
25	3-OCH_3	–CH_3	–Cl	30	45	65
26	3-OCH_3	–CH_2CH_3	–Cl	50	100	100
27	3-OCH_3	–$CH_2CH_2CH_3$	–Cl	30	100	100
28	3-OCH_3	–$CH(CH_3)_2$	–Cl	70	25	35
29	3-OCH_3	–$C(CH_3)_3$	–Cl	100	15	20
8	4-$C(CH_3)_3$	–Br	–H	20	40	55
14	4-$C(CH_3)_3$	–CF_3	–H	100	25	35
30	4-$C(CH_3)_3$	–CH_3	–H	30	60	70
31	4-$C(CH_3)_3$	–CH_2CH_3	–H	20	45	55
32	4-$C(CH_3)_3$	–$CH_2CH_2CH_3$	–H	15	50	65
33	4-$C(CH_3)_3$	–$CH(CH_3)_2$	–H	50	30	45
34	4-$C(CH_3)_3$	–CH_3	–Cl	100	100	100
35	4-$C(CH_3)_3$	–CH_2CH_3	–Cl	35	30	45
36	4-$C(CH_3)_3$	–$CH_2CH_2CH_3$	–Cl	100	10	20
37	4-$C(CH_3)_3$	–$CH(CH_3)_2$	–Cl	60	30	40
38	4-$C(CH_3)_3$	–$C(CH_3)_3$	–Cl	100	75	80
Tebufenozide				100	100	100

Table 2
Dosage-dependent *in vivo* insecticidal activity (mortality) of **7**, **14**, **29**, **34**, **36**, **38** and tebufenozide against *Mythimna Separata*.

Compd.	Mortality (%) at different concentrations (mg/L)				
	600	200	100	50	10
7	100	20	nt[a]	nt	nt
14	100	20	nt	nt	nt
29	100	20	nt	nt	nt
34	100	100	100	100	60
36	100	40	nt	nt	nt
38	100	60	nt	nt	nt
Tebufenozide		100	100	100	60

[a] nt = not tested.

was considered to study the interactions of these compounds with EcR. The binding conformation of compound **34** and tebufenozide with the important residues of EcR were shown in Fig. 3a and b. The carbonyl oxygen of the amide group for compound **34** established a hydrogen bonding interaction with Tyr408 (Fig. 3a). The residues Asn504, and Thr343 were formed in the hydrogen bonding interactions with tebufenozide (Fig. 3b). Tyr408 is the important residue to ensure small molecules to keep the inhibiting activity to EcR. The docking results showed that compound **34** may be the potential inhibitor to EcR and its docking conformation was similar as that of tebufenozide. To analyze the binding affinity of small molecules to EcR, molecular dynamics simulations were performed for EcR complexed with compound **34** and tebufenozide, respectively. The calculated binding free energy is −64.8 kJ/mol for the complex of compound **34** and EcR, which is nearly close to that (−69.66 kJ/mol) for the complex of tebufenozide and EcR (Fig. S1 in Supporting information). These data further showed compound **34** might have binding affinity with EcR. We will carry out the [3]PonA-labeled binding experiments as enzymatic assay testing EC_{50} on EcR/USP to confirm the above supposition in future work.

In addition, our previous study showed that the binding modes of **6e** or **6i** with the EcR subunit were similar to that of tebufenozide [10]. Here, we aligned and compared the equilibrating conformations for **6e**, **6i** and tebufenozide in the pocket of EcR (Fig. 3c). The pyrazole rings of **6e**, **6i** located in the hydrophobic region in the binding pocket, which had the similar position as the *t*-butyl substituent of tebufenozide at the binding pocket (red cycle). Moreover, the hydrophobic *t*-butyl group interacting with the hydrophobic residues of EcR is a key factor affecting the hydrophobic parameters of the ligands, which is also important to the binding affinity and activity *in vivo* of DBHs [21,22]. The better *in vivo* activity observed for the **6e** and **6i** may also be attributed to the hydrophobic effect of the substituted pyrazole. Then, we analyzed the superimposed conformations between tebufenozide and **34**. Fig. 3d showed that the pyrazole ring of **34** almost fully occupied in the position where the hydrophobic *t*-butyl group of tebufenozide exited (red cycle). So increasing the hydrophobic effect and considering the suitable bulk effect on pyrazole ring, such as 3-methyl and 4-chloro substituents on pyrazole ring, will be beneficial to the inhibiting activity to EcR.

4. Conclusion

Through this study, a series of novel substituted pyrazole amides derivatives were obtained by structure-guided optimization method in basis of the core structures of the two active compounds *N*-(3-methoxy phenyl)-3-(*tert*-butyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**6e**) and *N*-(4-(*tert*-butyl)phenyl)-3-(*tert*-butyl)-1-phenyl-1*H*-pyrazole-5-carboxamide (**6i**). In particular, the preliminary assays for insecticidal activity indicated that one of the compounds of the series, **34**, showed excellent activities against lepidopteran pests, such as *M. separate*, that was particularly comparable to that displayed by tebufenozide. Selected examples from molecule docking and molecular dynamics studies demonstrated that compound **34** could be a potential inhibitor against EcR/USP receptor which binding conformation was similar to that of tebufenozide. Particularly, the comparison of the binding conformations indicated the increasing of hydrophobic effect and the suitable substituent effects of pyrazole ring were essential for the inhibiting activity to EcR and activity *in vivo*. These

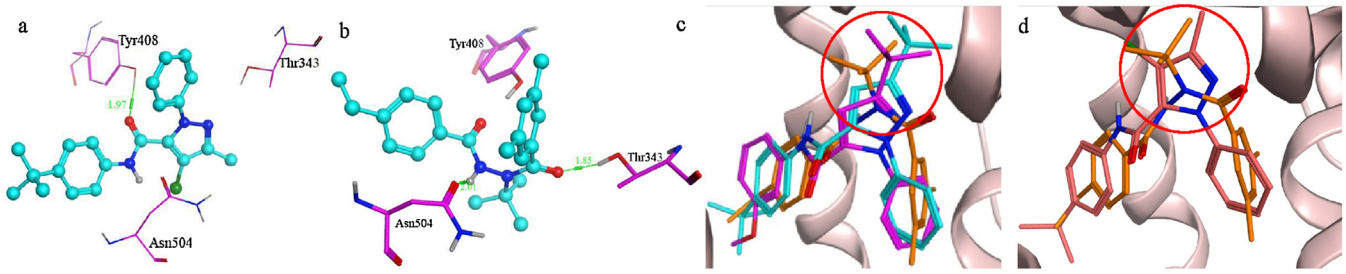

Fig. 3. Hydrogen bonding interactions between the residues at the binding pocket of the EcR subunit and compounds (a) **34** and (b) tebufenozide. Carbons in tebufenozide and **34** are represented by blue spheres. Oxygens and nitrogen atoms in both the structures are displayed as red and dark blue solid spheres, respectively. H-bonds are indicated by green dotted lines. (c) The comparison of the binding conformation between tebufenozide (in brown), **6e** (in pink) and **6i** (in blue). (d) The comparison of the binding conformation between tebufenozide (in brown) and **34** (in red).

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results offer valuable insights toward discovering new active ecdysone analogs by modifying the nature of the substituent groups on the pyrazole ring.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.02.009.

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