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Synthesis, larvicidal activity, and SAR studies of new benzoylphenylureas containing oxime ether and oxime ester group

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ABSTRACT

A series of new structural benzoylphenylureas (BPUs) containing oxime ether and oxime ester group were designed and synthesized. The larvicidal activities against Oriental armyworm and mosquito of these benzoylphenylureas were evaluated and the result of bioassay displayed specific structure–activity relationship (SAR). Most of the compounds exhibited excellent larvicidal activities against Oriental armyworm and mosquito. Interestingly, some compounds showed different structure–activity relationship towards diamondback moth, beet armyworm, and corn borer although three tested insects all belong to the same insect order.

Pest control is at least as old as agriculture, as there has always been a need to keep crops free from pests. Many pests go through four life cycle stage of egg, larva, pupa, and adult. Insect growth regulators (IGRs) which interrupt or inhibit the life cycle of pests are a new type of pesticide and widely used in integrated pest management (IPM). Benzoylphenylureas (BPUs) are a familiar type of IGRs, which have attracted considerable attention for decades because of its unique mode of action and low toxicity to non-target organisms (including many beneficial arthropods).[1–9]

Oxime ether group was especially used in molecular design of benzoylphenylureas, for example, **Flucycloxuron** which was discovered by Solvay-Duphar B.V. as insect growth regulator.[6] We have reported that some of compound **A** containing *O*-alkyl oxime ether (e.g., compound **B**) exhibited excellent larvicidal activities against Oriental armyworm (Fig. 1).[5] In order to obtain compounds which exhibit higher larvicidal activity and study the structure–activity relationship, new benzoylphenylureas containing oxime ether and oxime ester group were designed and synthesized (Fig. 1). At first, hydrogen atom of imino group (CH=N) in compound **A** was replaced by methyl or cyano group according to the strategy for molecular modification in drug design to synthesize compounds **1–4**.[7] Then compounds **5**–**7**, and **16** in which hydrogen atom in anilide moiety was changed to fluorine or chlorine atom in different position according to bioisosterism and QSAR of benzoylphenylureas (BPUs) were designed and synthesized.[10,11] Oxime ester group as a high efficient pharmacophore was widely used in pesticide and drug molecular design.[12,13] Therefore, compounds **8**–**11** containing oxime ester group were designed and synthesized. Because 4-((*O*-alkoxyimino)methyl)phenyl benzoylureas exhibited good larvicidal activities against Oriental armyworm, compounds **12–15** in which *O*-alkyl group was substituted by *O*-aryl group were designed and synthesized. Compounds **17–18** were designed and synthesized to identify the different effect of the *ortho* and *meta* substituent group in anilide moiety on the larvicidal activities against Oriental armyworm. Compound **19** was designed to identify the conjugation effect of imino group (CH=N) with aromatic cycle in anilide moiety. The insecticidal activities against Oriental armyworm and mosquito of these benzoylphenyureas were evaluated. The larvicidal activities of the selected target compounds **6**, **16**, and **Flucycloxuron** against diamondback moth, beet armyworm and corn borer were tested, and the median lethal concentrations (LC_{50}) were calculated.

Compounds **1–2** were synthesized from (*E*)-1-(4-nitrophenyl)ethanone oxime (**m**) as shown in Scheme 1. *p*-Nitrophenylethanone was condensed with hydroxylamine hydrochloride to give intermediate **m**,[14] and subsequent reaction with R-X yielded compounds **1a–2a**, and further reduction using iron powder as a reductant provided compounds **1b–2b**,[15] which were combined with 2, 6-difluorobenzoyl isocyanate to afford compounds **1–2**.

Compounds **3–4** were synthesized from (*E*)-4-nitrobenzaldehyde oxime as shown in Scheme 2. Intermediate $\mathbf{m_1}$ was first produced from (*E*)-4-nitrobenzaldehyde oxime and butyl hypochlorite. Subsequently, intermediate $\mathbf{m_1}$ reacted with sodium

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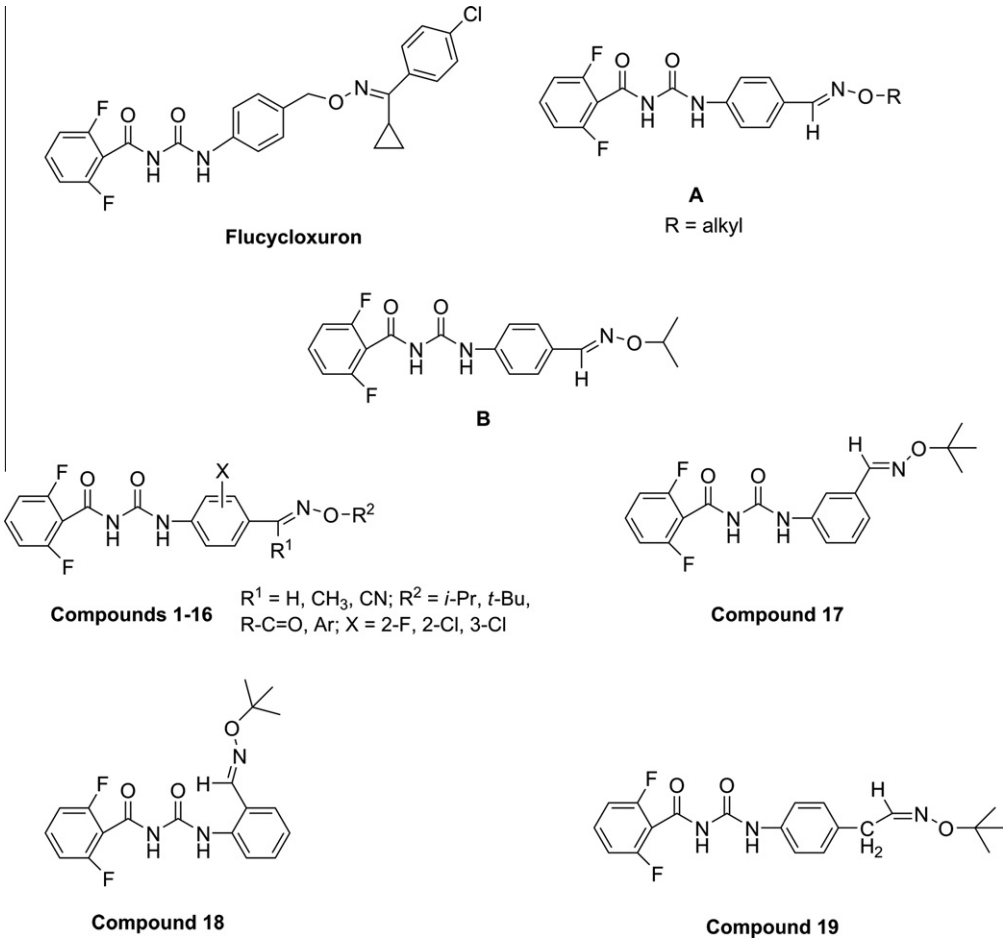
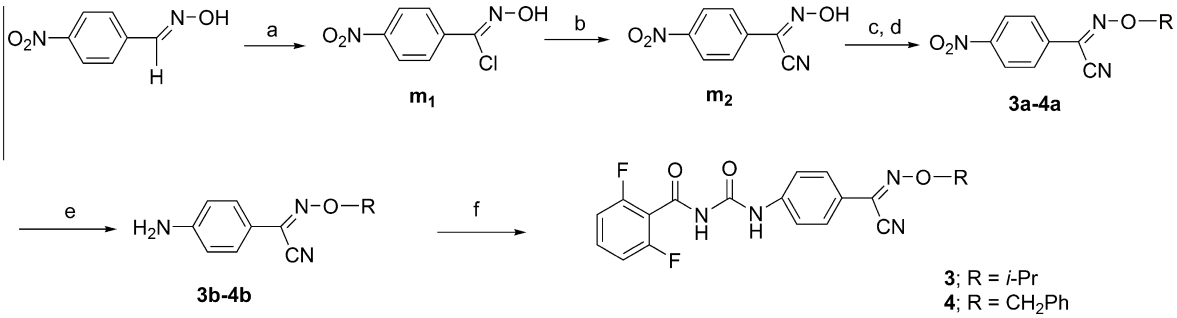
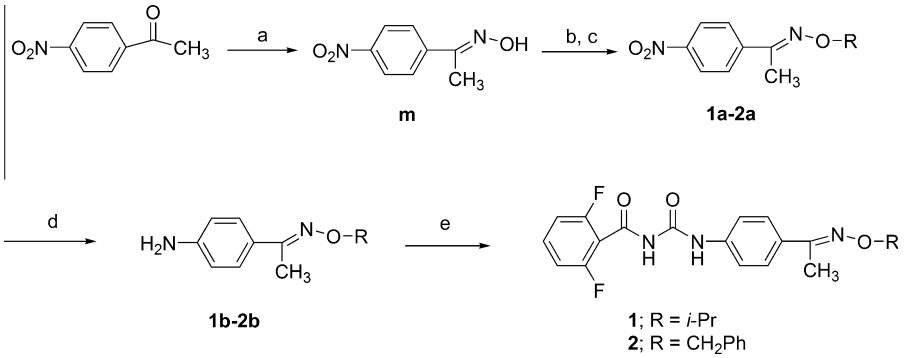


Figure 1. Design of compounds **1**–**19**.



Scheme 1. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, pyridine, THF, rt; (b) THF/H_2O, TBAB, NaOH; (c) substituted alkyl halides, 60–70 °C; (d) Fe/HCl, ethanol, 60–70 °C; (e) 2,6-diflurobenzoyl isocyanate, CH_2Cl_2, rt.



Scheme 2. Reagents and conditions: (a) *t*-BuOCl, *i*-PrOH/DCE, −10 °C; (b) NEt_3, NaCN, *i*-PrOH/DCE, −10 °C; (c) THF/H_2O, TBAB, NaOH; (d) substituted alkyl halides, 60–70 °C; (e) Fe/HCl, ethanol, 60–70 °C; (f) 2,6-diflurobenzoyl isocyanate, CH_2Cl_2, rt.

cyanide to give intermediate $\mathbf{m_2}$ in good yield. Afterward, compounds **3–4** were synthesized by using the similar method of compounds **1–2**.

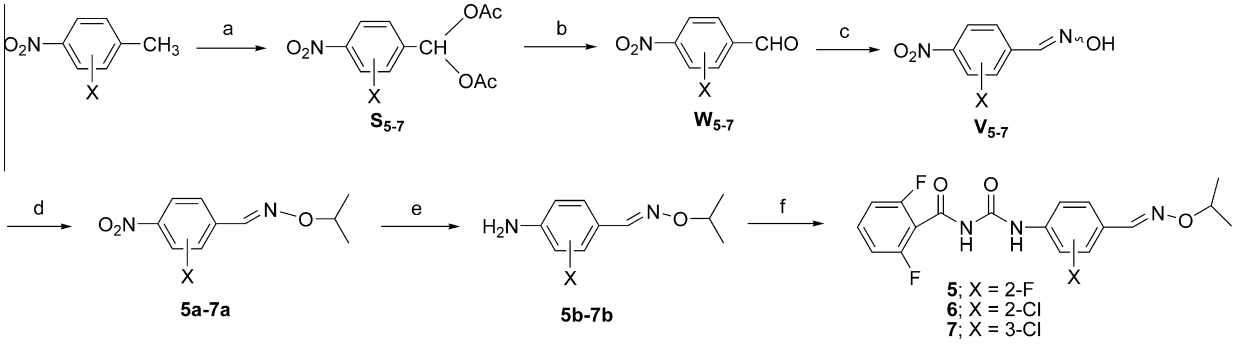
Compounds **5–7** were synthesized from substituted *p*-nitrotoluene as shown in Scheme 3. Intermediate $\mathbf{W_{5-7}}$ were obtained from oxidation of substituted *p*-nitrotoluene with chromium trioxide in acetic anhydride and subsequent hydrolysis of $\mathbf{S_{5-7}}$ in concentrated hydrochloride and 1,4-dioxane.[16,17] Then compounds 5–7 were synthesized by using the similar method of compounds **1–2**.

Compounds **8–11** were synthesized from *p*-nitrobenzaldehyde as shown in Scheme 4. The reduction of *p*-nitrobenzaldehyde provided *p*-aminobenzaldehyde according to reported procedure,[18] and subsequent combination with 2,6-difluorobenzoyl isocyanate afforded compound **N**, and further reaction with hydroxylamine hydrochloride gave compound **P**. Compound **P** reacted with acyl chloride in anhydrous THF to give compounds **8–11**.

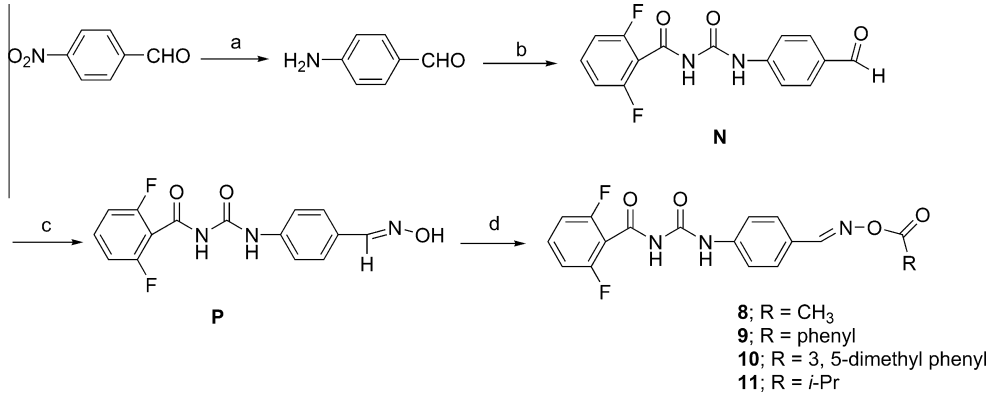
Compounds **12–15** were synthesized from *O*-(mesitylsulfonyl)hydroxylamine as shown in Scheme 5. The powerful aminating reagent O-(mesitylsulfonyl)hydroxylamine was treated with ArO-Na to provide *O*-arylhydroxylamines, which were used without further purification and reacted with compound **N** to afford compounds **12–15**.[19]

Compounds **16–18** were synthesized from *O*-(mesitylsulfonyl)hydroxylamine as shown in Scheme 6. The aminating reagent O-(mesitylsulfonyl)hydroxylamine was treated with potassium *tert*-butoxide to provide *O*-*tert*-butylhydroxylamine, which was used without further purification and reacted with different substituted benzaldehyde to afford compounds **16a–18a**. Then reduction of compounds **16a–18a** using hydrogen gas (cat. 10% Pd–C) as a reductant provided compounds **16b–18b**, which were combined with 2,6-difluorobenzoyl isocyanate to afford compounds **16–18**.

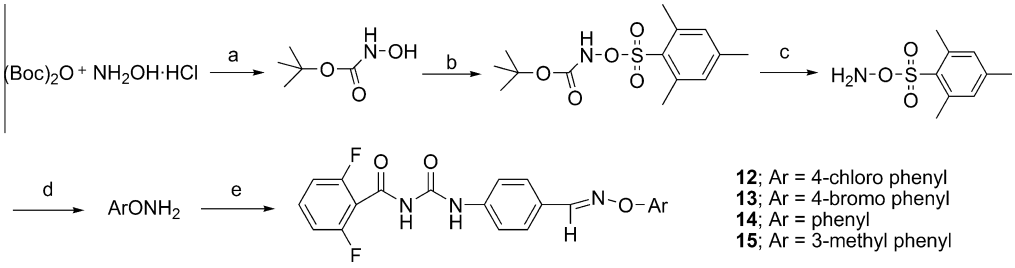
Compound **19** was synthesized from *p*-nitrobenzaldehyde as shown in Scheme 7. Intermediate $\mathbf{n_2}$ from *p*-nitrobenzaldehyde through Wittig reaction and subsequent hydrolysis in acetonitrile with 5% dilute hydrochloride. Then compound **19** was synthesized by using the similar method of compounds **1–2**. It could be seen from the X-ray single-crystal molecular structure of compound



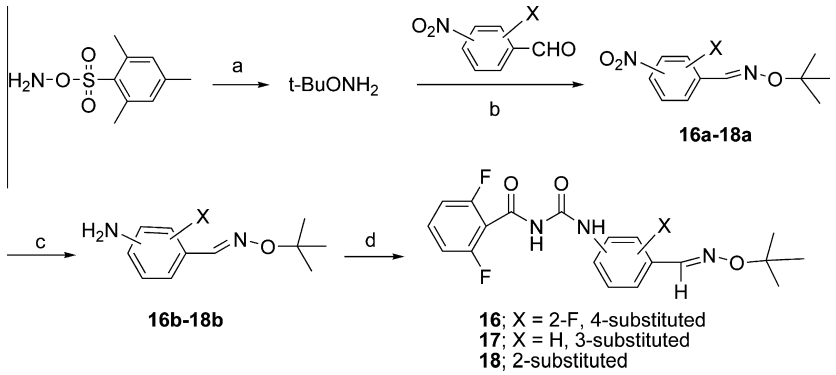
Scheme 3. Reagents and conditions: (a) CrO_3, Ac_2O, concd H_2SO_4; (b) concd HCl, 1,4-dioxane; (c) $NH_2OH{\cdot}HCl$, pyridine, THF, rt; (d) toluene/H_2O, TBAB, NaOH, *i*-PrI; (e) Fe/HCl, ethanol, 60–70 °C; (f) 2,6-diflurobenzoyl isocyanate, CH_2Cl_2, rt.



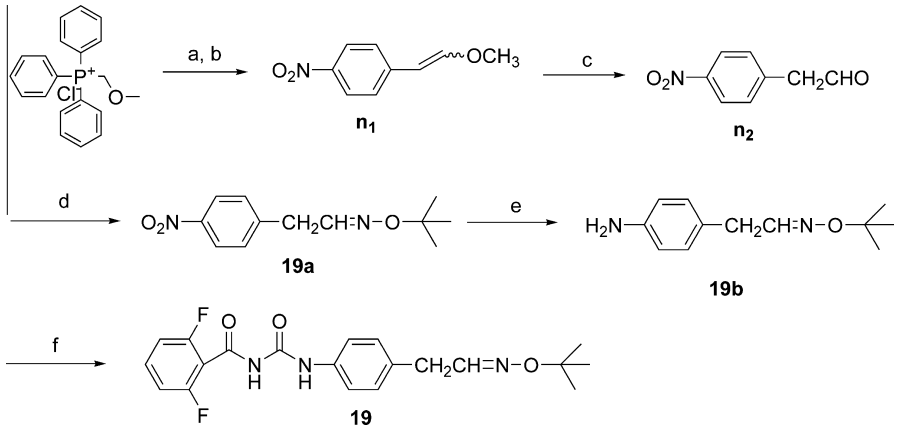
Scheme 4. Reagents and conditions: (a) $SnCl_2{\cdot}2H_2O$, ethanol, 70 °C; (b) 2,6-diflurobenzoyl isocyanate, CH_2Cl_2, rt; (c) $NH_2OH{\cdot}HCl$, pyridine, THF, rt; (d) THF, NEt_3, substituted carbonyl chloride.



Scheme 5. Reagents and conditions: (a) Na_2CO_3, Et_2O; (b) mesitylenesulfonyl chloride, Et_3N, Et_2O, −5 to 0 °C; (c) CF_3COOH, −5 to 0 °C; (d) ArONa, Et_2O, −10 to 0 °C; (e) **N**, AcOH (ca.).



Scheme 6. Reagents and conditions: (a) *t*-BuOK, Et_2O, −10 to 0 °C; (b) AcOH (ca.); (c) 10% Pd–C/H_2, Et_2O, 3 Å molecular sieve; (d) 2,6-diflurobenzoyl isocyanate, CH_2Cl_2, rt.



Scheme 7. Reagents and conditions: (a) *t*-BuOK, THF, 0 °C, 2 h; (b) 4-nitrobenzaldehyde, −10 to 0 °C; (c) 5% HCl, CH_3CN, reflux; (d) *t*-$BuONH_2$, ca. AcOH, Et_2O, −10 to 0 °C; (e) 10% Pd–C/H_2, Et_2O, 3 Å molecular sieve; (f) 2,6-diflurobenzoyl isocyanate, CH_2Cl_2, rt.

19 as shown in Figure 2 that the bond of C(15)–C(16) and the bond of N(3)–O(3) are of the opposite of the C=N double, thereby the compound **19** was mainly *Z* configuration.[20]

The larvicidal activities of compounds **1–19**, **Flucycloxuron** and compound **B** against Oriental armyworm were evalued. The results (Table 1) indicate that most compounds have excellent larvicidal activities against Oriental armyworm and some compounds exhibit higher larvicidal activities than compound **B**. For example, the larvicidal activities of compounds **6** and **19** against Oriental armyworm at 1.0 mg L^{-1} were 90% and 90% respectively, as compared with 50% mortality of compound **B** at the same concentration. The result in Table 1 shows that there exist steric effects and electric effects on the larvicidal activities. The activity becomes higher with smaller size of R_1 group in the structures, for example, compound **B** exhibited higher larvicidal activities against Oriental armyworm than compounds **1** and **3**. The larvicidal activities of **8**, **9**, **10**, **11** against Oriental armyworm increased sequentially with the size of R_2 group in the structures increasing. The larvicidal activities of compounds **12**, **14**, and **15** against Oriental armyworm reduced gradually while the electron density in aromatic ring of *O*-aryl group increasing. Small size and high electro-negativity substituent on the anilide moiety was favorable for larvicidal activities against Oriental armyworm, for example, the activity of compound **6** was higher than that of compound **5** and **7**. The larvicidal activities against Oriental armyworm of compounds **17** and **18** decreasing rapidly compared to compound **B** displayed that the *para* substituent at the anilide moiety in the structure of benzoylphenylurea was more favorable for enhancing the larvicidal activity than *ortho* or *meta* substituent. The larvicidal activity against Oriental armyworm of compound **19** which was much lower than compound **B** displayed that the conjugation of amino group (CH=N) with aromatic ring at the anilide moiety was important to the larvicidal activities against Oriental armyworm. It was seen from Table 1 that on the whole the larvicidal activities of the target compounds **1–15** against mosquito displayed similar structure–activity relationship (SAR) with that of Oriental armyworm, and most of them exhibited excellent larvicidal activities against mosquito. In particular, the larvicidal activities of compounds **7**, **12** and **13** against mosquito were higher than that of compound **B** and compound **12** exhibited best larvicidal activity against mosquito, which had 90% morality even at 0.005 mg L^{-1}.

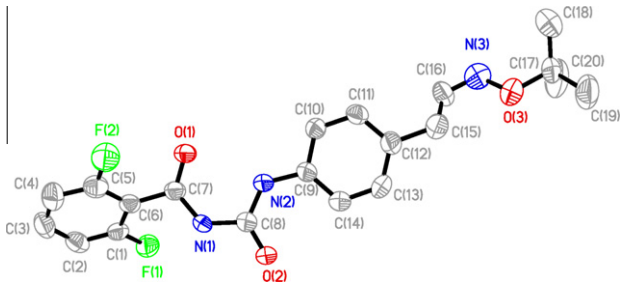
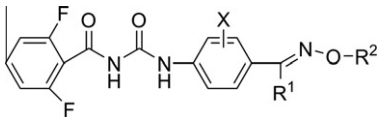
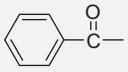
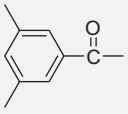
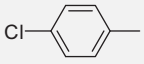
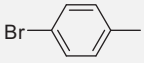


Figure 2. Molecular structure of compound **19**.

The larvicidal activities of selected compounds **6** and **16** against diamondback moth and beet armyworm were evalued. It was seen from Table 2 that compounds **6** and **16** exhibited much better lar-

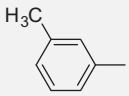
Table 1
Larvicidal activities against Oriental armyworm and mosquito of compounds **1**–**19**, **Flucycloxuron** and compound **B**



Compound	X	R^1	R^2	Toxicities against Oriental armyworm		Toxicities against mosquito	
				Concentration (mg L^{-1})	Larvicidal activity (%)	Concentration (mg L^{-1})	Larvicidal activity (%)
1	H	CH_3	$CH(CH_3)_2$	10	100	0.5	100
				5	100	0.25	100
				2.5	65	0.1	90
				1.0	10	0.05	90
				0.5	0	0.025	30
2	H	CH_3	$PhCH_2$	50	90	2	0
				25	80	1	0
				10	10		
3	H	CN	$CH(CH_3)_2$	50	100	0.25	100
				10	80	0.1	100
				5	40	0.05	50
				2.5	0	0.025	10
						0.01	0
4	H	CN	$PhCH_2$	200	0	0.5	100
						0.25	100
						0.1	90
						0.05	0
5	2-Cl	H	$CH(CH_3)_2$	5	100	0.5	100
				2.5	90	0.01	100
				1	10	0.005	30
				0.5	0		
6	2-F	H	$CH(CH_3)_2$	2.5	100	0.01	100
				1	100	0.005	100
				0.5	90	0.0025	50
				0.25	10	0.001	20
				0.125	0	0.0005	10
7	3-Cl	H	$CH(CH_3)_2$	5	100	0.01	100
				2.5	90	0.005	100
				1	10	0.0025	30
				0.5	0	0.001	10
8	H	H		200	100	2	100
				100	50	1	100
				50	20	0.5	20
				25	10	0.25	0
				10	0		
9	H	H		25	90	1	100
				10	80	0.5	100
				5	40	0.25	80
				2.5	0	0.1	30
10	H	H		25	100	0.5	100
				10	100	0.25	100
				5	90	0.1	90
				2.5	0	0.05	90
						0.025	10
11	H	H		10	100	0.5	100
				5	100	0.25	100
				2.5	20	0.1	70
				1.0	10	0.05	10
				0.5	0	0.025	0
12	H	**H**		10	100	0.0025	100
				5	100	0.001	100
				2.5	80	0.0005	90
				1.0	0	0.00025	20
13	H	**H**		25	100	0.01	100
				10	100	0.005	100
				5	90	0.0025	40
				2.5	90	0.001	0
				1.0	0		
14	H	**H**		200	100	0.025	100
				100	100	0.01	100
				50	90	0.005	20
				25	40	0.0025	10
				10	20		
				5	0		
15	H	**H**		200	100	0.5	90
				100	90	0.25	60

(*continued on next page*)

Table 1 (*continued*)

Compound	X	R^1	R^2	Toxicities against Oriental armyworm		Toxicities against mosquito	
				Concentration (mg L^{-1})	Larvicidal activity (%)	Concentration (mg L^{-1})	Larvicidal activity (%)
				50	50	0.1	20
				25	30		
				10	10		
				5	0		
16	2-F	**H**	$C(CH_3)_3$	2.5	100	/[a]	/
				1	100		
				0.5	90		
				0.25	10		
17				100	100	/	/
				50	100		
				25	90		
18				200	0	/	/
19				50	100	/	/
				25	100		
				10	80		
Flucycloxuron				10	95	0.1	100
				5	90	0.05	100
				2.5	50	0.025	15
				1.0	10	0.01	0
				0.5	0		
B				2.5	100	0.01	100
				1.0	100	0.005	75
				0.5	50	0.0025	15
				0.25	0	0.001	0

[a] /: This compound was not tested.

Table 2
Larvicidal activities against diamondback moth, beet armyworm and corn borer of compound **6**, **16** and **Flucycloxuron**

Compound	Toxicities against diamondback moth LC_{50} (mg L^{-1})	Toxicities against beet armyworm LC_{50} (mg L^{-1})	Toxicities against born borer LC_{50} (mg L^{-1})
6	2.75	4.32	7.59
16	0.57	3.37	10.02
Flucycloxuron	72.92	101.55	9.25

vicidal activities against diamondback moth and beet armyworm than **Flucycloxuron** from the LC_{50} values. However, compounds **6**, **16**, and **Flucycloxuron** displayed similar stomach activities against corn borer from the values of LC_{50}. The result that the stomach activity of compound **16** against diamondback moth was four times higher than that of compound **6**, at the same time, the stomach activities of compounds **6** and **16** against beet armyworm and corn borer were at the same level. The different stomach activities of compounds **6** and **16** toward diamondback moth, beet armyworm and corn borer indicated that compounds **6** and **16** showed insect-selective activities although three tested insects all belong to the same insect order.

In summary, a series of new structural benzoylphenylureas (BPUs) containing oxime ether and oxime ester group were designed and synthesized, and the larvicidal activities against Oriental armyworm and mosquito of these benzoylphenyureas were evaluated. The result shows that most compounds exhibited excellent larvicidal activities against Oriental armyworm and mosquito. It was discovered that compounds **6** and **16** exhibited better larvicidal activities against Oriental armyworm than compound **B** and **Flucycloxuron**, the larvicidal activities of compounds **6**, **7**, **12**, and **13** against mosquito were higher than compound **B** and **Flucycloxuron**. The structure–activity relationship (SAR) indicated that big size of R_2 and small size of R_1, small size and high electro-negativity of substituent group in anilide moiety increase the larvicidal activities against Oriental armyworm and mosquito. Interestingly, the larvicidal activity against Oriental armyworm of compound **19** which was much lower than compound **B** displayed that the conjugation of amino group (CH=N) with aromatic ring at the anilide moiety in the structure was important to the larvicidal activities against Oriental armyworm. Compounds **6** and **16** exhibited much better larvicidal activities against diamondback moth and beet armyworm than **Flucycloxuron** but similar larvicidal activity against corn borer with **Flucycloxuron**. Surprisingly, compound **6** and **16** showed insect-selective activities towards diamondback moth, beet armyworm and corn borer.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.144.

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20. CCDC **774638** contains the Supplementary data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.