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Synthesis and bioassay evaluation of 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas

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Abstract—A variety of novel 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas were designed and synthesized by the reaction of 4-substitutedideneaminooxymethyl aniline with 2,6-difluorobenzoyl isocyanates in good yields. The title compounds were soluble in most organic solvents, which should make them easier to use. The preliminary bioassay showed that some of the title compounds show excellent insecticidal activity against *Mythimna separata* at the dosage of 25 mg kg^{-1} and moderate insecticidal activity against *Nephotettix cincticeps* at the dosage of 500 mg kg^{-1}. Toxicity assays indicated that these title compounds cause in *M. separata* and *N. cincticeps* such symptoms of toxicity as discolouration, and weight loss, and cessation of feeding and lethal. One title compound exhibited acaricidal activity against *Tetranychus urticae*.

1. Introduction

Chitin is the most abundant organic skeletal component in the cuticle of insects, but it is absent in vertebrates (including mammals) and higher plants. Thus, the development of selective insecticides based on interference with chitin formation has become one of the aims in new pesticide design.[1] Benzoylphenylureas, discovered in the 1970s, are known well as commercial chitin formation inhibitors. In contrast to traditional pesticides, benzoylphenylurea and its derivatives mainly control the growth and development process of insects by interfering with chitin biosynthesis and breeding.[2–4] Consequently, toxicity of benzoylphenylureas to vertebrates and environmental impact are very low and a high insecticidal selectivity is achieved. Because of the above advantages, benzoylphenylureas have attracted considerable attentions for decades.[5–9]

Among them, a class of compounds of substituted benzoylphenylureas **1** (Scheme 1) shows good insecticidal and acaricidal activities.[10] When R^1 is cyclopropyl and R^2 is 4-chlorophenyl, the compound is a commercial pesticide (Flucycloxuron) and it also combats tumours.[11,12] When CR^1R^2 is C_4–C_8 monocyclo group containing 1 or 2 sulfur atoms, the compound is also a good pesticide to control insects and acaricide.[13] In the search for new compounds having insecticidal activity, basing on bioisosterism, we designed a variety of new compounds by using: (1) substituted pyrromonoazole or pyrrodiazole or 1,3-benzodioxole group replacing R^2 (phenyl group); (2) cyano or alkylthiol replacing R^1 (cyclopropyl); (3) opened-cyclo-alkylthiol replacing CR^1R^2 (C_4–C_8 monocyclo group). In this paper, we describe the synthesis and bioassay of these compounds.

2. Results and discussion

2.1. Chemistry

The synthetic route of the designed 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas (**1**) is summarized in Scheme 2. *p*-Nitrobenzyl bromide (**2**) was prepared by the reaction of *p*-nitrotoluene with

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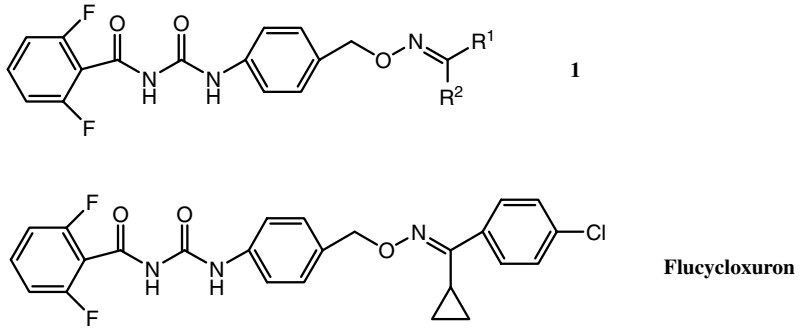


Scheme 1. The structures of benzoylphenylureas **1** and Flucycloxuron (**2**).

bromine according to the reported method.[14] Then **2** was condensed with oxime to give **3**, subsequent reduction using iron powder as a catalyst provided the key intermediate **4**. The reaction time of preparing compounds **3** and **4** is different for different compounds from 30 min to 8 h and the reaction was traced by TLC. The compound **4** was reacted with 2,6-difluorobenzoyl isocyanate in dichloromethane at room temperature for 30 min to obtain the title compounds **1** in 58.3–87.0% yields.

All the compounds **1** were soluble in most organic solvents, which should make them easier to use. Most commercial benzoylphenylureas have limited solubility in common organic solvents generalfly used in pesticide formulations. Consequently, these commercial benzoylphenylureas have to be formulated in solid state. The particle size of the active material in the formulation has a considerable influence on the biological activity and the rate of degradation of the compound in soil.[15]

The structures of all the title compounds **1** were characterized by ^{1}H NMR spectroscopy and elemental analyses. In ^{1}H NMR, because 2,6-difluoro atoms and 4-hydrogen atom have the same coupling constant to 3,5-dihydrogen atoms, all compounds **1** have a trifid peak at about 7 ppm (δ value). At the same time, there is a multi-peak at about 7.5 ppm (δ value) because of 2,6-difluoro atoms and 3,5-dihydrogen atoms coupling to 4-hydrogen atom.

2.2. Bioassay

The insecticidal activities of the title compounds **1** against *Mythimna separata*, *Nephotettix cincticeps*, *Tetranychus urticae* were investigated using commercial Flucycloxuron as controls. As shown in Table 1, all tested compounds **1** had no or very poor acaricidal activity against *T. urticae* at the dose of 200 mg kg^{-1} except for **4j** (76% and 43% mortality for egg and larvae, respectively).

The results of insecticidal activity tests given in Table 1 indicate that some of the title compounds show excellent insecticidal activity against *M. separata*. For example, compounds **1f** and **1g** exhibit 100% and 70% insecticidal activity against *M. separata* at the dosage of 25 mg kg^{-1}. When the concentration was reduced to 10 mg kg^{-1}, compound **1f** still exhibits 50% insecticidal activity against *M. separata*. For *N. cincticeps*, some of the title compounds, such as **1a**, **1b**, **1c**, **1h**, **1i** and **1m**, exhibited moderate insecticidal activity with the mortalities ranging from 45.7% to 69.7% at the dosage of 500 mg kg^{-1}, whereas a commercial Flucycloxuron exhibits 42.8% insecticidal activity against *N. cincticeps* at the same dosage. Toxicity assays indicated that these title compounds cause in *M. separata* and *N. cincticeps* such symptoms of toxicity as discolouration, and weight loss, and cessation of feeding and lethal.

3. Conclusions

In summary, a variety of novel 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas were designed and synthesized by the reaction of 4-substitutedideneaminooxymethyl aniline with 2,6-difluorobenzoyl isocyanates in good yields. The title compounds were soluble in most organic solvents, which should make them easier to use. The preliminary bioassay showed that some of the title compounds show excellent insecticidal activity against *M. separata* at the dosage of 25 mg kg^{-1} and moderate insecticidal activity against *N. cincticeps* at the dosage of 500 mg kg^{-1}. Toxicity assays indicated that these title compounds cause in *M. separata* and *N. cincticeps* such symptoms of toxicity as discolouration, and weight loss, and cessation of feeding and lethal. One title compound exhibited acaricidal activity against *T. urticae*.

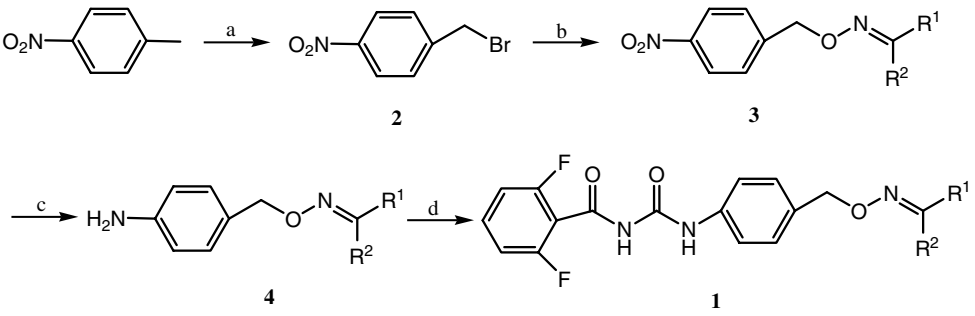
4. Experimental

4.1. Materials

Solvents were dried by standard methods and distilled prior to use. 2,6-Difluorobenzoyl isocyanate was synthesized by the method of literature.[16] Oxime was synthesized according to the method of literature.[17,18]

4.2. Analysis and instruments

The title compounds were synthesized under a nitrogen atmosphere. Proton NMR spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer in



Scheme 2. Synthesis of 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas. Reagents and condition: (a) Br_2; (b) HON = CR^1R^2, NaOH, THF; (c) Fe, HCl (37%); (d) 2,6-difluorobenzoyl isocyanate, CH_2Cl_2, rt.

Table 1. Insecticidal and acaricidal activities of compounds **1**

Compound	*Mythimna separata* (mg kg^{-1})						*Nephotettix cincticeps* (mg kg^{-1})	*Tetranychus urticae* (mg kg^{-1})	
	500	200	100	50	25	10	500	Eggs 200	Larvae 200
1a	100	40	0	0	0	0	62.5	—	—
1b	100	100	50	0	0	0	69.7	—	—
1c	30	0	0	0	0	0	50.0	—	—
1d	60	0	0	0	0	0	24.3	—	—
1e	100	100	100	50	0	0	19.2	12	10
1f	100	100	100	100	100	50	33.3	11	10
1g	100	100	100	90	70	15	—	10	7
1h	25	0	0	0	0	0	50.0	—	—
1i	80	65	40	25	0	0	56.3	—	—
1j	100	100	50	—	0	0	41.0	76	43
1k	75	15	10	—	10	0	—	—	—
1l	30	0	—	—	—	—	18.2	—	—
1m	30	0	—	—	—	—	45.7	—	—
1n	0	—	—	—	—	—	—	—	—
Flucycloxuron	—	—	—	—	100	100	42.8	100	100

CDCl3 solution with TMS as internal standard. Chemical shift values (δ) are given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas–Hoover melting-point apparatus and are uncorrected. Yields were not optimized.

4.3. General synthetic procedure for 3

p-Nitrobenzyl bromide (5 mmol) and sodium hydroxide (10 mmol) were added into water (10 ml) and tetrahydrofuran (20 ml). Then oxime (5 mmol) was added to the mixture. The mixture was stirred at room temperature. The reaction was traced by TLC. After the *p*-nitrobenzyl bromide reacted completely, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and evaporated to yield **3**, which were used without further purification except **3l**.

Data for ***3l***. Yield, 80.0%; mp, 66–67 °C. ^{1}H NMR: 1.31 (s, 9H, $(CH_3)_3$), 5.28 (s, 2H, CH_2), 7.39 (d, 2H, $^3J_{HH}$ = 7.5 Hz, Ph), 7.49 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.56 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 8.16 (s, 1H, CH), 8.22 (d, 2H, $^3J_{HH}$ = 7.5 Hz, Ph).

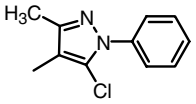
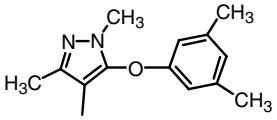
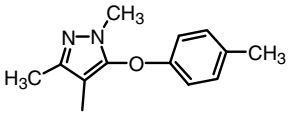
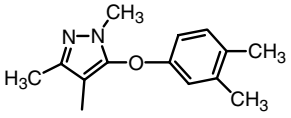
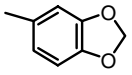
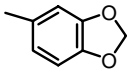
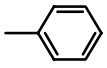
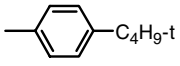
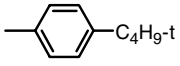
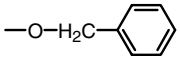
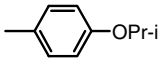
4.4. General synthetic procedure for 4

Into a three-necked flask equipped with a thermometer, condenser and mechanical stirrer, and under nitrogen, 2.2 g of iron powder, 8 ml of (95%) ethanol, 2 ml of water, 0.25 ml hydrochloric acid at 37% and then compound **3** (5 mmol) dissolved in 2 ml of ethyl alcohol were dissolved in the order as listed. The temperature was kept controlled between 40 and 50 °C. The reaction was traced by TLC. After the reaction completed, untreated iron was filtered off and the filtrate was diluted with 50 ml of water. The mass was extracted with ethyl ether and dehydrated with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by vacuum column chromatography on silica gel using petroleum ether (60–90 °C) and ethyl acetate as the eluent to yield **4**. The melting points and yields of the compounds **4** are listed in Table 2.

4.5. General synthetic procedure for 1

A solution of compound **4** (3 mmol) and 2,6-difluorobenzoyl isocyanate (3 mmol) in 20 ml of dichloromethane reacted at room temperature for 30 min. The solvent was evaporated off under reduced pressure,

Table 2. The melting points and yields of the compounds **4**

Compound	R^1	R^2	Mp (°C)	Yield (%)
4a	H		73–76	63.4
4b	H		93–95	87.5
4c	H		83–85	68.6
4d	H		90–91	73.8
4e	CH_3		87–89	78.3
4f	H		98–100	88.9
4g	CH_3		130–132	83.7
4h	CN		105–106	68.3
4i	SC_4H_9-*n*		71–74	83.3
4j	SC_2H_5	$CH(CH_3)_2$	64–66	65.3
4k	CH_3	$SCH_2CH_2CH_3$	62–63	74.3
4l	H		81–82	88.2
4m	H		111–113	84.1
4n	H		87–90	78.3

and the residue was recrystallized in acetonitrile or chloroform-*n*-hexane to obtain the title compounds **1**.

The melting points, yields and elemental analysis of the title compounds **1** are listed in Table 3. The ^1H NMR of compounds **1** are listed in Table 4.

4.6. Determination of the insecticidal and acaricidal activities

4.6.1. Biological assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis and mortality rates were corrected using Abbott's formula.[19] Evaluations are based on a percentage scale of 0–100 in which 0 = no activity and 100 = total kill.

4.6.2. Larvicidal activity against *M. separata*. The larvicidal activities of the title compounds **1** against *M. separata* were evaluated by foliar application using a previously reported procedure.[8,20–22]

4.6.3. Larvicidal activity against *N. cincticeps*. The larvicidal activities of the title compounds **1** against

Table 3. The melting points, yields and elemental analysis of the title compounds **1**

	Mp (°C)	Yield (%)	Formula	Elemental analysis (%, calcd)		
				C	H	N
1a	169–171	75.0	$C_{26}H_{20}ClF_2N_5O_3$	59.58 (59.60)	4.09 (3.85)	13.51 (13.37)
1b	181–183	80.8	$C_{29}H_{27}F_2N_5O_4$	63.52 (63.61)	5.12 (4.97)	13.01 (12.79)
1c	167–169	87.0	$C_{28}H_{25}F_2N_5O_4$	62.96 (63.03)	4.76 (4.72)	12.92 (13.13)
1d	152–154	71.4	$C_{29}H_{27}F_2N_5O_4$	63.50 (63.61)	5.17 (4.97)	12.85 (12.79)
1e	178–180	74.6	$C_{19}H_{16}F_2N_6O_3$	54.96 (55.07)	3.95 (3.89)	20.32 (20.28)
1f	169–171	79.5	$C_{23}H_{17}F_2N_3O_5$	61.02 (61.00)	4.23 (3.78)	9.34 (9.27)
1g	179–181	80.3	$C_{24}H_{19}F_2N_3O_5$	61.87 (61.67)	4.03 (4.10)	9.05 (8.99)
1h	207–209	72.9	$C_{23}H_{16}F_2N_4O_3$	63.64 (63.59)	4.00 (3.71)	13.09 (12.90)
1i	162–164	58.3	$C_{30}H_{33}F_2N_3O_3S$	64.99 (65.08)	6.09 (6.01)	7.76 (7.59)
1j	131–133	75.5	$C_{21}H_{23}F_2N_3O_3S$	57.95 (57.92)	5.38 (5.32)	9.75 (9.65)
1k	126–128	83.3	$C_{20}H_{21}F_2N_3O_3S$	57.04 (57.00)	4.93 (5.02)	9.89 (9.97)
1l	197–199	83.5	$C_{26}H_{25}F_2N_3O_3$	67.09 (67.09)	5.34 (5.41)	9.08 (9.03)
1m	176–178	82.1	$C_{23}H_{19}F_2N_3O_4$	67.62 (67.57)	4.41 (4.50)	8.19 (8.15)
1n	159–161	78.7	$C_{25}H_{23}F_2N_3O_4$	64.32 (64.23)	5.03 (4.96)	9.07 (8.99)

Table 4. ^{1}H NMR of the title compounds **1**

	δ (ppm)
1a	2.46 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 7.03 (t, 2H, $^3J_{HH}$ = 7.5 Hz, Ph), 736–7.56 (m, 10H, Ph), 8.12 (s, 1H, CH), 9.48 (s, 1H, NH), 10.47 (s, 1H, NH)
1b	2.27 (s, 6H, $(CH_3)_2$), 2.39 (s, 3H, CH_3), 3.58 (s, 3H, NCH_3), 4.99 (s, 2H, CH_2), 6.48 (s, 2H, Ph), 6.73 (s, 1H, Ph), 7.02 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.25 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.40 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.49 (m, 1H, Ph), 7.81 (s, 1H, CH), 9.49 (s, 1H, NH), 10.42 (s, 1H, NH)
1c	2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.59 (s, 3H, NCH_3), 4.97 (s, 2H, CH_2), 6.77 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.01 (t, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.09 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.24 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.38 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.49 (m, 1H, Ph), 7.80 (s, 1H, CH), 9.69 (s, 1H, NH), 10.44 (s, 1H, NH)
1d	2.21 (s, 6H, $(CH_3)_2$), 2.38 (s, 3H, CH_3), 3.58 (s, 3H, NCH_3), 4.98 (s, 2H, CH_2), 6.60 (m,1H, Ph), 6.67 (d, 1H, $^3J_{HH}$ = 2.1 Hz, Ph), 6.99-7.04 (m, 3H, Ph), 7.26 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.42 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.50 (m, 1H, Ph), 7.80 (s, 1H, CH), 9.13 (s, 1H, NH), 10.41 (s, 1H, NH)
1e	2.50 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 7.04 (t, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.34 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.48 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.52 (m, 1H, Ph), 7.99 (s, 1H, CH), 8.66 (s, 2H, NCH_2), 9.59 (s, 1H, NH), 10.50 (s, 1H, NH)
1f	5.13 (s, 2H, CH_2), 5.98 (s, 2H, CH_2), 6.79 (d, 1H, $^3J_{HH}$ = 8.4 Hz, Ph), 6.94 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.01 (t, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.20 (s, 1H, Ph), 7.34 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.44 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.49 (m, 1H, Ph), 8.03 (s, 1H, CH), 9.59 (s, 1H, NH), 10.45 (s, 1H, NH)
1g	2.22 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 5.97 (s, 2H, CH_2), 6.79 (d, 1H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.00–7.11 (m, 3H, Ph), 7.22 (s, 1H, Ph), 7.36 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.45–7.55 (m, 3H, Ph), 9.20 (s, 1H, NH), 10.42 (s, 1H, NH)
1h	5.43 (s, 2H, CH_2), 7.26 (t, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.48 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.52–7.75 (m, 8H, Ph), 10.22 (s, 1H, NH), 11.46 (s, 1H, NH)
1i	0.76 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.27 (m, 2H, CH_2), 1.32 (s, 9H, $(CH_3)_3$), 1.43 (m, 2H, CH_2), 2.59 (t, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 5.23 (s, 2H, CH_2), 7.00 (t, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.33–7.50 (m, 9H, Ph), 9.91 (s, 1H, NH), 10.45 (s, 1H, NH)
1j	1.20 (d, 6H, $^3J_{HH}$ = 6.9 Hz, $(CH_3)_2$), 1.26 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 2.69 (m, 1H, CH), 2.88 (q, 2H, $^3J_{HH}$ = 6.6 Hz, CH_2), 5.09 (s, 2H, CH_2), 7.02 (t, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.30 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.39 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.52 (m, 1H, Ph), 9.84 (s, 1H, NH), 10.44 (s, 1H, NH)
1k	0.96 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.71 (s, 3H, CH_3), 2.75 (t, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 5.02 (s, 2H, CH_2), 6.94 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.22 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.31 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.44 (m, 1H, Ph), 9.82 (s, 1H, NH), 10.35 (s, 1H, NH)
1l	1.32 (s, 9H, $(CH_3)_3$), 5.17 (s, 2H, CH_2), 7.01 (t, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.34–7.54 (m, 9H, Ph), 8.12 (s, 1H, CH), 9.58 (s, 1H, NH), 10.45 (s, 1H, NH)
1m	5.08 (s, 2H, OCH_2), 5.14 (s, 2H, CH_2ON), 6.95–7.03 (m, 4H, Ph), 7.33–7.54 (m, 12H, Ph), 8.09 (s, 1H, CH), 9.76 (s, 1H, NH), 10.46 (s, 1H, NH)
1n	1.34 (d, 6H, $(CH_3)_2$, $^3J_{HH}$ = 6.0 Hz), 4.54–4.62 (m, 1H, CH), 5.14 (s, 2H, CH_2), 6.87 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.01 (t, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.35 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph),7.43–7.52 (m, 3H, Ph), 8.08 (s, 1H, CH), 9.47 (s, 1H, NH), 10.44 (s, 1H, NH)

N. cincticeps were evaluated using a previously reported procedure.[23–25]

4.6.4. Activity against *T. urticae*. The larvicidal activities of the title compounds **1** against *T. urticae* were evaluated using a previously reported procedure.[26,27]

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