Synthesis and Biological Evaluation of Nitromethylene Neonicotinoids Based on the Enhanced Conjugation

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Ⓢ Supporting Information

ABSTRACT: The neonicotinoids with a nitroconjugated system had excellent bioactivity, which could rival imidacloprid, and has been previously reported. However, the photodegradation and hydrolysis of this series of neonicotinoids was very quick according to our further investigation, which cannot be developed as a pesticide further. The approach to further enhance the conjugation was tried not only to increase the bioactivities but also to improve the stability in water and in the sun. A substituted phenyl group was introduced into the furan ring of compound **3**. A total of 13 novel neonicotinoid analogues with a higher conjugation system were designed and synthesized. The target molecular structures have been confirmed on the basis of satisfactory analytical and spectral data. All compounds presented significant insecticidal activities on cowpea aphid (*Aphis craccivora*), cotton aphid (*Aphis gossypii*), and brown planthopper (*Nilaparvata lugens*). The stability test exhibited that the stability of novel analogues in water and under the mercury lamp has been improved significantly in comparison to compound **3**.

KEYWORDS: Neonicotinoids, conjugation, insecticidal activity

INTRODUCTION

Neonicotinoids, as a milestone of integrated pest management (IPM) during the past 30 years, are a kind of insecticide that acts selectively on the central nervous system of the insect and can be efficient ligands for the nicotinic acetylcholine receptors (nAChRs) of insects.[1−3] However, with the increase of neonicotinoids used on the crop protection for a long time, the problems of resistance, cross-resistance,[4−7] and bee toxicity[8] have received more attention, which calls for a new strategy of molecular design to find new leading compounds.

The mode of action of neonicotinoids targeting nAChRs attracted widely interests,[9−11] several papers about acetylcholine receptor binding protein imidacloprid (AChBPs-IMI) were reported.[2,12] Qian et al. also proposed a new mode of action by computational modeling, which demonstrated the importance of hydrogen bonding and the cooperative π−π interaction between the molecule and amino acid residues.[13] On the basis of this model, series **1** of phenylazoneonicotinoids (compound **1** in Figure 1) were designed and synthesized. The diazene moiety was introduced to enhance the π−π stacking interaction to increase the electron scope and density of the conjugated system.[14,15] Some of synthesized compounds with electron-donating groups (EDGs) on *ortho* positions of the phenyl ring presented higher insecticidal activity than imidacloprid against cowpea aphid (*Aphis craccivora*). Encouraged by this molecular design of phenylazoneonicotinoids with well-conjugated systems, we pay more attention to the neonicotinoids with a nitroconjugation system (compound **2** in Figure 1). Series **2** exhibited excellent insecticidal activity comparable to that of imidacloprid against cowpea aphid. Especially compound **3**

exhibited a very high insecticidal activity against cowpea aphid (*A. craccivora*) with a LC$_{50}$ value of 3.72 μmol L^{-1}.[16]

Unfortunately, the half-life of compound **3** was 0.77 min under the irradiation of a 300 W high-pressure mercury lamp, and its hydrolysis half-life in water was only 2.40 h. It is well-known that the degradation of compounds as pesticides occurring in the environment is a key factor in insecticide research and development. Inspired by the model, we tried to enhance the conjugation system and improve the conjugation effect of the nitromethylene pharmacophore for the sake of improved stability, which was contributed to the formation of the π−π interaction.

Therefore, a substituted phenyl group was introduced into the furan ring. In addition, the binding affinity and insecticidal activity were also expected to be enhanced by a possible π−π interaction. Synthesis of 13 nitromethyleneneonicotinoids, their significant insecticidal activities, and increased stabilities were reported in this paper.

MATERIALS AND METHODS

Instrumentation and Chemicals. High-resolution mass spectra were recorded under electron impact (70 eV) conditions using a MicroMass GCT CA 055 instrument. Melting points (mp) were recorded on Büchi B540 apparatus and are uncorrected. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with CDCl₃ or DMSO-d₆ as the solvent and tetramethylsilane (TMS) as the internal standard.
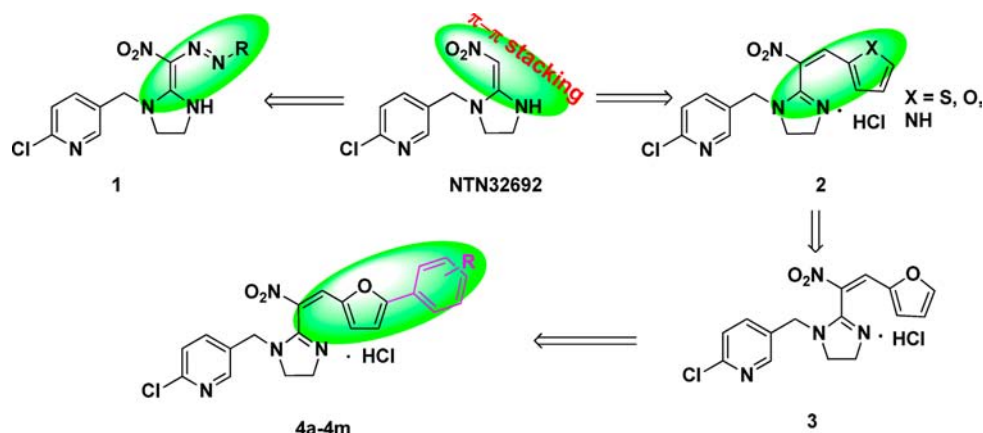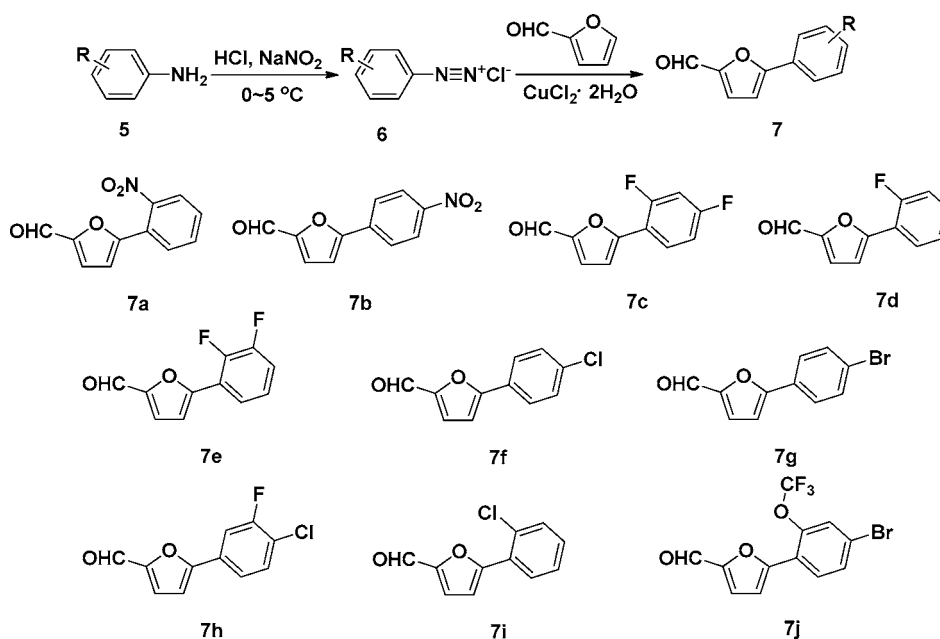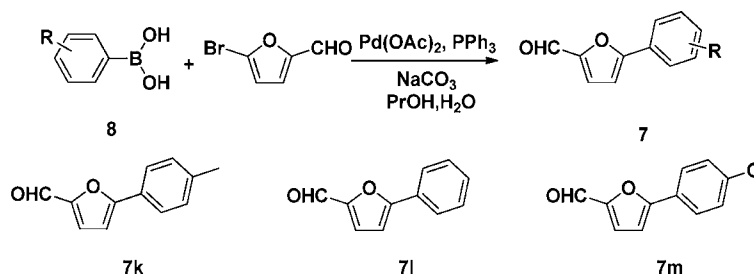
Figure 1. Design of compounds.

Scheme 1. Preparation of Intermediates 7a–7j
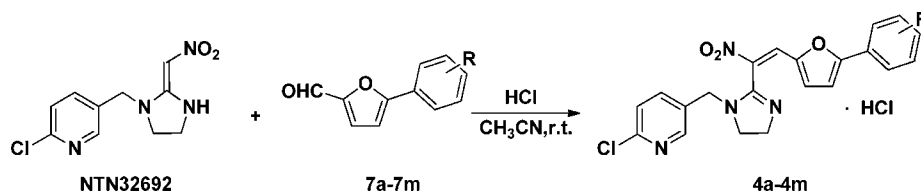

Scheme 2. Preparation of Intermediates 7k–7m

Chemical shifts are reported in δ (parts per million) values. Gas chromatography (GC)−mass spectra were recorded using a HP 6890 gas chromatograph and a HP 5973 mass selective detector. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. An XPA series type merry-go-round photochemical reactor (Xujiang Machine Factory, Nanjing, China) was equipped with a 300 W high-pressure mercury lamp. The working current of a 300 W high-pressure mercury lamp was 2.2 A, and the operating voltage was 138.1 V.

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

Synthetic Procedures. *Synthesis of Intermediates 7a–7j.* Intermediates **7a–7j** were prepared as described in the literature (Scheme 1).[17,18]

Substituted aniline (15 mmol) and concentrated hydrochloric acid (10 mL) were stirred in H_2O (50 mL) at 25 °C for 30 min and then cooled to 0 °C. $NaNO_2$ (18 mmol) in 5 mL of H_2O was added dropwise to the solution. After 1 h of stirring at 0 °C, furfural (15 mmol) in acetone (8 mL) and $CuCl_2\cdot2H_2O$ (3 mmol) in H_2O (5 mL) were slowly added successively. The resulting mixture was stirred for

Scheme 3. Preparation of Compounds 4a−4m

12 h at room temperature and monitored by TLC (1:10 EtOAc/PE). The solution was filtrated, and the filter cake was washed with EtOH, giving the title compound.

Intermediates **7k−7m** were prepared as described in the literature (Scheme 2).[19−21]

Substituted phenylboronic acid (3.2 mmol), 5-bromo-2-furaldehyde (3 mmol), and $NaCO_3$ (8 mmol) were mixed in n-propanol (10 mL). To the mixture with stirring, tetrakis(triphenylphosphine)palladium (0.3 mmol) was added. The mixture was heated to reflux under an argon atmosphere and monitored by TLC. The solution was filtrated thought celite and extracted with EtOAc (10 mL × 3). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Crude product was purified by column chromatography (1:10 EtOAc/PE) to give a yellow solid product.

General Synthetic Procedure for Compounds 4a−4m. A catalytic amount of hydrochloric acid (12 M, 0.4 mL) was added to the mixture of NTN32692 (4.0 mmol) and compound **7** (4.0 mmol) in MeCN (20 mL). The resulting solution was stirred at 25 °C and monitored by TLC. After filtration, the filter cake was rinsed with MeCN (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL), and then the resulting filtrate was concentrated under reduced pressure to obtain pure crystals (Scheme 3).

Biological Assay. According to statistical requirements, the bioassay was repeated 3 times at 25 ± 1 °C. All compounds were dissolved in dimethylsulfoxide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with water containing Triton X-100 (0.1 mg L^{-1}) to obtain series concentrations of 1, 0.5, and 0.25 mg L^{-1} and others for bioassays. For comparative purposes, imidacloprid (IMI) and compound **3** were tested under the same conditions.

Insecticidal Test for Cowpea Aphid (A. craccivora). The insecticidal activities of title compounds against cowpea aphid (A. craccivora) were tested according to the previously reported procedure.[22] Horsebean seedling with 40−60 healthy apterous adults were dipped in diluted solutions of the chemicals containing Triton X-100 (0.1 mg L^{-1}) for 5 s, and then the shoots were placed in the conditioned room [25 ± 1 °C and 50% relative humidity (RH)]. Water containing Triton X-100 (0.1 mg L^{-1}) was used as a control. The mortality rates were assessed after 24 h. Each treatment had three repetitions, and the data were corrected and subject to probit analysis.

Insecticidal Test for Cotton Aphids (Aphis gossypii). The activities against cotton aphid were tested by Zhejiang Research Institute of Chemical Industry, Ltd. Cotton cotyledons with 30−40 healthy nymphs in Petri dishes were sprayed solutions (2.5 mL) with a Potter spray tower (pressure, 5 lb/in²; settlement, 4.35 mg/cm²), and then the cotyledons were placed in the conditioned room (25 ± 1 °C and 50% RH). Water containing Tween 80 (0.1%) was used as a control. The mortality rates were assessed after 48 h. Each treatment had three repetitions, and the data were corrected and subject to probit analysis.

Insecticidal Test for Brown Planthopper (Nilaparvata lugens). The activities against brown planthopper were tested by Zhejiang Research Institute of Chemical Industry, Ltd. The insecticidal activity against brown planthopper was tested by foliar application. Rice seedlings were placed on moistened pieces of filter paper in Petri dishes. The dishes were infested with third instar larvae and then sprayed with the compound solutions (2.5 mL) using a Potter spray tower (pressure, 5 lb/in²; settlement, 4.35 mg/cm²). Samples were placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subject to probit analysis as before.

Insecticidal Test for Armyworm (Pseudaletia separata Walker). The activities of insecticidal compounds against armyworm were tested by Zhejiang Research Institute of Chemical Industry, Ltd. The insecticidal activity against armyworm was tested by foliar application. Individual corn (Zea mays) leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the compound solution and exposed to dry. The dishes were infested with 10 s instar larvae and placed in the conditioned room. The mortality rates were evaluated 48 h after treatment. Each treatment had three repetitions, and the data were adjusted and subject to probit analysis as before.

Hydrolysis and Photolysis Experiments. *Ultraperformance Liquid Chromatography (UPLC) Analysis Method.* The concentrations of irradiated solutions **4a, 4b, 4c, 4f, 4g, 4i, 4k, 4l, 3,** and IMI were determined by UPLC. A Waters UPLC (Acquity UPLC H-Class) equipped with a BEH C18 column (2.1 × 100 mm, 1.7 μm), column oven (Acquity UPLC CH-B), quarter pump (Acquity UPLC QSM), and Rheodyne injector (10 μL loop) was used. The following instrumental parameters were adopted: eluent flow rate of 0.5 mL min^{-1}, gradient elution (0−1 min, 90:10% buffer/acetonitrile; 1−8 min, linear gradient to 100% acetonitrile; and 8−10 min, 100% acetonitrile), 2 μL of injector volume, and 40 °C of column temperature. A 5 min post-run time, back to the initial mobile-phase composition, was used after each analysis. The buffer solution was prepared by adding 0.01 M trifluoroacetic acid to Milli-Q water. λ_{max} of 424, 424, 427, 437, 438, 437, 420, 450, 373, and 270 nm for compounds **4a, 4b, 4c, 4f, 4g, 4i, 4k, 4l, 3,** and IMI, respectively, were adopted for analyst quantification. Quantification was performed by an external standard calibration. Calibration curves were prepared in the range from 0.02 to 0.1 mg/mL. Acetonitrile (Merck) was of high-performance liquid chromatography (HPLC) grade, and water was purified by a Millipore Milli-Q equipment.

Hydrolysis and Photolysis Experiments. To investigate the hydrolysis, representative compounds **4a, 4b, 4f, 4i, 4k, 4l,** and **3** were dissolved in Milli-Q water, respectively, and 1 mL of compounds **4a, 4b, 4f, 4i, 4k, 4l,** and **3** aqueous solution (5 × 10^{-5} mol L^{-1}) contained in 1.5 mL brown sampler vials [9 mm, amber, screw top vial, 12 × 32 mm with cap and preslit polytetrafluoroethylene (PTFE)/silicone septa] were prepared. The aqueous solutions were filtered by an organic phase filter (13 × 0.22 μm) and then analyzed by UPLC to monitor the peak area changes of compounds **4a, 4b, 4f, 4i, 4k, 4l,** and **3** in water. The hydrolysis experiments would not stop until the residues of compounds **4a, 4b, 4f, 4i, 4k, 4l,** and **3** were <1%. All tests were conducted at room temperature (25 ± 3 °C). These data were used to calculate half-lives.

Compounds **4c, 4g, 4k,** and **4l** have better stability in water than others based on the hydrolysis test above. Then, these four compound as representatives were selected to investigate the photolysis stability, and **3**, IMI, and NTN32692 were selected as controls. Compounds were dissolved in Milli-Q water, and 40 mL of compounds **4c, 4g, 4k, 4l, 3,** IMI, and NTN32692 aqueous solution (5 × 10^{-5} mol L^{-1}) contained in quartz cylindrical tubes (50 mL and 20 cm in height) were prepared and irradiated with the 300 W high-pressure mercury lamp. Dark control experiments were carried out at the conditions similar to those described above, except that the tube was covered by aluminum foil. Aliquots of 1 mL irradiated solutions and control solutions were taken out at appropriate intervals, stored at 4 °C in the dark, and then analyzed by UPLC to monitor the peak area changes of compounds **4c, 4g, 4k, 4l, 3,** IMI, and NTN32692. The experiments would not stop until the residues of compounds were <1%.

Table 1. Insecticidal Activities of Compounds 4a–4m

compound	R	A. craccivora		A. gossypii	N. lugens	P. separata Walker
		mortality (%, 1 mg L^{-1})	LC$_{50}$ (μmol L^{-1})	LC$_{50}$ (μmol L^{-1})	LC$_{50}$ (μmol L^{-1})	mortality (%, 100 mg L^{-1})
4a	2-NO$_2$	67.0	1.67	1.20	0.38	30
4b	4-NO$_2$	88.0	1.34	0.88	0.39	57
4c	2,4-2F	100	0.33	0.69	0.42	54
4d	2-F	100	0.38	0.85	0.54	80
4e	2,3-2F	100	1.00	1.14	0.75	25
4f	4-Cl	97.0	0.51	1.28	0.71	67
4g	4-Br	88.4	0.80	0.42	0.29	82
4h	3-F-4-Cl	100	0.82	1.03	0.47	27
4i	2-Cl	97.6	0.63	0.72	0.34	40
4j	2-OCF$_3$-4-Br	90.0	0.59	0.98	0.22	77
4k	4-CH$_3$	100	0.78	1.63	0.12	13
4l	4-H	69.4	1.30	1.31	0.17	100
4m	4-OCH$_3$	92.6	0.91	1.13	0.28	30
IMI		nt	0.63	nt	1.09	nt
3		62.1	2.04	nt	nt	nt
NTN32692		nt	0.64	nt	nt	nt

RESULTS AND DISCUSSION

Synthesis. Two routes were used to synthesize the intermediates **7a–7m**. Compounds **7a–7j** were synthesized from furfural and aniline bearing electron-withdrawing groups (EWGs) via Meerwein reactions. Reactions proceeded smoothly. The products precipitated in the reaction mixtures were filtrated and washed with MeCN and CH$_2$Cl$_2$, affording the pure yellow solids.

Nevertheless, trace products and many byproducts were obtained during the synthesis of intermediates **7k–7m** bearing EDGs or no substitute via Meerwein reactions. In view of above results, the Suzuki coupling reaction was used in the synthesis of intermediates **7k–7m**. Because many byproducts would cause difficult workup, reactions must be carried out under an argon atmosphere at mild temperatures of 40–80 °C. The yield and purity of **7k–7m** were improved through this attempt.

During the synthesis of target compounds, compounds that the benzene ring was substituted at the *para* position had a high yield, such as the yield of compound **4f** of 96%. A lower yield of *ortho*-substituted products may be attributed to the increased steric hindrance.

Biological Activities. Compounds **4a–4m** exhibited significant insecticidal activities against cowpea aphid (*A. craccivora*), cotton aphid (*A. gossypii*), brown planthopper (*N. lugens*), and armyworm (*P. separata* Walker). The insecticidal activities were shown in Table 1. The bioactivities of all of the synthesized compounds against cowpea aphid were better than that of compound **3** and commercialized IMI. Among the synthesized compounds, compound **4c** showed excellent insecticidal activities against cowpea aphid, with the LC$_{50}$ value of 0.33 μmol L^{-1}. Compound **4g** exhibited the best insecticidal activity against cotton aphid, with the LC$_{50}$ value of 0.42 μmol L^{-1}, while compound **4k** showed the best insecticidal activities against brown planthopper, with the LC$_{50}$ value of 0.12 μmol L^{-1}. Different substituents did not lead to obvious change of activities against cowpea aphid. It was also found that those compounds bearing strong EWGs presented lower insecticidal activities, such as compounds **4a** and **4b**. Fluoro substituted at the *ortho* and *para* positions enhanced the activities of compounds **4c** and **4d**; however, compound **4e** with difluorine substituted at *ortho* and *meta* positions exhibited an obviously lower activity than compounds **4c** and **4d**.

Intriguingly, non-EDG-substituted compounds **4k**, **4l**, and **4m** maintained high insecticidal activities.

The test showed that all of the synthesized compounds did not exhibited high activities against armyworm (*P. separata* Walker) at the dosage of 100 mg L^{-1} except for compound **4l** based on the data of Table 1.

Hydrolysis and Photolysis. According to the data of bioactivities shown in Table 1, typical EWG/EDG-substituted compounds with high bioactivities, such as compounds **4a**, **4b**, **4c**, **4f**, **4g**, **4i**, **4k**, and **4l**, were selected to measure their half-life of hydrolysis. Their degradation kinetics constants were calculated by the residues of peak area versus time. The relative concentrations of compounds **4a**, **4b**, **4c**, **4f**, **4g**, **4i**, **4k**, **4l**, and **3** fitted well to the following pseudo-first-order kinetic equation:

$$\ln(C_t/C_0) = -kt \tag{1}$$

where C_0 is the initial concentration of compounds **4a**, **4b**, **4c**, **4f**, **4g**, **4i**, **4k**, **4l**, and **3**, C_t is the concentration of compounds **4a**, **4b**, **4c**, **4f**, **4g**, **4i**, **4k**, **4l**, and **3** at time t, and k is the observed reaction rate constant [obtained from the slope of the line in the plot of $\ln(C_t/C_0)$ versus time]. Figure 2 shows the
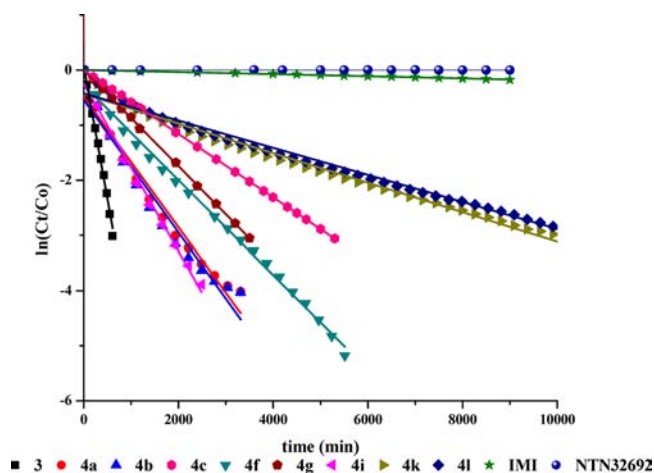

Figure 2. Degradation curve of compounds **4a**, **4b**, **4c**, **4f**, **4g**, **4i**, **4k**, **4l**, IMI, **3**, and NTN32692 in water.

best fit of eq 1 to the observed changes. The data of hydrolysis rate constants (k), half-lives ($t_{1/2}$), and linear response (R^2) for compounds are shown in Table 2. In this study, selected

Table 2. Hydrolysis Rate Constants (k), Half-Lives ($t_{1/2}$), and Linear Response (R^2) for Compounds 4a, 4b, 4f, 4i, 4k, 4l, and 3

compound	k	$t_{1/2}$ (h)	R^2
4a	0.0011836	9.8	0.966
4b	0.0011997	9.6	0.952
4c	0.0005763	20.0	0.999
4f	0.0008598	13.4	0.995
4g	0.0008720	13.2	0.999
4i	0.0015173	7.6	0.991
4k	0.0002679	43.0	0.987
4l	0.0002459	47.0	0.987
3	0.00482	2.4	0.994

compounds showed significantly improved stability in water. The half-life of compounds **4k** and **4l** was longer than other compounds, whose half-life was 43.0 and 47.0 h, respectively, while that of compound **3** was only 2.4 h. The stability of synthesized compounds increased about 18-fold. The stability of eight selected compounds in water improved significantly, which means that the molecular design is reasonable and valuable.

The photodegradation of our synthesized compounds was also a concern. Compounds **4c**, **4g**, **4k**, and **4l** were selected because of their better stability in water. The photolysis half-life of compounds **4c**, **4g**, **4k**, **4l**, **3**, IMI, and NTN32692 were measured. The photolysis data for compounds were shown in Table 3, and the degradation curves were shown in Figure 3.

Table 3. Photolysis Rate Constants (k), Half-Lives ($t_{1/2}$), and Linear Response (R^2) for Compounds 4c, 4g, 4k, and 4l under the Irradiation of a 300 W High-Pressure Mercury Lamp

light source	sample	λ_{max} (nm)	k	$t_{1/2}$ (min)	R^2
300 W high-pressure mercury lamp	4c	427	0.0303	22	0.907
	4g	438	0.0163	42	0.930
	4k	420	0.0091	76	0.941
	4l	450	0.0205	34	0.911
	3	373	0.904	0.77	0.988
	IMI	270	0.0669	10	0.997
	NTN32692	322	0.2807	2.47	0.992

The half-life of compound **4k** was the longest among seven compounds, which was 76 min. The photostability of compounds was enhanced significantly in comparison to that of compound **3**, which had a half-life of only 0.77 min. In comparison to NTN32692, the synthesized compounds after irradiation of the mercury lamp were also more stable than NTN32692, with the half-life of 2.47 min.

In addition, we observed that the main product of both hydrolysis and photolysis of synthesized compounds was the important intermediate NTN32692. It suggested that these compounds might be pro-insecticide, and there are more works being investigated to further verify it.

A series of novel conjugated neonicotinoids were designed and synthesized on the basis of enhanced conjugation. The introduction of the substituted phenyl group was beneficial to
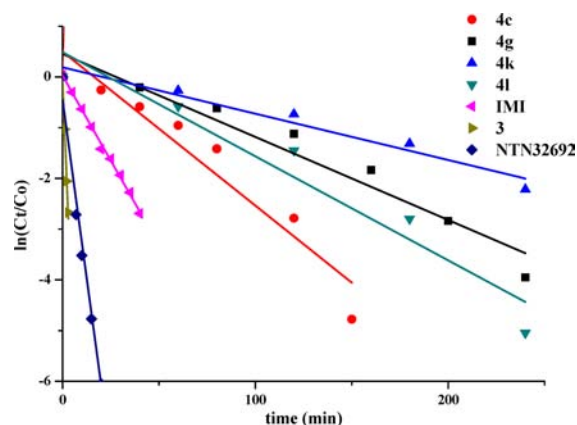

Figure 3. Photolysis rate constants (k), half-lives ($t_{1/2}$), and linear responses (R^2) for compounds **4c**, **4g**, **4k**, **4l**, IMI, **3**, and NTN32692 under the irradiation of a 300 W high-pressure mercury lamp.

increase the conjugation effect. The bioassays showed that all 13 compounds exhibited excellent insecticidal activities against cowpea aphid (*A. craccivora*), cotton aphid (*A. gossypii*), and brown planthopper (*N. lugens*). Hydrolysis and photolysis of synthesized compounds were also investigated. The results exhibited that the stabilities of synthesized compounds in water or after irradiation of mercury lamp improved obviously compared to leading compound **3**. Enhanced bioactivities and stability suggested that the strategy of molecular design was significative for further research.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
^{1}H and ^{13}C NMR, infrared (IR), and high-resolution mass spectrometry (HRMS) data of compounds **4a−4m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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