Synthesis and Insecticidal Activities of 1,3,5-Trisubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines

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A new series of 1,3,5-trisubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines (**3a**—**3j**) were designed and synthesized as novel neonicotinoid analogues, and their structures were characterized by ^{1}H NMR, IR, elemental analysis and MS. The preliminary bioassay tests showed that most of the target compounds had good insecticidal activities against *Nilaparvata lugens* as well as *Aphis medicaginis* at 500 mg/L, while compound **3i** had 100% mortality against *Nilaparvata lugens* at 20 mg/L.

Keywords neonicotinoid analogues, hexahydrotriazine, insecticidal activities

Introduction

Neonicotinoid insecticides (NNs), which act agonistically on the insect nicotinic acetylcholine receptors (nAChRs), have recently received considerable interests from both agricultural chemistry and medicinal fields, due to their broad spectrum of biological activities and high selectivity for crop protection and public health.[1,2] The first successful member of this family was imidacloprid (1a) in 1991.[3] Six other neonicotinoids insecticides (NNs): acetamiprid,[4] nitenpyram,[5] thiamethoxam,[6,7] thiacloprid,[8] clothianidin[9] and dinotefuran[10] were successively commercialized, which are all nAChR agonists that act on the ligandgated ion channels responsible for rapid neurotransmission of insects.[11]

However, a recent potential problem of the resistance facing NNs is more and more serious, due to the frequent field applications of NNs during the past decades.[12-17] Especially, recently collected strains of the whitefly exhibited much stronger resistance to imidacloprid and clothianidin.[18,19] Hence, development of noval neonicotinoids with good insecticidal activities and less resistance is highly desirable.

Structure modification of the existing NNs is one of the most effective resistance-management tactics. Until recently, most of the researches about structure optimization of NNs are based on cyclic neonicotinoid insecticides, such as imidacloprid.[20,21] Previous studies show that compounds containing the structure segment of hexahydrotriazine have high insecticidal activities.[22] Hence we developed a new structure developing strategy, using acyclic clothianidin as the lead compound (Figure 1), and a series of novel 1,3,5-trisubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines were designed by introducing a new substituted amide into clothianidin and forming a hexahydrotriazine ring. The structures of all new compounds have been confirmed by ^{1}H NMR, IR and elemental analysis. And most of these compounds exhibited good insecticidal activities against *Nilaparvata lugens* and *Aphis medicaginis*, and some of them had ≥85% mortality against *Nilaparvata lugens* at 20 mg/L.

Experimental

Materials and physical measurements

All chemical reagents and solvents were purchased

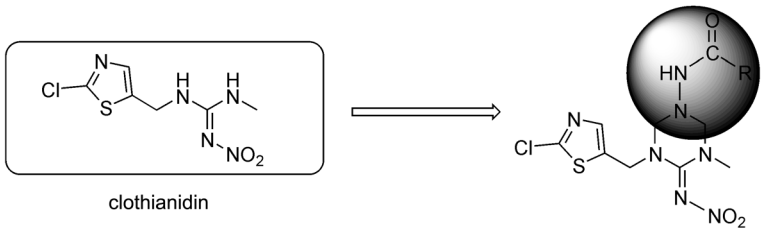

Figure 1 Chemical structures of the target compounds.

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and used as received without further purification. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Bruker AVANCE 400 MHz with TMS as an internal standard. Elemental analyses were performed with a Perkin-Elmer 2400 instrument and melting points were determined by an RK1 microscopic melting apparatus. IR spectra were obtained from KBr discs in the range 4000—400 cm^{-1} on a Nicolet 5DXFT-IR spectrophotometer. MS spectra were recorded on a Trace DSQ mass spectrograph.

Synthesis of 1-(2-chloro-5-thiazolylmethyl)-3-methyl-5-amido-1,3,5-hexahydrotriazine-2-*N*-nitroimines 3a—3j

Preparation of the target compound (**3a**): Benzoyl hydrazine (2.72 g, 0.02 mol), clothianidin (4.98 g, 0.02 mol) and paraformaldehyde (1.80 g, 0.06 mol) were dissolved under heating in anhydrous ethanol (50 mL). The reaction mixture was heated at reflux for 8 h and then concentrated under vacuum. The residue was purified by chromatography on silica gel using ethyl acetate∶ethanol (2∶1, *V*∶*V*) as eluent to yield **3a** as a white solid.

The syntheses of **3b**—**3j** were carried out by the similar method. The analytical data for the compounds **3a**—**3j** were summarized as follows:

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-benzamido-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3a) Yield 56%, m.p. 232—233 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.81 (s, 1H, NH), 7.45—7.61 (m, 5H, Ph-H), 7.42 (s, 1H, thiazole-H), 4.59 (s, 2H, thiazole-CH_2), 4.47 (d, J=22 Hz, 4H, triazine-H), 2.95 (s, 3H, NCH_3); IR (KBr) ν: 3182 (NH), 1645 (C=N), 1109 (CN) cm^{-1}; MS (ESI) *m*/*z*: 408 ([M－H]$^-$). Anal. calcd for $C_{15}H_{16}ClN_7O_3S$: C 43.96, H 3.93, N 23.92; found C 44.13, H 3.93, N 23.92.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-phenylacetamido-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3b) Yield 39%, white solid, m.p. 232—233 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.06 (s, 1H, NH), 7.34—7.35 (m, 6H, Ph-H, thiazole-H), 4.65 (s, 2H, thiazole-CH_2), 4.44 (d, J=12.4 Hz, 4H, triazine-H), 3.47 (s, 2H, Ph-CH_2), 3.03 (s, 3H, NCH_3); IR (KBr) ν: 3206, 1671, 1135 cm^{-1}; MS (ESI) *m*/*z*: 422 ([M－H]$^-$). Anal. calcd for $C_{16}H_{18}ClN_7O_3S$: C 39.05, H 3.53, N 24.52; found C 41.11, H 3.45, N 23.91.

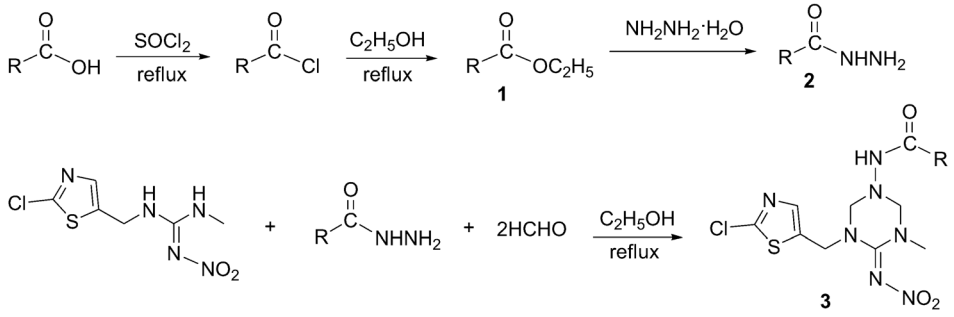
1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-(-3-methylbenzamido)-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3c) Yield 55%, white solid, m.p. 166—167 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.23 (s, 1H, N-H), 7.54 (s, 1H, thiazole-H), 7.47 (s, 1H, Ph-H), 7.33—7.44 (m, 3H, Ph-H), 4.85 (s, 2H, thiazole-CH_2), 4.66 (s, 4H, triazine-H), 3.19 (s, 3H, NCH_3), 2.43 (s, 3H, Ph-CH_3); IR (KBr) ν: 3206, 1671, 1135 cm^{-1}; MS (ESI) *m*/*z*: 422 ([M－H]$^-$). Anal. calcd for $C_{16}H_{18}ClN_7O_3S$: C 43.34, H 4.28, N 23.13; found C 44.13, H 3.71, N 24.09.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-(-4-*tert*-butyl benzamido)-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3d) Yield 52%, white solid, m.p. 162—163 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.22 (s, 1H, NH), 7.48—7.63 (m, 5H, thiazole-H, Ph-H), 4.86 (s, 2H, thiazole-CH_2), 4.66 (d, J=6 Hz, 4H, triazine-H), 3.15 (s, 3H, NCH_3), 1.34 (s, 9H, CCH_3); IR (KBr) ν: 3128, 1645, 1093 cm^{-1}; MS (ESI) *m*/*z*: 464 ([M－H]$^-$). Anal. calcd for $C_{19}H_{24}ClN_7O_3S$: C 48.98, H 5.19, N 21.04; found C 46.76, H 6.11, N 22.15.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-(-3-*N*,*N*-dimethylaminobenzamido)-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3e) Yield 41.3%, white solid, m.p. 141—142 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.322 (s, 1H, NH), 7.544 (s, 1H, thiazole-H), 7.313 (d, J=8 Hz, 1H, Ph-H), 7.107 (s, 1H, Ph-H), 6.920—6.936 (m, 2H, Ph-H), 4.826 (s, 2H, thiazole-CH_2), 4.654 (s, 4H, triazine-H), 3.167 (s, 3H, triazine-CH_3), 3.025 (s, 6H); MS (ESI) *m*/*z*: 452 ([M－H]$^-$); IR (KBr) ν: 3122, 1637, 1098 cm^{-1}. Anal. calcd for $C_{17}H_{21}ClN_8O_3S$: C 45.08, H 4.67, N 24.74; found C 46.38, H 4.19, N 24.31.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-(-4-chlorobenzamido)-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3f) Yield 40%, white solid, m.p. 145—146 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.41 (s, 1H, N-H), 7.43—7.67 (m, 5H, thiazole-H, Ph-H), 4.84 (s, 2H, thiazole-CH_2), 4.67 (s, 4H, triazine-H), 3.19 (s, 3H, N-CH_3); IR (KBr) ν: 3127, 1619, 1114 cm^{-1}; MS (ESI) *m*/*z*: 443 ([M－H]$^-$). Anal. calcd for $C_{15}H_{15}Cl_2N_7O_3S$: C 40.55, H 3.40, N 22.07; found C 41.76, H 3.40, N 22.07.

Scheme 1



3a: R = C_6H_5, **3b**: R = $C_6H_5CH_2$, **3c**: R = 3-MeC_6H_4, **3d**: R = 4-*t*-BuC_6H_4, **3e**: R = 3-$N(CH_3)_2C_6H_4$, **3f**: R = 4-ClC_6H_4, **3g**: R = 2-thienyl, **3h**: R = 2-furfuryl, **3i**: R = CH_3, **3j**: R = C_8H_{17}

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-(2-thenamido)-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3g) Yield 39%, pale yellowish solid, m.p. 84—85 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.19 (s, 1H, NH), 7.46 (s, 1H, thiazole-H), 6.90—6.95 (m, 3H, thiophene-H), 4.70 (s, 2H, thiazole-CH_2), 4.48 (d, J=4 Hz, 4H, triazine-H), 2.99 (s, 3H, NCH_3); IR (KBr) v: 3210, 1619, 1122 cm^{-1}; MS (ESI) m/z: 414 ($[M-H]^-$). Anal. calcd for $C_{13}H_{14}ClN_7O_3S_2$: C 37.57, H 3.39, N 23.58; found C 40.03, H 3.48, N 22,19.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-(2-furancarboxamido)-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3h) Yield 42%, white solid, m.p. 97—98 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.99 (s, 1H, NH), 7.52 (s, 1H, thiazole-H), 7.34—7.35 (m, 1H, furan-H), 6.41—6.42 (m, 2H, furan-H), 4.69 (s, 2H, thiazole-CH_2), 4.47 (d, J=4 Hz, 4H, triazine-H), 3.01 (s, 3H, NCH_3); IR (KBr) v: 3158, 1624, 1108 cm^{-1}; MS (ESI) m/z: 398 ($[M-H]^-$). Anal. calcd for $C_{13}H_{14}ClN_7O_4S$: C 39.05, H 3.53, N 24.52; found C 41.11, H 3.45, N 23.91.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-acetamido-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3i) Yield 39%, white solid, m.p. 117—118 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.72 (s, 1H, NH), 7.65 (s, 1H, thiazole-H), 4.72 (s, 2H, thiazole-CH_2), 4.53 (d, J= 8.4 Hz, 4H, triazine-H), 2.89 (s, 3H, NCH_3), 2.50 (s, 3H, CCH_3); IR (KBr) v: 3134, 1630, 1100 cm^{-1}; MS (ESI) m/z: 347 ($[M-H]^-$). Anal. calcd for $C_{10}H_{14}ClN_7O_3S$: C 34.54, H 3.53, N 28.19; found C 35.63, H 3.77, N 27.45.

1-(2-Chloro-5-thiazolylmethyl)-3-methyl-5-pelargonamido-1,3,5-hexahydrotriazine-2-*N*-nitroimines (3j) Yield 41%, white solid, m.p. 81—82 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.05 (s, 1H, NH), 7.56 (s, 1H, thiazole-H), 4.85 (s, 2H, thiazole-CH_2), 4.54—4.55 (d, J=4.4 Hz, 4H, triazine-H), 3.13 (s, 3H, NCH_3), 2.07 (t, J=4.4 Hz, 2H, $COCH_2$), 1.57 (s, 2H, $C_6H_{13}CH_2$), 1.28—1.32 (s, 2H); IR (KBr) v: 3129, 1615, 1112 cm^{-1}; MS (ESI) m/z: 445 ($[M-H]^-$). Anal. calcd for $C_{17}H_{28}ClN_7O_3S$: C 45.78, H 6.33, N 21.99; found C 43.93, H 6.75, N 22.68.

Biology assay

The bioassay was measured according to the standard test[23] with a slight modification. Insecticidal activities of the compounds (**3a**—**3j**) were tested against *Nilaparvata lugens* as well as *Aphis medicaginis.* All compounds were dissolved in DMF and serially diluted with water containing Triton X-80 (0.1 mg/L) to get the required test concentrations. All experiments were carried out in three replicates according to statistical requirements. The insects were reared at 25(±1) ℃, and groups of 10 were transferred to glass Petri dishes and sprayed with the aforementioned solutions using a Potter sprayer. Assessments were made after 72 h by the number and size of live insects relative to that in the negative control, and evaluations are based on a percentage scale of 0—100, in which 100 total kill and 0 no activity. The mortality rates were subjected to probit analysis.[24]

The reference compound was clothianidin, and water containing Triton X-80 (0.1 mg/L) was used as a negative control.

Results and discussion

Synthesis

A three-step synthetic strategy was adopted for the synthesis of 1,3,5-trisubstituted-1,3,5-hexahydrotriazine-2-*N*-nitroimines (**3a**—**3j**). The general schematic representation describing the routes of syntheses is furnished in Scheme 1. The intermediates of hydrazides (**2a**—**2l**) were synthesized with carboxylic acids as raw materials via esterification and nucleophilic substitution. The target products (**3a**—**3j**) were obtained, using intermediate **2**, clothianidin and paraformaldehyde by Mannich reaction. In addition, the products were purified by chromatography on silica gel using ethyl acetate∶ethanol (2∶1, V∶V) as eluent.

Biological activity

The compounds **3a**—**3j** were tested for insecticidal activities against *Nilaparvata lugens* as well as *Aphis medicagini*s at the different concentration. The procedure of operation is presented in the experimental part. As indicated in Table 1, most of our designed compounds exhibited good insecticidal activities against *Nilaparvata lugens* as well as *Aphis medicagini*s and had ⩾90% mortality at 500 mg/L. Among all the analogues, **3i** afforded the best *in vitro* activity against *Nilaparvata lugens*, and had 100% mortality at 20 mg/L, which is comparable to that of clothianidin. Other compounds' potential varied drastically, depending upon the size and types of the R substitutions of the title compounds. When the R substitutions are the substituted phenyl substitutions, the substituent groups holding big size group have lower activity than small size group; meanwhile, compounds with electron donating group have better activity than those with electron withdrawing group: **3a**>**3c**>**3e**>**3f**.

Conclusions

In summary, a series of novel neonicotinoid analogues (**3a**—**3j**), which were designed based on the acyclic NNs (clothianidin), were synthesized. These compounds were characterized by IR, ^{1}H NMR, elementary analysis and MS. Preliminary bioassay show that all the target compounds had ⩾90% mortality against *Nilaparvata lugens* and *Aphis medicagini*s at 500 mg/L, especially the two compounds, **3g** and **3i** afforded the best *in vitro* activity, and had ⩾85% mortality against *Nilaparvata lugens* at 20 mg/L.

Table 1 Insecticidal activities of the target compounds (**3a**—**3j**) against *Nilaparvata lugens* as well as *Aphis medicaginis*

Compd. **3**	R	mortality (%) at different concentrations (mg/L)					
		Nilaparvata lugens			*Aphis medicaginis*		
		500	100	20	500	100	20
3a	C_6H_5	100	100	30	90	30	nt
3b	$C_6H_5CH_2$	100	75	10	100	75	10
3c	3-MeC_6H_4	100	80	10	100	50	10
3d	4-*t*-BuC_6H_4	90	40	nt	90	35	nt
3e	*N*,*N*-dimethylamino phenyl	100	75	10	100	90	10
3f	4-ClC_6H_4	100	65	20	100	10	nt
3g	2-thienyl	100	100	85	100	80	40
3h	2-furfuryl	100	80	10	90	20	nt
3i	CH_3	100	100	100	100	30	nt
3j	C_8H_{17}	90	55	10	90	50	10
	clothianidin	100	100	100	100	100	100

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