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Note

Effects of Halogen Introduction at the C5 Position of the Imidacloprid Pyridine Ring upon Insecticidal Activity

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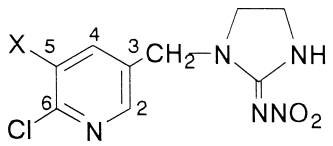
Following a recent report of unexpectedly high affinity of 5-azidoimidacloprid to insect nicotinic acetylcholine receptor, derivatives with four halogen atoms and cyano and nitro were prepared, and the insecticidal effect was evaluated in American cockroaches by injection alone and with synergists, piperonyl butoxide and propargyl propyl benzenephosphonate. The log (1/MLD) value, the minimal lethal dose in mol, was 8.96 for imidacloprid, and 8.82 for the fluoro derivative. The other derivatives were less active. Synergists enhanced the activity of all compounds. The log (1/MLD) value for 5-azidoimidacloprid, 7.37 without or 8.18 with synergists, was not striking in this experiment.

Keywords: neonicotinoid insecticide, imidacloprid, American cockroach, insecticidal activity, synthesis of substituted pyridine.

INTRODUCTION

Imidacloprid (**1a**, Fig. 1), the first neonicotinoid insecticide acting on a nicotinic acetylcholine receptor (nAChR), is widely used to control not only various plant pests, but also fleas on cats and dogs, and termites.[1–3] Following imidacloprid, six products were developed by replacing the pyridine ring with a thiazol ring or a saturated heterocyclic ring, changing the nitroimino group to an isoelectronic nitromethylene or cyanoimine group, or reconstructing the imidazolidine ring with bioisosteric cyclic or acyclic moieties.[4] In the course of trials of various structural modifications to obtain new active compounds, less attention seems to have been paid to variation of the substituents on the pyridine ring. In fact, structure-activity relationship studies have found that other substituents, regardless of their nature and position, did not improve the activity achieved with a chlorine atom at the C6 position on the pyridine ring.[5] Recently, however, Casida *et al*. found that the introduction of an azido group at the C5 position maintains or even improves the activity toward the insect nAChRs.[6–9]



1a: imidacloprid (X=H)
1b: 5-azidoimidacloprid (X=N_3)

Fig. 1. 5-Substituted imidacloprid derivatives.

The new dimension opened by the introduction of a pseudohalogen group at this position drove us to prepare derivatives with four halogen atoms and a cyano group, another pseudohalogen, at the particular position. The insecticidal activity was tested on American cockroaches after injection and compared with that of imidacloprid (**1a**) and of azidoimidacloprid (**1b**; Fig. 1).

MATERIALS AND METHODS

1. *Preparation of Compounds*

All melting points (mp) are uncorrected. NMR spectra were obtained using a Varian Gemini 2000 C/H (400 MHz). The chemical shifts were recorded in δ (ppm) and the coupling constant J in Hz. Mass spectra were recorded with a JEOL JMS-700. 5-Azidoimidacloprid prepared according to a published description[6] was stored at −20°C sheltered from light until immediately before use.

5-Bromo-6-chloro-3-pyridinemethanol (**4** in Fig. 2). 5-Bromo-6-chloronicotinic acid (**2**)[10] (3.71 g, 16 mmol) was converted to 5-bromo-6-chloronicotinoyl chloride (**3**) by mixing with thionyl chloride (7 ml) at 80°C for 3 hr and worked-up. The yield was 3.83 g (94%). Mp: 47°C. ^{1}H NMR δ ($CDCl_3$): 8.56 (1H, d, J=2.2 Hz), 9.01 (1H, d, J=2.2 Hz); ^{13}C NMR δ ($CDCl_3$): 120.9, 129.1, 143.6, 149.7, 157.3, 164.9. Compound **3** (3.12 g, 12 mmol) in 3 ml of THF (3 ml) was added slowly to a solution of $NaBH_4$ (2.05 g, 54 mmol) in 44 ml of 0.01 M aq. NaOH with cooling on ice. The mixture was stirred at this temperature for 40 min and at room temperature for a further 40 min. A mixture of 8 ml of ethyl acetate and 13 ml of 1 M NaH_2PO_4 was added and the stirring was continued for 1 hr. The ethyl acetate phase was separated and the aqueous phase was extracted with ethyl acetate (10 ml×3). All the organic phase was combined and dried. Chromatography on SiO_2 with isopropyl ether (IPE) as eluate afforded 1.76 g (65% yield) of product. Mp: 103–105°C. H NMR δ ($CDCl_3$): 4.74 (2H, s), 8.01 (1H, d, J=2.2 Hz), 8.31 (1H, d, J=2.2 Hz); ^{13}C NMR δ ($CDCl_3$): 60.5, 120.2, 140.7, 142.2, 147.9, 148.7. MS m/z (%): 225 (20), 224 (17), 223 (M^+, 78), 222 (48), 221 (64), 220 (37),

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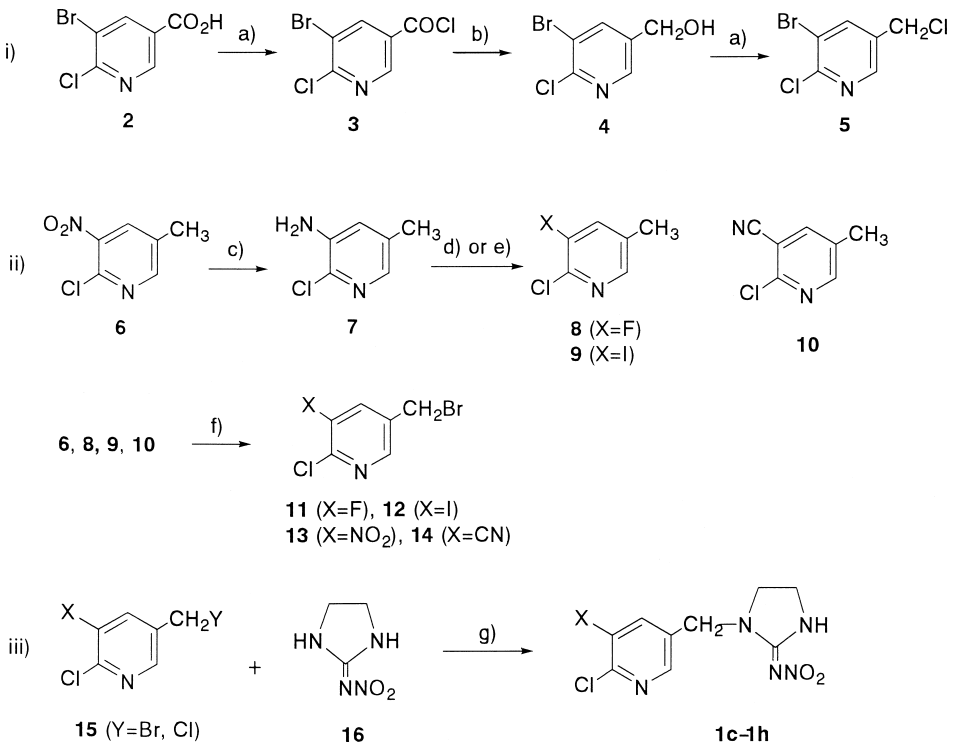

Fig. 2. Scheme for synthesizing 5-substituted imidacloprid derivatives.

196 (25), 195 (23), 194 (100), 193 (92), 192 (82), 191 (77), 158 (56), 157 (48), 156 (52), 155 (34), 142 (33), 141 (27).

5-Bromo-6-chloropyridin-3-ylmethyl chloride (**5** in Fig. 2). Alcohol (**4**) (1.79 g, 8.06 mmol) in 20 ml of chloroform was treated with thionyl chloride (7 ml) and the solution was stirred at 60°C for 1 hr. The mixture was poured into ice water and extracted with chloroform; the organic phase was washed successively with aq. $NaHCO_3$ and brine, and then dried. Column chromatography on SiO_2 with hexane/IPE 10 : 1 as eluate afforded 1.49 g of product (77%). Mp: 43–44°C. ^{1}H NMR δ ($CDCl_3$): 4.55 (2H, s), 8.00 (1H, d, J=2.2 Hz), 8.35 (1H, d, J=2.2 Hz); ^{13}C NMR δ ($CDCl_3$): 41.2, 120.3, 133.6, 142.2, 147.3, 150.7. MS *m*/*z* (%): 243 (18), 242 (16), 241 (M^+, 38), 240 (34), 239 (24), 208 (25), 207 (19), 206 (100), 205 (59), 204 (77), 127 (10), 125 (28), 124 (14).

3-Amino-2-chloro-5-methylpyridine (**7** in Fig. 2). The published procedure[11] was modified. A suspension of **6**[11] (10.0 g, 58 mmol) and activated iron powder (14.0 g, 251 mmol) in acetic acid (100 ml) was stirred at 90°C for 15 min. The hot reaction mixture was filtered under weak suction and acetic acid was evaporated from the filtrate. The residual liquid, after being weakly alkalized with a 40% NaOH solution, was extracted with IPE (3×20 ml). The solid on the filter paper was rinsed with IPE (30 ml). The combined IPE extract was dried and the solvent was evaporated. Recrystallization from heptane gave 3.36 g (41%) of product of mp 90–92°C (88–89°C).[11]

2-Chloro-3-fluoro-5-methylpyridine (**8** in Fig. 2). The published procedure[11] was modified. To a solution of **7** (1.0 g, 7.0 mmol) in 10 ml of absolute ethanol was added dropwise 40% tetrafluoroboric acid (3.2 ml) at −5°C and the solution was stirred for 30 min at this temperature. Isoamyl nitrite (0.8 g, 6.8 mmol) was added dropwise while keeping the temperature in the vessel below −5°C. After 2 h of stirring, the precipitates were filtered quickly and rinsed with dry ether, and vacuum dried. The solid was suspended in 100 ml dry heptane and the suspension was stirred at the refluxing temperature. After the evolution of nitrogen had ceased, the mixture was heated for further 30 min. The heptane was evaporated and the brown residue was subjected to column chromatography on SiO_2 with *n*-hexane/IPE 10 : 1. The product was separated as white solid of mp 29–30°C (bp 90–92°C/25 mmHg[11]). Yield: 536 mg (53%).

2-Chloro-3-iodo-5-methylpyridine (**9** in Fig. 2). Compound **7** (2.0 g, 14.2 mmol) was dissolved in 12 ml of 6 M HCl and the solution was cooled under 5°C. A solution of sodium nitrite (2.0 g) in 10 ml of water was added dropwise, keeping the temperature under 10°C. Setting aside the cooling bath, a solution of potassium iodide (4.0 g) in 10 ml of water was added dropwise and the mixture was stirred at room temperature for 3 hr, and then warmed gradually to 95°C. After the evolution of nitrogen had ceased, the vessel was cooled to room temperature. The resulting mixture was alkalized with 10% aq. NaOH and then extracted with chloroform (20 ml×3). The chloroform solution was washed successively with a satd. sodium thiosulfate solution and

water, and dried over anhyd. magnesium sulfate. After evaporation of the chloroform, the crude product was crystallized from ether (2.36 g, 66% yield). Mp: 61–63°C. For analysis a small crop was sublimed. ^{1}H NMR δ ($CDCl_3$): 2.34 (3H, s), 7.99 (1H, d, J=1.5 Hz), 8.18 (1H, d, J=1.5 Hz); ^{13}C NMR δ ($CDCl_3$): 17.1, 94.3, 133.5, 149.1, 149.3, 151.5. MS *m/z* (%): 255 (33), 253 (M^+, 100), 252 (79), 127 (24), 126 (34), 125 (25), 99 (30), 90 (36). HRMS (EI) M/z (M^+): Calcd. for C_6H_5ClIN: 252.9155, Found: 252.9167.

6-Chloro-5-fluoropyridin-3-ylmethyl bromide (**11** in Fig. 2). A suspension of **8** (134 mg, 0.92 mmol) and *N*-bromosuccinimide (NBS, 246 mg, 1.38 mmol) in CCl_4 (10 ml) was stirred with a catalytic amount of benzoyl peroxide at the reflux temperature for 10 hr. After cooling, the precipitates were filtered, and the filtrate was evaporated. Column chromatography of the residual liquid on SiO_2 with *n*-hexane/IPE 10 : 1 gave 75 mg (36% yield) of product as pale yellow liquid. ^{1}H NMR δ ($CDCl_3$): 4.45 (2H, s), 7.55 (1H, d, J=1.4 Hz), 8.23 (1H, d, J=1.4 Hz); ^{13}C NMR δ ($CDCl_3$): 27.4, 125.0 (d, J_{C-F}=19.8 Hz), 134.8, 144.0 (d, J_{C-F}=5.0 Hz), 151.5 (d, J_{C-F}=263.1 Hz), 155.8. MS *m/z* (%): 225 (M^+, 7), 223 (6), 146 (32), 144 (100), 110 (12), 108 (24).

Compounds **12** and **13** were similarly prepared.

6-Chloro-5-iodopyridin-3-ylmethyl bromide (**12**). Mp: 110–112°C. ^{1}H NMR δ ($CDCl_3$): 4.38 (2H, s), 8.19 (1H, d, J=2.2 Hz), 8.36 (1H, d, J=2.2 Hz); ^{13}C NMR ($CDCl_3$): δ 26.9, 94.7, 133.7, 148.6, 149.2, 154.3. MS *m/z* (%): 334 (8), 333 (M^+, 12), 332 (12), 331 (10), 330 (8), 254 (36), 253 (31), 252 (100), 251 (75), 127 (125), 126 (12), 125 (8).

6-Chloro-5-nitropyridin-3-ylmethyl bromide (**13**). Mp: 110-112°C. ^{1}H NMR δ ($CDCl_3$): 4.51 (2H, s), 8.28 (1H, d, J=2.2 Hz), 8.63 (1H, d, J=2.2 Hz); ^{13}C NMR δ ($CDCl_3$): 26.3, 116.1, 134.2, 134.6, 143.0, 152.0. MS *m/z* (%): 252 (M^+, 5), 173 (100), 171 (36), 127 (14), 125 (42), 98 (10), 90 (24).

Compound **14** was similarly prepared from 2-chloro-5-methylnicotinonitrile[12] contained *ca*. 30% of the starting material. It was used in the next step without further purification.

1-(5-Bromo-6-chloro-3-pyridylmethyl)-2-nitroiminoimidazolidine (**1e** in Fig. 2). A solution of 2-nitroimino-4-imidazoline[13] (**16**; 214 mg, 1.65 mmol) in DMF (15 ml) was treated with sodium hydride (60% oil dispersion, 72 mg, 1.80 mmol) under 5°C. The mixture was stirred at room temperature until no hydrogen was evolved and then cooled again to 0°C. A solution of **5** (400 mg, 1.66 mmol) in DMF (5 ml) was added dropwise. The cooling bath was set aside and the solution was stirred at room temperature for 2 hr. The reaction was quenched with one drop of acetic acid and the DMF was evaporated in vacuum. Chromatography on SiO_2 with hexane/ethyl acetate 1 : 10 gave 245 mg (44% yield) of product, which was purified by recrystallization from methanol. Mp: 166–167°C. ^{1}H NMR δ (DMSO-d_6): 3.53 (2H, m), 3.65 (2H, m), 4.48 (2H, s), 8.20 (1H, d, J=1.3 Hz), 8.39 (1H, d, J=1.3 Hz), 9.00 (1H, bs); ^{13}C NMR δ (DMSO-d_6): 42.9, 45.4, 46.6, 120.6, 134.9, 143.5, 149.1, 149.7, 161.6. MS *m/z* (%): 336 (M^++1, 2), 291 (20), 289 (70), 287 (56), 208 (31), 207 (36), 56 (100). *Anal*. Found: C, 32.22; H, 2.90; N, 20.84. Calcd. for $C_9H_9BrClN_5O_2$: C, 32.31; H, 2.71; N, 20.93.

The following compounds were similarly prepared.

1-(6-Chloro-5-fluoro-3-pyridylmethyl)-2-nitroiminoimidazolidine (**1c**). Mp: 154–156°C. ^{1}H–NMR δ (acetone-d_6): 3.56 (2H, dd, J=9.2/8.8 Hz), 3.84 (2H, dd, J=9.2/8.8 Hz), 4.57 (2H, s), 7.55 (1H, d, J=1.5 Hz), 7.86 (1H, d, J=1.5 Hz), 8.22 (1H, bs); ^{13}C NMR δ (acetone-d_6): 41.5, 45.0, 45.3, 124.5 (d, J_{C-F}=19.0 Hz), 128.3, 132.3, 144.0 (d, J_{C-F}=5.3 Hz), 154.8 (d, J_{C-F}=263.9 Hz), 161.3. MS *m/z* (%): 273 (M^+, 1), 227 (74), 191 (26), 143 (14), 56 (100). *Anal*. Found: C, 39.61; H, 3.40; N, 25.41. Calcd. for $C_9H_9ClFN_5O_2$: C, 39.50; H, 3.31; N, 25.59.

1-(5,6-Dichloro-3-pyridylmethyl)-2-nitroiminoimidazolidine (**1d**). This compound was prepared from 5,6-dichloro-3-chloromethylpyridine.[14] Mp: 163–165°C. ^{1}H NMR δ (DMSO-d_6): 3.53 (2H, m), 3.64 (2H, m), 4.49 (2H, s), 8.08 (1H, s), 8.36 (1H, s), 9.01 (1H, bs); ^{13}C NMR δ (DMSO-d_6): 42.9, 45.5, 46.6, 130.4, 135.0, 140.2, 147.9, 148.6, 161.6. MS *m/z* (%): 289 (M^+, 1), 245 (68), 244 (53), 243 (100), 208 (27), 207 (55), 160 (27), 124 (18). *Anal*. Found: C, 37.41; H, 3.10; N, 24.29. Calcd. for $C_9H_9Cl_2N_5O_2$: C, 37.26; H, 3.13; N, 24.14.

1-(6-Chloro-5-iodo-3-pyridylmethyl)-2-nitroiminoimidazolidine (**1f**). Mp: 208–211°C. ^{1}H NMR δ (DMSO-d_6): 3.51 (2H, m), 3.65 (2H, m), 4.45 (2H, s), 8.32 (1H, d, J=1.3 Hz), 8.37 (1H, d, J=1.3 Hz), 9.00 (1H, bs); ^{13}C NMR δ (DMSO-d_6): 40.8, 42.4, 44.7, 133.6, 134.3, 149.1, 149.3, 153.2, 161.0. MS *m/z* (%): 381 (M^+, 5), 337 (35), 336 (27), 335 (100), 334 (75), 299 (10), 207 (9), 56 (18). *Anal*. Found: C, 28.42; H, 2.50; N, 18.19. Calcd. for $C_9H_9ClIN_5O_2$: C, 28.33; H, 2.38; N, 18.35.

1-(6-Chloro-5-cyano-3-pyridylmethyl)-2-nitroiminoimidazolidine (**1g**). Mp: 215–217°C. ^{1}H NMR δ (DMSO-d_6): 3.56 (2H, m), 3.66 (2H, m), 4.53 (2H, s), 8.44 (1H, d, J=2.6 Hz), 8.66 (1H, d, J=2.6 Hz), 9.02 (1H, bs); ^{13}C NMR δ (DMSO-d_6): 42.9, 45.4, 46.5, 110.8, 116.2, 133.7, 144.3, 151.3, 154.0, 161.6. MS *m/z* (%): 280 (M^+, 4), 236 (33), 234 (100), 199 (38), 198 (45), 153 (13), 151 (43), 150 (22), 116 (23). *Anal*. Found: C, 42.68; H, 3.29; N, 29.60. Calcd. for $C_{10}H_9ClN_6O_2$: C, 42.79; H, 3.23; N, 29.95.

1-(6-Chloro-5-nitro-3-pyridylmethyl)-2-nitroiminoimidazolidine (**1h**). Mp: 185–186°C. ^{1}H NMR δ (DMSO-d_6): 3.50–3.70 (4H, m), 4.60 (2H, s), 8.52 (1H, d, J=1.8 Hz), 8.69 (1H, d, J=1.8 Hz), 9.00 (1H, bs); ^{13}C NMR δ (DMSO-d_6): 40.1, 44.2, 45.47, 133.8, 134.3, 140.3, 144.3, 152.1, 160.4. MS *m/z* (%): 300 (M^+, 3), 263 (6), 262 (7), 183 (14), 87 (33), 74 (48), 61 (52), 55 (24), 43 (100).

2. *Insecticidal Tests*

2.1. *Chemicals*

Reagent-grade piperonyl butoxide (PB) was used as an inhibitor of oxidative metabolism. NIA16388 (propargyl propyl benzenephosphonate; NIA), which was originally reported as an inhibitor of the hydrolytic metabolism of tetramethrin,[15] a pyrethroid, was also used. NIA was the same sample used in previous studies.[16–19]

2.2. *Insecticidal test*

The insecticidal test against male adult American cockroaches,

Periplaneta Americana L., was carried out as described previously.[16,19,20] Various volumes (1–10 μl) of each compound dissolved in dimethyl sulfoxide containing some amount of methanol were injected into the abdomen of a cockroach. Organic solvents alone in this range did not have any toxic effect. Details of the dosage were fundamentally the same as described previously.[20] The doses were varied by 0.1 log units. In some experiments, a methanol solution (1 μl) containing NIA (50 μg) or a mixture of PB (50 μg) and NIA (50 μg) was injected 1 hr before injection of the test compound. The metabolic inhibitors in these amounts did not have any toxic effect. Three insects were used to test each dose of each compound and were kept at 24–26°C for 24 hr after injection. The minimum lethal doses (MLD; mol) for the test compounds were determined. For the sake of quantitative structure-activity analyses, which will be published elsewhere, the activity values were expressed by log(1/MLD) and are listed in Table 1. Each value is the mean of at least two experimental runs with a deviation of $\pm$0.2.

RESULTS AND DISCUSSION

1. *Synthesis*

Newly substituted imidacloprid derivatives (**1c**–**1h** in Table 1) were prepared by the coupling reaction of 5-substituted 6-chloro-3-pyridylmethyl bromide or chloride (**15**) with 2-nitroiminoimidazolidine (**16**) in DMF using sodium hydride as an acid acceptor (iii in Fig. 2). 5-Bromo-6-chloro-3-pyridylmethyl alcohol (**4**) was obtained by treating acid chloride (**3**) with excess $NaBH_4$ in water (i in Fig. 2). The introduction of a fluorine or iodine atom at the fifth position of the pyridine ring was carried out via the diazonium salt of 3-amino-2-chloro-5-methylpyridine (**6**) (ii in Fig. 2), and the corresponding 5-cyano derivative (**10**) was well reproducible from propylidene malononitrile.[12] Methyl halogenides (**15**) were obtained either by chlorination of the corresponding alcohol or by NBS bromination of the methyl group.

2. *Insecticidal Activity*

The insecticidal activity 24 hr after injection into American cockroaches is listed in Table 1. Without a synergist (alone), the minimum lethal dose (log 1/MLD, mol) of imidacloprid (**1a**) was in the nanomolar range, with the fluoro derivative (**1c**) showing comparable potency and the chloro derivative (**1d**) slightly less active. The introduction of other groups at the C5 position reduced the activity. Cyano and nitro compounds (**1g**, **1h**) were too weak to determine definitive MLD values. Our previous experiments suggested that the synergistic effect of NIA on neonicotinoids should be due to the inhibition of oxidative metabolism at the α-carbon(s) to the imidazolidine nitrogen atom(s).[16,18,19] Recent experiments with houseflies revealed a retarded degradation of [^{3}H]imidacloprid in the presence of NIA.[21] The present result reflected well the effect; NIA increased the level of activity by one log unit equally for each compound. Even under these conditions, compounds (**1g**, **1h**) were still too weak to give definitive activity values. We have reported that the activity of neonicotinoid compounds could further be enhanced by adding of PB, another inhibitor of oxidative metabolism. A synergistic effect was observed for most compounds tested, so that all the compounds gave a determinable lethal dose. Under these conditions, compounds **1a** and **1c** stood out at 10^{-10} molar lethal dose level. Introduction of Cl and Br (compounds **1d**, **1e**) reduced the activity slightly, while the iodo-substituted compound (**1f**) was considerably less active. These results suggest that the permissible space around the position in question on the pyridine ring should be small. In contrast with lipophilic halogen atoms, polar and strong electron-attracting groups like CN and NO_2 reduced the activity greatly (compounds **1g**, **1h**).

Table 1. Insecticidal activities of compounds tested[a]

No.	X	log(1/MLD) (M)		
		Alone	+NIA	+(PB+NIA)
1a	H	8.96	10.15	10.15
1b	N_3	7.37	8.18	8.18
1c	F	8.82	9.91	9.91
1d	Cl	8.35	9.05	9.05
1e	Br	8.02	9.11	9.11
1f	I	7.54	8.64	8.64
1g	CN	<6.30	<6.30	6.30
1h	NO_2	<5.77	<5.77	5.77

[a] See Fig. 1 for the general structure.

Recently, high affinity of 5-azidoimidacloprid (**1b**) for the imidacloprid receptor on nAChR of *Myzus* and *Drosophila* was reported.[8,9] In the present insecticidal experiment using American cockroaches, however, the potency of **1b** was about 1/100 that of imidacloprid with or without synergist treatment. Although the activity was about 80-fold that of the pseudohalogen CN compound (**1g**), the effect of azide (**1b**) was not so well recognized. The structural diversity and functionality of the insect nAChR is not fully understood.[22,23] The subtle difference in receptors among these insect species may influence the behavior of this compound.

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