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# Trifluoroacetyl Neonicotinoid Insecticides with Enhanced Hydrophobicity and Effectiveness

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Neonicotinoids with nitro- or cyanoimino substituents are extensively utilized as plant-mobile (systemic) insecticides controlling the piercing−sucking insect pests. This investigation considers structural features of neonicotinoids with trifluoroacetyl pharmacophores, which may confer enhanced hydrophobicity and effectiveness. Fifteen trifluoroacetyl neonicotinoid analogues [=NC(O)-$CF_3$ and =CHC(O)$CF_3$] are therefore prepared to evaluate the hydrophobicity index, toxicity to houseflies (*Musca domestica*), and binding affinity to the *Musca* nicotinic receptor. The =NC(O)$CF_3$ and =CHC(O)$CF_3$ compounds showed a higher hydrophobicity than that of nitro- or cyanoimino analogues. The intrinsic insecticidal activities (defined by intrathoracic injection with a synergist pretreatment) of test compounds were well-correlated to their target site potencies. Although nitro or cyano neonicotinoids were not toxic via the topical application route in the absence of a synergist, trifluoroacetyl analogues exhibited excellent insecticidal activity under the same condition. Accordingly, the increased hydrophobicity of trifluoroacetyl neonicotinoids presumably improves the penetrability of compound into insect integument and insecticidal effectiveness.

**KEYWORDS: Neonicotinoid insecticides; nicotinic acetylcholine receptor; trifluoroacetyl pharmacophore**

## INTRODUCTION

Neonicotinoids, exemplified by imidacloprid (IMI) and thiacloprid (THIA) providing nitro- and cyanoimino pharmacophores, respectively (**Figure 1a**), are utilized throughout the world as systemic (plant-mobile) insecticides for crop protection against piercing−sucking insect pests (*1*−*5*). Neonicotinoid selectively acts on the insect nicotinic acetylcholine receptor (nAChR), and the binding site interactions in chemical or atomic resolution have been defined by comparative chemical and structural neurobiology approaches using mollusk acetylcholine binding protein (AChBP), which is a suitable structural surrogate of the extracellular ligand binding domain of the nAChRs (*6*−*10*).

In our previous studies, the systematic pharmacophore modifications of neonicotinoid molecules gave highly active compounds with diverse chemotypes of pharmacophores, and three-dimensional structural models of the binding site interactions were predictive of the observed structure−activity relationships (SARs) (*11*−*13*). Intriguingly, a neonicotinoid analogue with a trifluoroacetyl substituent, replacing the nitro or cyano pharmacophore, is highly insecticidal, apparently associated with the unique binding site interactions of the trifluoroacetyl moiety (**Figure 1b**) (*11*, *14*). The present investigation examines the hypothesis that the trifluoroacetyl substituent enhances the hydrophobicity of neonicotinoid and thereby confers the improved insecticidal effectiveness relative to those of the nitro and cyano compounds. Therefore, we designed and prepared trifluoroacetyl neonicotinoid analogues (**Figure 2**) to comprehensively consider the SARs regarding the nAChR affinity and insecticidal potency in comparison with those of the nitro and cyano neonicotinoids.

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## MATERIALS AND METHODS

**Chemistry.** Compounds **1**−**5**, **8**, **10**, **15**, and **17**−**19** were available from our previous studies or prepared according to published methods (*12*, *14*−*18*). Synthesis procedures for the new chemicals (compounds **6**, **7**, **9**, **11**−**14**, **16**, and **20**−**22**) are summarized in **Scheme 1**, and the details and analytical results for structural confirmation are given in the Supporting Information. All melting points (mp) are uncorrected. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded using a JEOL ECA-500 spectrometer at 500, 125, and 376.3 MHz, respectively. The chemical shifts were recorded in $\delta$ (ppm), and the coupling constants $J_{H-H}$ were recorded in Hz unless otherwise stated. Mass spectra were recorded at 70 eV with the JEOL JMS-700 instrument.

**Physicochemistry.** Partition coefficients of test compounds between 1-octanol and water (log $P_{ow}$) were determined by Kagabu et al. (*18*). The maximal absorption wavelength ($\lambda_{max}$) of neonicotinoids was measured with a HITACHI U-4000S spectrophotometer.

**Biology.** The potency of test compounds as inhibitors of [$^3$H]IMI binding to the native housefly (*Musca domestica*) brain nAChR was assayed according to Tomizawa et al. (*19*). $IC_{50}$ values (molar concentrations of test compounds necessary for 50% inhibition of specific [$^3$H]IMI binding) were determined by iterative nonlinear least-squares regression


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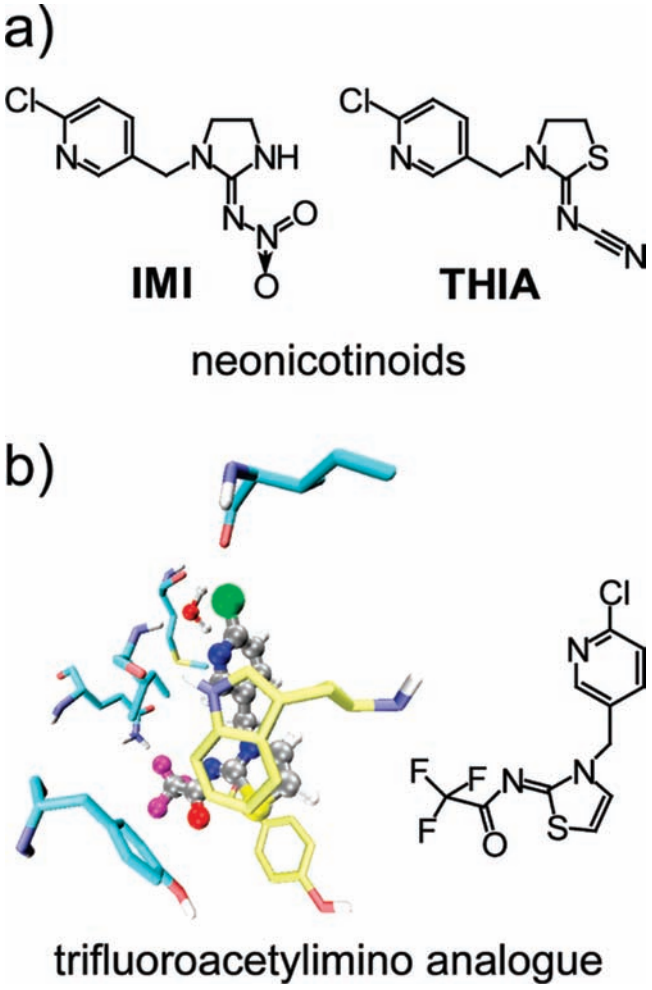



**Figure 1.** (**a**) Structures of representative neonicotinoid insecticides IMI and THIA. (**b**) Predictive binding site interactions of a trifluoroacetyl neonicotinoid (compound **15**) with the agonist binding pocket of the *Aplysia californica* AChBP (*11*), which is a structural surrogate for the insect nAChR extracellular domain (*7*, *9*). A water molecule near the pyridine nitrogen atom, captured in the AChBP-IMI crystal structure (Protein Data Bank code 3C79) (*8*), is superimposed onto this image. The pyridine nitrogen forms a water bridge to two neighboring isoleucines at the loop E domain (*8*, *13*). The three fluorine atoms of the compound, facing toward multiple directions, undergo various interactions with an interfacial region of loops C and D of the AChBP via hydrogen bonding and van der Waals contact. These interactions are fundamentally consistent with those observed in the insect nAChR structural model (*11*).

using SigmaPlot software (SPSS Inc., Chicago, IL). Insecticidal activity was evaluated with adult female houseflies via intrathoracic injection and topical application in the absence or the presence of a cytochrome P450 inhibitor [*O*-propyl *O*-(2-propynyl) phenylphosphonate], which serves as a synergist by reducing the oxidative detoxification rate (*20*).

## RESULTS

**Hydrophobicity and Photostability (Table 1).** Six nitroimino (or cyanoimino) compounds (**1**−**6**) including IMI (**1**) and THIA (**4**) had log $P_{ow}$ values of −0.16−1.26. In contrast, the 2-trifluoroacetylimino [=NC(O)$CF_3$] analogues (**7**−**16**) showed the greatly enhanced log $P_{ow}$ values (0.99−3.40). Acetylimino analogue [=NC(O)$CH_3$] (**17**) had a log $P_{ow}$ of 1.32, which is significantly lower than that of the corresponding $CF_3$ compound (**12**) (3.06). Furthermore, the 2-trifluoroacetylmethylene [=CHC(O)$CF_3$] compounds (**18**−**22**) retained a high level of hydrophobicity (log $P_{ow}$ values of 0.80−2.10) relative to those of nitro or

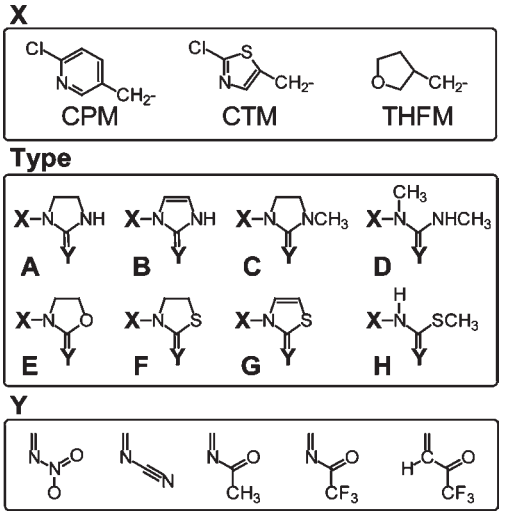
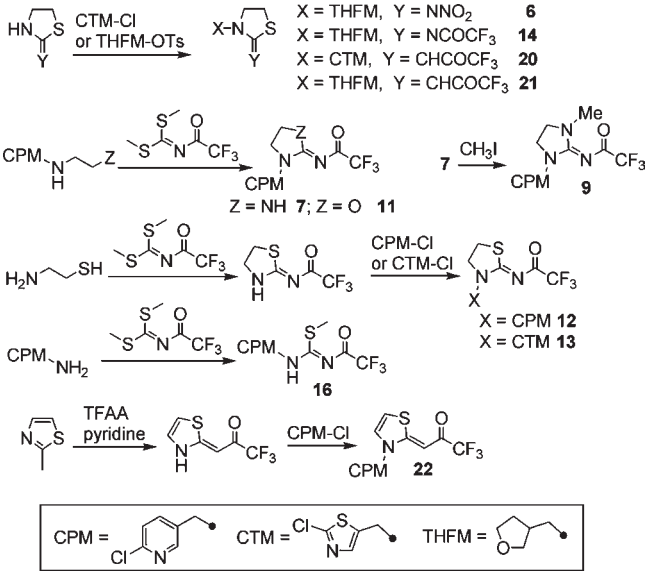



**Figure 2.** Chemical structures of neonicotinoid analogues providing nitro (or cyano) and trifluoroacetyl substituents examined in the present investigation. The neonicotinoid compounds consist of three structural moieties.

**Scheme 1.** Preparation of Trifluoroacetyl Neonicotinoid Analogues




cyanoimino compounds. Among the =NC(O)$CF_3$ analogues, the hydrophobicity was varied by the heterocyclic moieties: that is, thiazolidine (**12**) or thiazoline (**15**) > imidazoline (**8**) > imidazolidine (**7**) > oxazolidine (**11**) or acyclics (**10** and **16**) > *N*-methylimidazolidine (**9**). In the series of 2-substituted thiazolidines [=$NNO_2$, =NC(O)$CF_3$, or =CHC(O)$CF_3$], their log $P_{ow}$ values reduced in the order of chlorothiazolylmethyl (CTM) (**5**, **13**, and **20**) > chloropyridinylmethyl (CPM) (**3**, **12**, and **19**) > tetrahydrofurylmethyl (THFM) (**6**, **14**, and **21**).

On the ground level, sunlight of 290−400 nm wavelength affects the field stability of neonicotinoid insecticide (*21*, *22*). Therefore, the $\lambda_{max}$ is defined as a superficial index for neonicotinoid photostability and analogues with $\lambda_{max} \geq 290$ nm may possibly be photolabile. Nitro- or cyanoimino compounds (**1**−**6**) had $\lambda_{max}$ values < 290 nm. Fascinatingly, the =NC(O)$CF_3$/$CH_3$ analogues (**7**−**17**) also showed the $\lambda_{max}$ values < 290 nm, except for an analogue (**15**) with thiazoline heterocycle (307 nm). In marked contrast, all compounds with the =CHC(O)$CF_3$ substituent (**18**−**22**) had $\lambda_{max}$ values > 290 nm. In addition, for a

**Table 1.** SARs of Neonicotinoid Insecticides with Nitro (or Cyano) and Trifluoroacetyl Pharmacophores

| compound[a] | | | | parameters | | binding to *Musca* nAChR | toxicity to *Musca* $LD_{50}$ ($\mu$g/g female)[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| no. | X | type | Y | log $P_{ow}$ | $\lambda_{max}$ | $IC_{50}$ (nM ± SD) ($n$ = 3) | injection synergist[d] | topical synergist[d] | topical alone[e] |
| **1** | CPM | A | $NNO_2$ | 0.57 | 269 | 10 ± 0.4 | 0.021 | 0.20 | >100 (20%) |
| **2** | CPM | D | $NNO_2$ | −0.16 | 264 | ~100000 (53%)[b] | >1 (0%) | >10 (0%) | >100 (0%) |
| **3** | CPM | F | $NNO_2$ | 1.16 | 279 | 24 ± 3.9 | 0.081 | 0.11 | >100 (0%) |
| **4** | CPM | F | NCN | 1.26 | 250 | 4.8 ± 0.3 | 0.032 | 0.14 | >100 (30%) |
| **5** | CTM | F | $NNO_2$ | 1.20 | 281 | 56 ± 1.8 | 0.11 | 0.60 | >100 (0%) |
| **6** | THFM | F | $NNO_2$ | 0.14 | 284 | 1310 ± 200 | 0.55 | 1.12 | >100 (0%) |
| **7** | CPM | A | $NC(O)CF_3$ | 1.92 | 248 | 68 ± 8.9 | 0.15 | 0.39 | >100 (40%) |
| **8** | CPM | B | $NC(O)CF_3$ | 2.41 | 270 | 22 ± 2.1 | 0.25 | 0.33 | 17.0 |
| **9** | CPM | C | $NC(O)CF_3$ | 0.99 | 247 | 50800 ± 8100 | >1 (0%) | >10 (10%) | >100 (0%) |
| **10** | CPM | D | $NC(O)CF_3$ | 1.53 | 244 | >100000 (19%)[b] | >1 (0%) | >10 (0%) | >100 (0%) |
| **11** | CPM | E | $NC(O)CF_3$ | 1.56 | 254 | 2750 ± 110 | >1 (0%) | >10 (20%) | >100 (20%) |
| **12** | CPM | F | $NC(O)CF_3$ | 3.06 | 265 | 28 ± 1.5 | 0.060 | 0.040 | 2.0 |
| **13** | CTM | F | $NC(O)CF_3$ | 3.40 | 266 | 300 ± 51 | 0.60 | 0.51 | >100 (0%) |
| **14** | THFM | F | $NC(O)CF_3$ | 1.51 | 264 | 36600 ± 6400 | >1 (6.7%) | 4.0 | >100 (0%) |
| **15** | CPM | G | $NC(O)CF_3$ | 2.93 | 307 | 5.2 ± 0.4 | 0.020 | 0.043 | 1.1 |
| **16** | CPM | H | $NC(O)CF_3$ | 1.70 | 263 | 44600 ± 2300 | >1 (0%) | >10 (0%) | >100 (0%) |
| **17** | CPM | F | $NC(O)CH_3$ | 1.32 | 262 | 1470 ± 170 | >1 (0%) | 3.2 | 80 |
| **18** | CPM | A | $CHC(O)CF_3$ | 1.76 | 293 | 3.0 ± 0.3 | 0.012 | 0.058 | 3.8 |
| **19** | CPM | F | $CHC(O)CF_3$ | 1.84 | 322 | 3.2 ± 0.4 | 0.0052 | 0.0040 | 0.75 |
| **20** | CTM | F | $CHC(O)CF_3$ | 2.10 | 321 | 78 ± 19 | 0.11 | 0.12 | >100 (20%) |
| **21** | THFM | F | $CHC(O)CF_3$ | 0.80 | 321 | 19200 ± 5000 | >1 (3.4%) | >10 (10%) | >100 (0%) |
| **22** | CPM | G | $CHC(O)CF_3$ | 1.83 | 352 | 1.2 ± 0.1 | 0.0038 | 0.0070 | 1.6 |

[a] Chemical structures are given in **Figure 2**. Compounds **1** and **4** are IMI and THIA, respectively. [b] Inhibition % at the indicated concentration. [c] Numbers in parentheses are mortality % at the indicated dose. [d] Pretreated with *O*-propyl *O*-(2-propynyl) phenylphosphonate at 100 $\mu$g/g female. [e] Chlorpyrifos as the control insecticide had a $LD_{50}$ value of 1.9 $\mu$g/g female as compared with those of other standard insecticides parathion, propoxur, dieldrin, and DDT of 1.3, 23, 0.7, and 14 $\mu$g/g female (*11*, *23*).

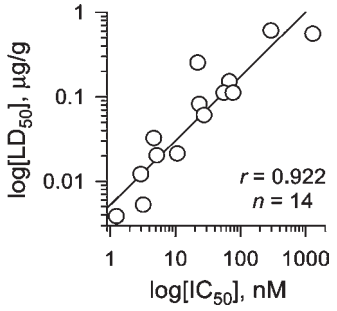



**Figure 3.** Correlation plot between $IC_{50}$ and $LD_{50}$ values as indexes for receptor potency and intrinsic insecticidal activity (determined by intrathoracic injection with synergist pretreatment), respectively, of 14 neonicotinoid analogues. Eight inactive compounds showing $LD_{50}$ values of >1 $\mu$g/g and very low binding affinities were excluded.

representative compound **12**, almost none of the hydrolytic product was detected in neutral aqueous solution until 96 h (data not shown).

**Binding Affinity** (**Table 1**)**.** Nitroimino or cyanoimino analogues with imidazolidine and thiazolidine rings (**1** and **3**−**5**) had relatively high binding affinities, while the acyclic analogue was inactive. Among the 2-nitroiminothiazolidines, the binding potency was diminished depending on the substituent structure with the order of CPM (**3**) > CTM (**5**) > THFM (**6**). Trifluoroacetylimino analogues with imidazolidine (**7**), imidazoline (**8**), thiazolidine (**12**), and thiazoline (**15**) showed high binding affinities comparable to those of nitroimino neonicotinoids. The thiazoline analogue (**15**) displayed the highest affinity in the $=NC(O)CF_3$ series. However, the compounds with *N*-methylimidazolidine (**9**), oxazolidine (**11**), and two acyclic analogues (**10** and **16**) had largely reduced potencies. As with nitroimino compounds, the potency rank order was CPM (**12**) > CTM (**13**) > THFM (**14**) among the 2-trifluoroacetyliminothiazolidines. The $=NC(O)CH_3$ compound (**17**) was 53-fold less active than that of the corresponding $CF_3$ analogue (**12**). Intriguingly, the $=CHC(O)CF_3$ analogues with a CPM moiety (**18**, **19**, and **22**) were outstandingly active, although their CTM (**20**) and THFM (**21**) analogues had moderate and low binding affinities, respectively. The thiazoline compound (**22**) gave a higher binding potency than that of the thiazolidine analogue (**19**).

**Insecticidal Activity** (**Table 1**)**.** Adult female houseflies were used for quantitative evaluation of insecticidal activity via two administration routes. First, intrathoracic injection of test compounds into flies, which were pretreated with a cytochrome P450 inhibitor (synergist), was determined to define intrinsic toxicity. Second, test compounds were administrated by a topical application route (in the presence or the absence of synergist), involving the penetration aspect of a compound into the insect body through the epidermal cuticle.

Importantly, the intrinsic toxicities of 14 neonicotinoids were well-correlated to their target site potencies ($r$ = 0.92) (**Figure 3**). Eight inactive compounds had very low binding affinities as well. The toxicity range of $=NC(O)CF_3$ analogues was similar to that of nitroimino (or cyanoimino) neonicotinoids. The $=CHC(O)CF_3$ compounds (**18**, **19**, and **22**) exhibited excellent intrinsic toxicity, except for compounds **20** and **21** with CTM and THFM moieties. Intrinsically, toxic compounds were generally insecticidal via topical application experiment in the presence of a synergist. Most of test compounds including IMI (**1**) and THIA (**4**) were inactive in the topical application without the synergist pretreatment. In marked contrast, six compounds with $=NC(O)CF_3$ and $=CHC(O)CF_3$ pharmacophores (**8**, **12**, **15**, **18**, **19**, and **22**) provocatively showed outstanding insecticidal activity, rivaling those of an organophosphate insecticide chlorpyrifos and other standard insecticides (**Table 1** footnote) (*11*, *23*).

## DISCUSSION

Exploration of novel nicotinic pharmacophore chemotypes, undergoing the unique or atypical binding mechanism(s), may expand the insecticidal spectrum and circumvent the possible resistance caused by activated detoxification systems and a modified target site (*24*, *25*). The present investigation considers

exhaustive SARs of neonicotinoid analogues with a trifluoroacetyl pharmacophore, which may advance the chemical property and insecticidal effectiveness of the present nitro and cyano neonicotinoids.

The SARs of trifluoroacetyl neonicotinoids, in terms of target site potency and toxicity, are nearly consistent with those of nitro or cyano neonicotinoid analogues (*20*, *26*−*28*). Interestingly, comparative SARs between the $=NC(O)CF_3$ and the $=CHC(O)CF_3$ analogues are almost identical to those between the nitroimino ($=NNO_2$) and nitromethylene ($=CHNO_2$) neonicotinoids. The receptor binding affinity is predictive of the intrinsic toxicity based on a good correlation. A specific combination of three structural moieties determines the potency at the target site. The $=NC(O)CH_3$ is less active than the corresponding $=NC(O)CF_3$ compound, establishing that the trifluoromethyl head plays an important role on the selective binding interaction with the receptor subsite(s) via H-bonding and van der Waals contact (*11*, *12*). Furthermore, an electron-withdrawing effect of the $CF_3$ apparently facilitates $\pi$-stacking interaction of the amidine moiety with the loop C aromatic residue (*11*, *14*). The neonicotinoid $=NC(O)CF_3$ substituent is embraced by an interfacial niche between the $\alpha$ and the $\beta$ subunits, whereas the nitroguanidine or cyanoamidine moiety of IMI or THIA is primarily recognized by the $\alpha$ subunit (*9*, *11*).

The neonicotinoids generally have low log $P_{ow}$ values (−0.7−1.3), which makes the basis of their outstanding plant systemic performance to control the piercing−sucking insects (*3*). Some organophosphates (1−5.5) and methylcarbamates (−1−3) also have good plant-mobile action. However, the more lipophilic organochlorines (5.5−7.5) and pyrethroids (4−9) are efficacious against *lepidopterous* larvae as contact insecticides (*3*). The $=NC(O)CF_3$ and $=CHC(O)CF_3$ substituents (log $P_{ow}$ values 1.0−3.4 and 0.8−2.1, respectively) greatly enhance the hydrophobicity of nitro- and cyanoimino neonicotinoids. On the basis of the present findings, the increased hydrophobicity of trifluoroacetyl analogues presumably improves the penetrability of the neonicotinoid compound into the insect integument, thereby conferring the enhanced insecticidal efficacy relative to that of IMI (**1**) or THIA (**4**). Moreover, the neonicotinoid with $=NC(O)CF_3$ pharmacophore appears to retain adequate photostability comparable to that of the $=NNO_2$ or =NCN neonicotinoid; yet, the $=CHC(O)CF_3$ analogues are conceivably photolabile as with the $=CHNO_2$ compounds (*21*, *22*).

In summary, the present SAR investigation identifies several trifluoroacetyl neonicotinoids with excellent insecticidal effectiveness associated with the high receptor potency and the enhanced hydrophobicity, thereby illustrating that the nicotinic receptor target further warrants continuing study to discover novel nicotinic insecticides with unique biological properties.

## ABBREVIATIONS USED

AChBP, acetylcholine binding protein; IMI or [$^3$H]IMI, imidacloprid or its tritiated radioligand; log $P_{ow}$, partition coefficient of compound between 1-octanol and water; nAChR, nicotinic acetylcholine receptor; SAR, structure−activity relationship; THIA, thiacloprid.

**Supporting Information Available:** Synthesis procedures and analysis data for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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