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Crown-capped imidacloprid: A novel design and insecticidal activity

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ABSTRACT

Imidacloprid (IMI) derivatives conjugated with benzo-15-crown-5 and benzo-18-crown-6 structures, applied for the first time to explore novel insecticidal molecule, elicited strong excitatory toxic signs to the house flies and stunningly exhibited three to five times higher insecticidal activity than that of the parent IMI, yet the two benzo-crown structures themselves had no effect.

The use of crown ethers expanded in analytical chemistry, organic synthesis, biological systems, molecular electronics, and other material technologies, resulting in an increasing number of recent breakthroughs.[1] However, to our knowledge, pesticides designed using supramolecular aspects have not been published.[2] The present investigation applies for the first time the crown-ether structure to design novel insecticidal molecules, leading to benzo-15-crown-5 or benzo-18-crown-6 conjugated imidacloprid (IMI). IMI is the current top-selling insecticide acting at the insect nicotinic receptor.[3] The prosthetic crown-ether moiety with a specific Na^+ carrier and amphiphilic functions may give unexpected biological properties. Intriguingly, we found that the crown-capped IMI derivatives showed high insecticidal activity consistent to or greater than that of the parent IMI.

Benzo-15-crown-5 and benzo-18-crown-6 capped imidacloprids (**2**, **3**) were prepared by the reaction of 2-nitroiminoimidazolidine-1-ylmethyl-benzo-crown (**7**, **8**) with 6-chloro-3-pyridylmethyl chloride and resulted in yields of 33% and 45%, respectively (Fig. 1).[4]

A test compound (0.22 μL, dissolved in 80% DMSO) was injected into the thorax of female adult house flies (*Musca domestica*).[5] Mortality was determined at 24 h after treatment. The LD_{50} values were calculated using log dose-probit mortality analysis. The toxicity signs of the poisoned flies were observed in the following sequence: convulsions with leg tremor and wing motion followed by paralysis, and death with a curled abdomen or out-stretched legs, similar to that of IMI itself, suggesting that the crowned derivatives presumably act on the insect nervous system. The LD_{50}s were 25 ± 4.4 and 17 ± 2.4 ng/fly (n = 5) for **2** and **3**, respectively. Under these conditions, the LD_{50} for IMI was 84 ± 5.1 ng/fly (n = 3). Interestingly, neither of benzo-15-crown-5 nor benzo-18-crown-6 showed toxic effect even at doses as high as 1100 ng/fly. Moreover, the insecticidal activities of the crowned compounds were determined in the presence of the metabolic inhibitor, propyl 2-propynyl phenylphosphonate known to synergize the insecticidal potency of IMI.[6] Insecticidal potency of compounds **2** and **3** in the presence of the metabolic inhibitor were 4.8 ± 1.8 and 4.3 ± 1.1 ng/fly (n = 3), respectively, which were higher than that of IMI.[7] When the compounds topically-applied to the insect integument at a dose of 15 μg/fly, the mortality was 44% and 38% for **2** and **3**, respectively. These values were higher than the 24% observed for IMI. Lipophilic ingredients are generally more effective upon insects in integument penetration and distribution in the body, which results in efficient delivery to the site of action through the lipid-protein membrane. Several experiments using IMI-related compounds have actually shown that the higher the hydrophobicity of the molecules, the higher the insecticidal or neurophysiological activity.[8]

One of the most prevalent hydrophilicity/lipophilicity quotient is the partition coefficient between octanol and water (Pow). The log Pow for **2** and **3** were 0.15 and 0.28 (n = 4), respectively. These values were smaller than observed 0.57 for IMI.[9] This suggested that crowned derivatives are more hydrophilic than IMI. The unexpectedly higher dermal insecticidal potencies of the crowned derivatives despite their smaller Pows may be explained by the amphiphilic properties of crown ether. Crown ether can be lipophilic or hydrophilic depending on the ring conformation, which can change according to the properties of the surrounding fluid (Fig. 2).

We showed that crown-capped IMI derivatives have higher insecticidal activity compared with the parent IMI. Considering that molecules having potencies comparable to the most active product in this insecticide class have rarely been found despite the number

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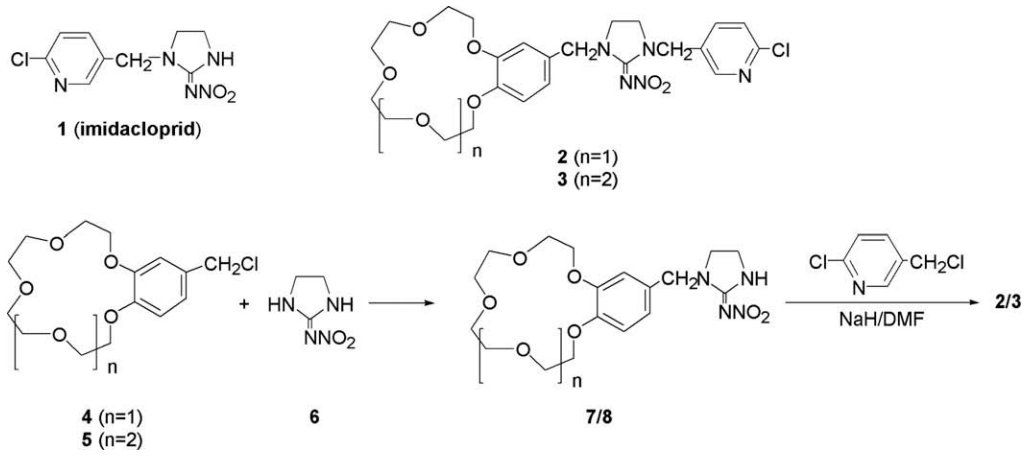

Figure 1. limidacloprid (IMI) and preparation of crowned derivatives.

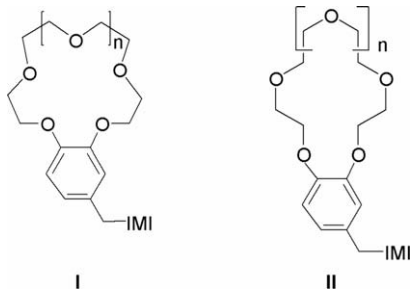

Figure 2. Conformational change of benzocrowns. **I** and **II** in lipophilic and hydrophilic fluids, respectively.

of structural modifications testing various angles that have been attempted over the past 30 years, it was surprising that the activity of IMI was enhanced by crown-bridging to the extent we observed.[10] Therefore we questioned whether the crowned-IMI was the real active species at the target site, or if we were observing the effect of a physiologically regenerated IMI. Our experiments showed that no detectable amount of liberated IMI were observed after 24 h in a physiological salt solution. This result caused us to exclude the effect of a spontaneous prodrug from our observations.[11]

To approach the effect of crown-capping on the biological action of IMI, we examined the complexing behavior of the derivatives in the presence of several molar ratios of sodium thiocyanate by NMR in $CDCl_3/CD_3OD$ (1:50 *v*/*v*) according to the standard protocol.[12] Both insecticidal molecules showed a typical profile representing a loosely bound 1:1 complex with Na^+. The binding constants were as high as 440 ± 30 and 16,000 ± 3000, respectively, at 25 °C ($n = 3$) for **2** and **3**, comparable to those of the uncapped benzo-crown compounds.[13] Therefore, the crown-capped derivatives have prominent ion-capturing properties, conceivably attenuating physiology of the nervous system and ultimately conferring the enhanced insecticidal potency.

In conclusion, the novel crown-capped IMI derivatives had high insecticidal potency, suggesting an action at the insect nervous system presumably mediated by nicotinic receptor. The biochemical and physiological studies should be conducted to define the unique mode of action for the crown-capped insecticide.

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4. Compound **2**: mp 27–29 °C (from ether). ^{1}H NMR δ ($CDCl_3$): 3.50 (4H, m, NCH_2CH_2N), 3.76 (8H, m, $OCH_2CH_2OCH_2CH_2O$), 3.91 (4H, m, 2 × $PhOCH_2CH_2$), 4.13 (4H, 2 × $PhOCH_2CH_2$), 4.40 (2H, s, Py-CH_2), 4.48 (2H, s, Ph-CH_2), 6.82 (3H, m, Ph*H*), 7.36 (1H, d, $J = 8.2$ Hz), 7.72 (1H, dd, $J = 8.2/2.6$ Hz), 8.31 (1H, d, $J = 2.6$ Hz). ^{13}C NMR δ ($CDCl_3$): 44.59, 45.11, 47.53, 50.61, 69.04, 69.096, 69.51, 69.55, 70.49, 71.14, 113.86, 113.98, 121.80, 125.01, 126.46, 128.97, 139.27, 149.48, 149.57, 149.78, 152.02, 161.22. FABHRMS for $C_{24}H_{30}ClN_5O_7$: Calcd 536.1912. Found: 536.1934. Compound **3**: mp 33–36 °C (from ether). ^{1}H NMR δ ($CDCl_3$): 3.50 (4H, m, NCH_2CH_2N), 3.68 (4H, br s, OCH_2CH_2O), 3.71 (4H, m, OCH_2CH_2O), 3.77 (4H, m, OCH_2CH_2O), 3.92 (4H, m, 2 × $PhOCH_2CH_2$), 4.14 (4H, 2 × $PhOCH_2CH_2$), 4.40 (2H, s, Py-CH_2), 4.48 (2H, s, Ph-CH_2), 6.81 (3H, m, Ph*H*), 7.37 (1H, d, $J = 8.2$ Hz), 7.73 (1H, dd, $J = 8.2/2.6$ Hz), 8.31 (1H, d, $J = 2.6$ Hz). ^{13}C NMR δ ($CDCl_3$): 44.60, 45.08, 47.54, 50.61, 69.17, 69.22, 69.61, 69.65, 70.78, 70.94, 113.91, 114.12, 121.81, 125.05, 126.43, 128.96, 139.29, 149.42, 149.48, 149.62, 152.06, 161.22. FABHRMS for $C_{26}H_{34}ClN_5O_8$: Calcd 580.2174. Found: 580.2173.
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