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Insecticidal quinoline and isoquinoline isoxazolines

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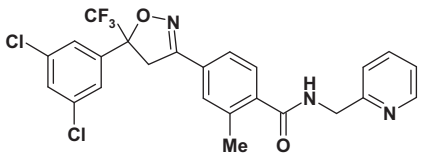
ABSTRACT

A series of quinoline and isoquinoline isoxazolines have been designed as pesticides for crop protection. Herein we reported the chemical synthesis, biological activity and structure–activity relationships. The isoquinoline derivative, such as **3i**, is discovered as potent new class of isoxazoline insecticide which is competitive with commercial insecticide **Indoxacarb**.

Due to the ability of insects to develop resistance to conventional pesticides, there is an ongoing need for the discovery and development of new products, particularly those that either represent novel chemical classes or work by new biochemical mechanisms. This is coupled with the need to identify new insecticides with low toxicity, favorable environmental profiles and good margins of safety toward beneficial insects, such as pollinator bees, to replace older products with less favorable attributes. New isoxazoline insecticides, such as those of structure **1**, were recently reported by Nissan (Fig. 1).[1] We also reported that 4-azolylphenyl isoxazoline of structure **2** is a highly effective insecticide and naphthalene isoxazoline of **Afoxolaner** is a new veterinary drug for dogs against fleas and ticks.[2] These isoxazoline classes exhibit their activity through inhibition of the GABA-gated chloride channel. [2,3]

We envisioned that the *ortho*-methyl substituent could be tied back into the central aromatic ring to provide new heterocyclic systems and provide new chemotypes of isoxazolines as potentially new insecticides (see Fig. 2).[4] Here we describe the synthesis and insecticidal activity from these types of quinoline and isoquinoline isoxazolines of structure **3**. Target molecules of **3**, with each of the *A* being replaced by one nitrogen atom were synthesized for insecticidal evaluation.

The isoquinoline isoxazoline **3a**, wherein N is at the 2 position, was prepared from 4-bromoisoquinoline **4** as outlined in Scheme 1. 4-Bromo-1-methylisoquinoline **5** was prepared from the commercially available 4-bromo-isoquinoline **4** according to the literature procedure in an overall yield of 50%.[5] Oxime **6** was obtained by treating **5** with *n*-BuLi and DMF to convert bromide to aldehyde, then reacting with NH_2OH. Styrene **7** can be prepared from coupling of 2-bromo-3,3,3-trifluoropropene and 3,5-dichlorophenylboronic acid.[1] Cycloaddition of the oxime **6** and the styrene **7** was accomplished to give isoxazoline **8** with NCS in



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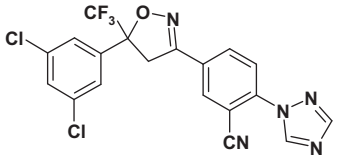

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Figure 1. Isoxazoline insecticides.

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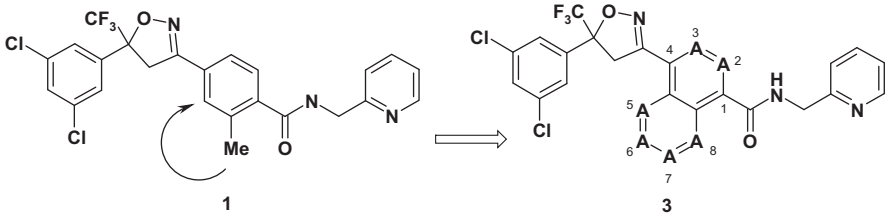
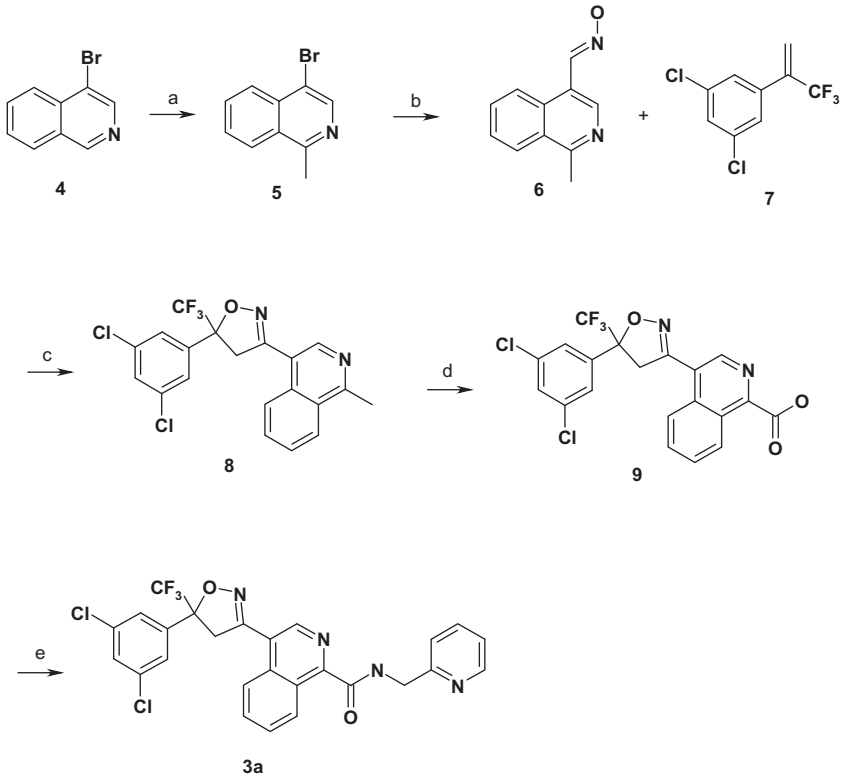
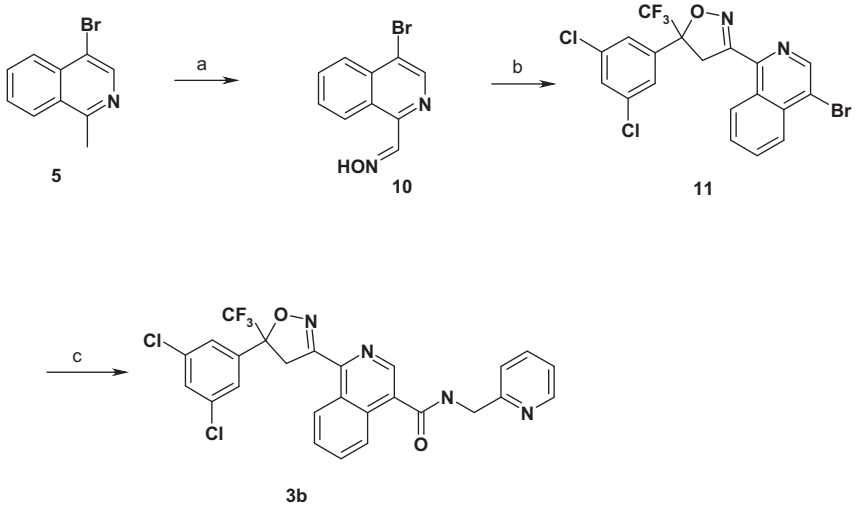


Figure 2. Novel quinoline and isoquinoline derivatives.



Scheme 1. Reagents and conditions: (a) (i) 30% H_2O_2, HOAc, 93%; (ii) $NCCH_2COOEt$, Ac_2O, pyridine, 60%; (iii) 30% H_2SO_4, 90%; (b) (i) *n*-BuLi, DMF, THF, 90%; (ii) NH_2OH, EtOH, 98%; (c) NCS, Et_3N, DMF, 50%; (d) (i) SeO_2, 1,4-dioxane; (ii) $KMnO_4$, CH_3COCH_3, pH = 7 buffer solution; (e) $(COCl)_2$, 2-(aminomethyl)pyridine, Et_3N, CH_2Cl_2, 50%.



Scheme 2. Reagents and conditions: (a) (i) SeO_2, 1,4-dioxane, 75%; (ii) NH_2OH, EtOH, 98%; (c) NCS, styrene **6**, Et_3N, DMF, 35%; (c) CO, 2-(aminomethyl)pyridine, $PdCl_2dppf$, Et_3N, toluene, 55%.