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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**.

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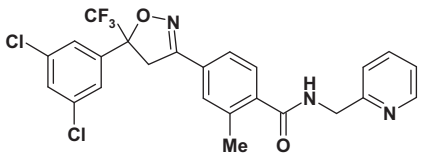
Due to the ability of insects to develop resistance to conventional pesticides, there is an ongoing need for the discovery and development of new products, particularly those that either represent novel chemical classes or work by new biochemical mechanisms. This is coupled with the need to identify 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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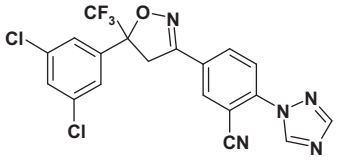

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Figure 1. Isoxazoline insecticides.

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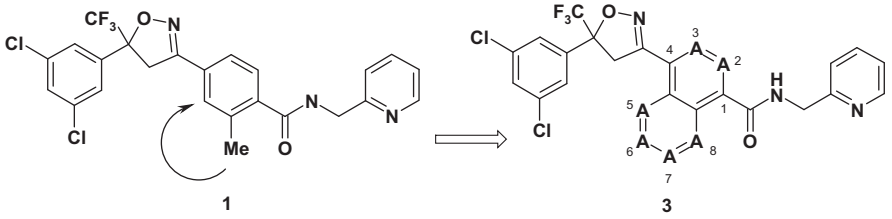
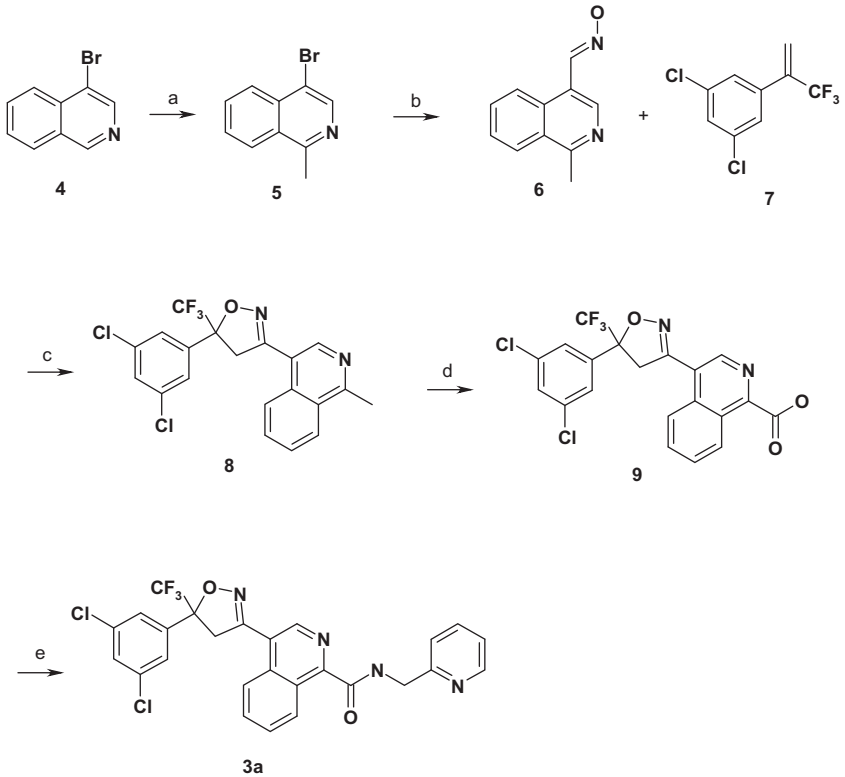
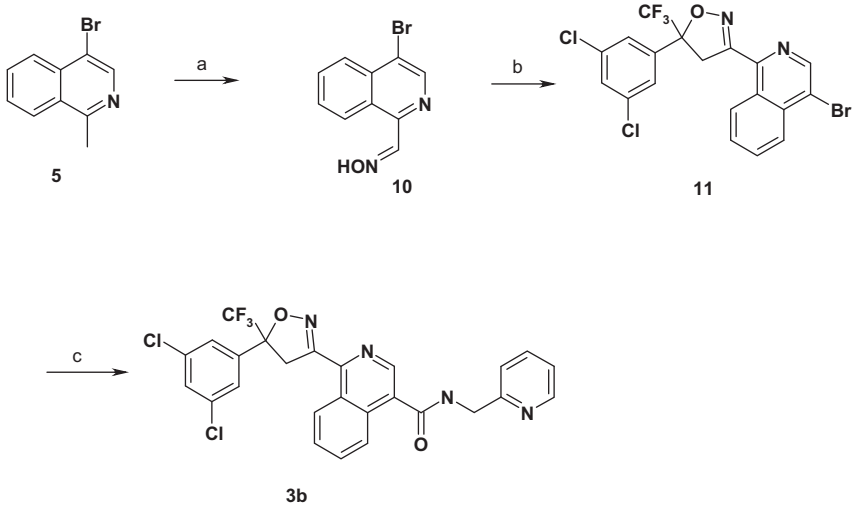


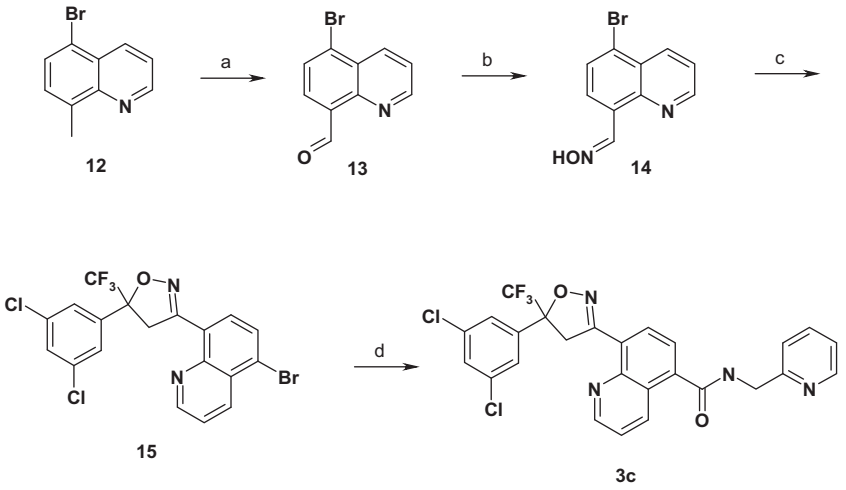
Figure 2. Novel quinoline and isoquinoline derivatives.



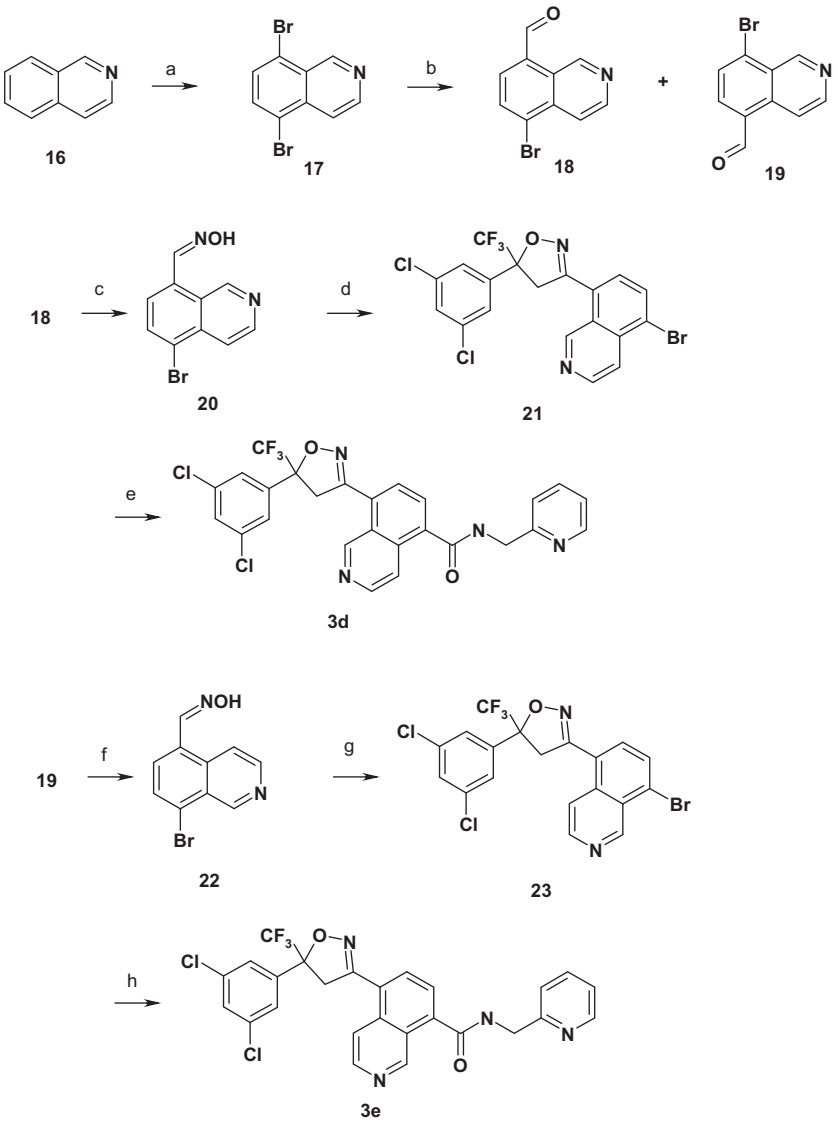
Scheme 1. Reagents and conditions: (a) (i) 30% H_2O_2, HOAc, 93%; (ii) $NCCH_2COOEt$, Ac_2O, pyridine, 60%; (iii) 30% H_2SO_4, 90%; (b) (i) *n*-BuLi, DMF, THF, 90%; (ii) NH_2OH, EtOH, 98%; (c) NCS, Et_3N, DMF, 50%; (d) (i) SeO_2, 1,4-dioxane; (ii) $KMnO_4$, CH_3COCH_3, pH = 7 buffer solution; (e) $(COCl)_2$,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



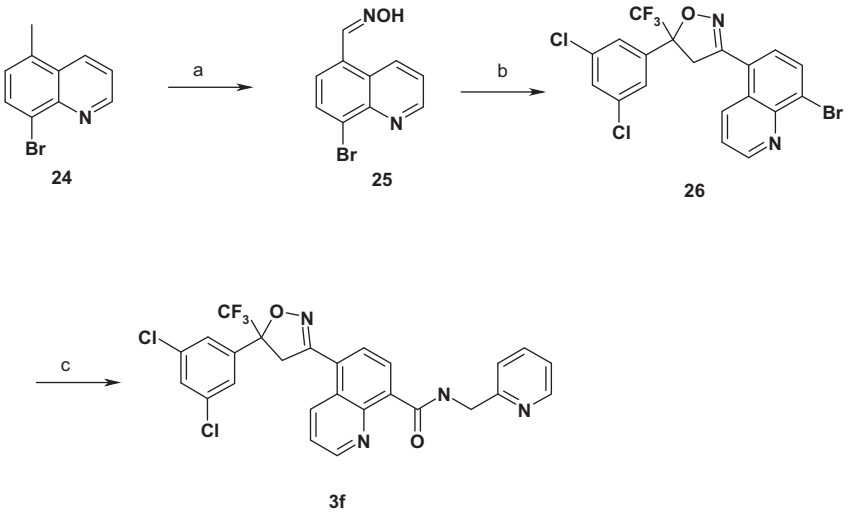
Scheme 2. Reagents and conditions: (a) (i) SeO_2, 1,4-dioxane, 75%; (ii) NH_2OH, EtOH, 98%; (c) NCS, styrene **6**, Et_3N, DMF, 35%; (c) CO, 2-(aminomethyl)pyridine, $PdCl_2dppf$, Et_3N, toluene, 55%.



Scheme 3. Reagents and conditions: (a) (i) NBS, AIBN, CCl_4, then NaOAc, DMF, 80%; (ii) MeOH, K_2CO_3, then Dess–Martin periodinane, CH_2Cl_2, 73%; (b) NH_2OH, EtOH, 99%; (c) NCS, styrene **6**, Et_3N, DMF, 45%; (c) CO, 2-(aminomethyl)pyridine, $PdCl_2$dppf, Et_3N, toluene, 72%.



Scheme 4. Reagents and conditions: (a) NBS, H_2SO_4, 60%; (b) *n*-BuLi, DMF, THF, 35% of **18** & 7% of **19**; (c) NH_2OH, EtOH, 98%; (c) NCS, styrene **6**, Et_3N, DMF, 20%; (c) CO, 2-(aminomethyl)pyridine, $PdCl_2$dppf, Et_3N, toluene, 60%; (f) NH_2OH, EtOH, 95%; (c) NCS, styrene **6**, Et_3N, DMF, 20%; (c) CO, 2-(aminomethyl)pyridine, $PdCl_2$dppf, Et_3N, toluene, 35%.



Scheme 5. Reagents and conditions: (a) (i) NBS, AIBN, CCl_4, then NaOAc, DMF, 75%; (ii) MeOH, K_2CO_3, then Dess–Martin periodinane, CH_2Cl_2, 85%; (iii) NH_2OH, EtOH, 98%; (c) NCS, styrene **6**, Et_3N, DMF, 61%; (c) CO, 2-(aminomethyl)pyridine, $PdCl_2$dppf, Et_3N, toluene, 10%.

the presence of Et_3N in DMF in 50% yield. Oxidation of **8** with SeO_2, then $KMnO_4$ in acetone/buffer solution[6] gave acid **9** which was used for next step directly. Amide formation of the acid **9** with 2-(aminomethyl)pyridine provided the isoquinoline isoxazoline **3a** in 50% yield with three steps.

As outlined in Scheme 2, target **3b** was prepared from the same intermediate 4-bromo-1-methylisoquinoline **5**. Oxime **10** was obtained from oxidation of **4** with SeO_2 to aldehyde, followed by reacting with NH_2OH. Same cycloaddition reaction of oxime **10** with styrene **7** gave isoxazoline **11**. Aminocarbonylation reaction of **11** with 2-(aminomethyl)pyridine in the presence of $PdCl_2$dppf provided the isoquinoline isoxazoline **3b** in 55% yield.[7]

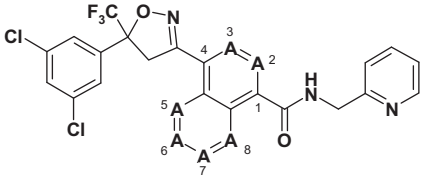
The quinoline isoxazoline **3c**, wherein N is at the 5 position, was prepared from 5-bromo-8-methylquinoline **12** as shown in Scheme 3. The 8-methyl group was converted to acetate by bromination with NBS and ester exchange with NaOAc in 80% yield. The aldehyde **13** was then obtained by hydrolysis and oxidation. Oxime formation and cycloaddition gave quinoline derivative **15** in 45% yield. The final aminocarbonylation with 2-(aminomethyl)pyridine gave target **3c** in 72%.

The synthesis of isoquinoline isoxazolines **3d** and **3e**, wherein nitrogen atoms are at the 6 and 7 positions correspondingly, was outlined in Scheme 4. We started with isoquinoline **16**. Bromination of **16** with NBS in H_2SO_4 gave dibromide **17**.[8] By treating **17** with *n*-BuLi at −78°C, then quenching with DMF, we obtained both aldehydes **18** and **19** which were separable by chromatography. Both of them were converted to the final targets **3d** and **3e** according to the chemistry discussed previously.

The last quinoline isoxazoline **3f** with N at the 8 position was prepared from 8-bromo-5-methyl-quioline **24** as shown in Scheme 5. Oxime **25** was obtained by converting methyl group of the starting **24** to aldehyde, then condensation with NH_2OH. Isoxazoline **26** was prepared from the cyclization of the oxime **25** and the styrene **7** in a yield of 61%. A similar aminocarbonylation coupling of **24** with 2-(aminomethyl)pyridine gave quinoline isoxazoline **3f** in low yield.

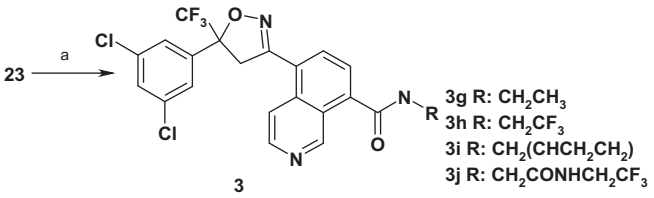
Insecticidal activity of quinoline and isoquinoline isoxazolines is summarized in Table 1. Compounds were applied to plants and evaluated against a series of insects under standard laboratory procedures.[9] Potency was evaluated on diamondback moth (*Plutella xylostella*, *Px*), fall armyworm (*Spodoptera frugiperda*, *Sf*), green peach aphid (*Myzus persicae*, *Mp*), potato leafhopper (*Empoasca fabae*, *Ef*), and western flower thrips (*Frankliniella occidentalis*, *Fo*).

Table 1
Insecticidal activity of quinoline and isoquinoline isoxazolines



Entry	A[a]	*Px*[b,c]	*Sf*[b,c]	*Mp*[c]	*Ef*[c]	*Fo*[b,c]
3a	2	10	50	>250	250	>250
3b	3	2	50	250	50	50
3c	5	50	250	>250	250	>250
3d	6	50	>50	>250	>250	>250
3e	7	0.4	2	50	>50	>50
3f	8	50	>250	>250	>250	>250

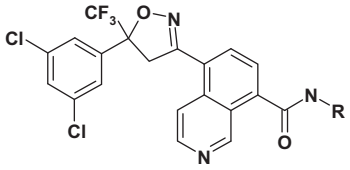
[a] Denotes positional isomer of nitrogen atom.
[b] Lowest rate tested (ppm) providing greater than 80% feeding protection.
[c] Lowest rate tested (ppm) providing greater than 80% insect mortality.



Scheme 6. Reagents and conditions: (a) CO, RNH_2, $PdCl_2$dppf, Et_3N, toluene, 20–50%.

Observations were taken six days after application on plant protection (*Px*, *Sf*, and *Fo*) and mortality (*Mp* and *Ef*). Isoquinolines **3e** was found to be the most active of the positional isomers showing excellent activity on both species of Lepidoptera, *Px* and *Sf*, two key indicators used to assess the global market potential on lepidopteran insects, currently valued at greater than $4 billion annually. Insecticidal activity was changed dramatically by moving nitrogen atom to a different position of the fused bicyclic ring. With this exceptional insecticidal activity of **3e**, more isoquinoline analogs with N at the 7 position were designed and synthesized by

Table 2
Insecticidal activity of isoquinoline isoxazolines



Entry	A	*Px*[a,b]	*Sf*[a,b]	*Mp*[b]	*Fo*[a,b]
3g	Et	0.4	0.4	50	2
3h	CH_2CF_3	0.4	2	—	2
3i	CH_2(cPr)	0.4	0.4	10	2
3j	$CH_2CONHCH_2CF_3$	50	50	>250	10
Indoxacarb		2	2	0.4	10

[a] Insecticidal activity reported as lowest rate tested providing greater than 80% feeding protection in ppm.
[b] Insecticidal activity reported as lowest rate tested providing greater than 80% insect mortality in ppm.

exchanging 2-(aminomethyl)pyridine with other amines to further improve their biological activity (Scheme 6).

As outlined in Scheme 6, the bromide **23** was converted to various amides via aminocarbonylation reaction as discussed before. Among them, cyclopropyl methylamine derivative **3i** shows excellent insecticidal activity in our screen.

Their insecticidal activity was summarized in Table 2 and **Indoxacarb** was used as the commercial standard. Analog **3i**, the cyclopropyl methyl amine derivative, shows unbroken activity on lepdidopteran insects (*Px* and *Sf*) down to 0.4 ppm. Most of the analogs screened here show great activity on *Px*, *Sf* and *Fo* below 2 ppm.

In summary, a series of quinoline and isoquinoline isoxazolines have been designed and synthesized as novel insecticides. Insecticidal screen results show that isoquinoline derivatives with N at the 7 position, the structure of **3e**, have excellent insecticidal activity. Further optimization of this class has identified compound **3i** to be more active than the commercial insecticide **Indoxacarb** on several species tested. This promising new class of chemistry for the modern crop protection industry is worth further exploration.

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