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Synthesis and anthelmintic properties of arylquinolines with activity against drug-resistant nematodes

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Abstract—2,4-Disubstituted quinolines with additional substituents in positions 5–8 have been found to have anthelmintic properties. A number of 2,4-dimethoxy-6- or 8-arylquinolines have potent activity against the sheep nematode *Haemonchus contortus*, with LD_{99} values of the same order of magnitude as levamisole. These arylquinolines maintain their activity against levamisole-, ivermectin- and thiabendazole-resistant strains of *H. contortus*.
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Parasitic nematode infections are a continuing threat in both human and animal medicine. The most commonly used classes of drugs to treat such infections are the benzimidazoles, such as thiabendazole **1**, imidazo-thiazoles, such as levamisole **2**, and avermectins (obtained from the fermentation products of *Streptomyces avermitilis*). There is evidence of emerging resistance to some drugs in the developing world,[1] and in some areas with high agricultural dependence multiple resistance to all major drug classes is appearing in livestock.[2] Alternatives to these classes of drug are now being sought (see Fig. 1).

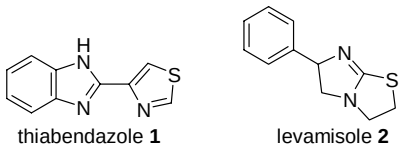

Figure 1.

We have recently published a concise synthesis of the phenylquinoline alkaloid atanine, **3**,[3] shown to be active against larval stages of the trematode parasite *Schistosoma mansoni*, the cause of schistosomiasis (bilharzia), a major health issue in developing countries (see Fig. 2).[4]

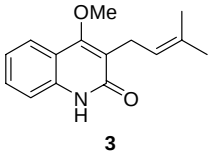

Figure 2.

As part of our programme of synthesis and testing of novel atanine analogues, we synthesized a number of intermediate trisubstituted quinolines with substituents in ring positions 5–8. Tests against *Sc. mansoni* larval stages and the model nematode *Caenorhabditis elegans* revealed that some of these intermediates exhibited anti-nematode activity, differing from the pattern of activity against schistosomes.[5]

From these early biological results, we became interested in aryl-substituted quinolines, and so we set out to investigate the synthesis of these novel 2,4-dimethoxy aryl-substituted quinolines by exploring the Suzuki coupling of 5-, 6-, 7- and 8-bromoquinoline intermediates.

Substituted 2,4-dimethoxyquinolines were synthesized by condensation/cyclization of the appropriately substituted

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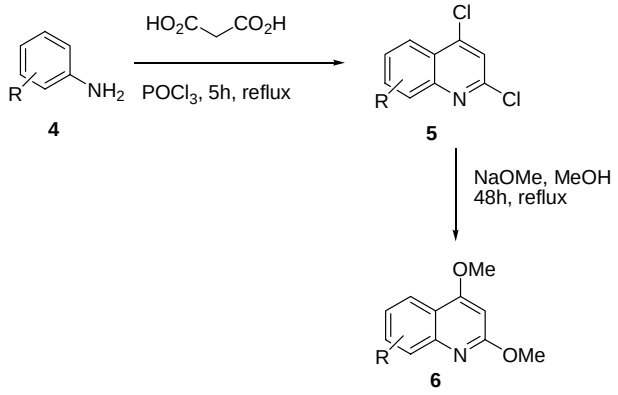
aniline **4** with malonic acid and phosphoryl chloride to give the 2,4-dichloroquinolines **5**, followed by displacement by methoxide ion to give the required quinolines **6** (Scheme 1).[6]

For our proposed synthesis of arylquinolines, the bromoquinoline precursors were required. The reaction of 3-bromoaniline gave a mixture of 5- and 7-bromoquinolines, which were separable by column chromatography (Table 1).

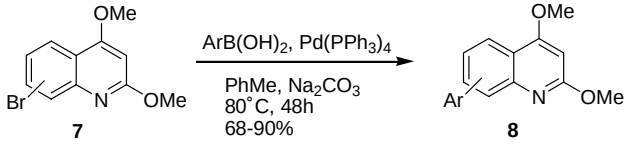


Scheme 1. Synthesis of substituted 2,4-dimethoxyquinolines.

Table 1. Yields of bromoquinolines **5** and **6** in Scheme 1

Entry	**4**	**5** (yield %)	**6** (yield %)
1	R = 2-Br	R = 8-Br (31)	R = 8-Br (64)
2[a]	R = 3-Br	R = 5-Br (6)	R = 5-Br (82)
		R = 7-Br (11)	R = 7-Br (76)
3	R = 4-Br	R = 6-Br (28)	R = 6-Br (93)

[a] 3-Bromoaniline led to a mixture of 5- and 7-bromoquinolines **5**. Yields refer to isolated, purified material.



Scheme 2. Synthesis of arylquinolines via Suzuki coupling.

The bromo-2,4-dimethoxyquinolines **7** were then coupled to the required aryl groups under Suzuki conditions[7] to yield the arylquinolines **8** (Scheme 2). They proceeded in good yield, although it was observed that 8-bromoquinolines were much more sensitive, requiring careful purification of substrate, reagents and solvent along with strictly oxygen-free reaction conditions to give consistent yields.[8]

A number of 2,4-disubstituted quinolines (ca. 80) were tested against the agriculturally important parasitic nematode *Haemonchus contortus*, using the commercial NemaTox larval development screen used for determining drug susceptibility.[9] It was observed that greater than 40% of these compounds exhibited nematocidal activity ($LD_{99} < 100$ μg/mL), with those exhibiting LD_{99} better than 25 μg/mL shown in Table 2.

In particular, it appeared that 6- and 8-substituted 2,4-dimethoxyquinolines showed the greatest activity against *H. contortus*. Five compounds, including the arylquinolines **13**–**16**, had LD_{99} of 12.5 μg/mL or lower in this first screen, showing potential for useful antinematode activity. The LD_{99} of compounds **15** and **16**, 3.1 μg/mL, was of the same order as the commercial nematocides, levamisole and closantel. These five most active compounds were resynthesized in gram quantities for further investigation (see Fig. 3).

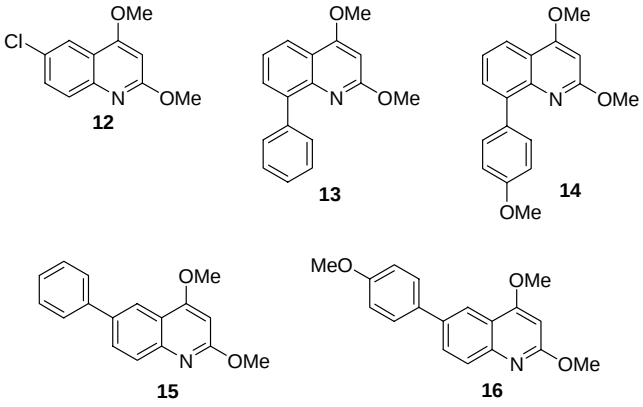


Figure 3.

Table 2. LD_{99} values for compounds **9**–**16** (substituted at positions 2–8) against *H. contortus*

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	LD_{99} (μg/mL)
9[a]	OMe	Ph	OMe	H	H	H	H	25
10	OMe	H	OMe	Me	H	Me	H	25
11[b]	Cl	H	OMe	H	H	H	H	25
12	OMe	H	OMe	H	Cl	H	H	12.5
13	OMe	H	OMe	H	H	H	Ph	12.5
14	OMe	H	OMe	H	H	H	4-MeO-C_6H_4	12.5
15	OMe	H	OMe	H	Ph	H	H	3.1
16	OMe	H	OMe	H	4-MeO-C_6H_4	H	H	3.1

[a] Synthesized from 2,4-dimethoxyquinoline by bromination at position 3 and subsequent Suzuki coupling.[5,10]
[b] Product of incomplete substitution of 2,4-dichloroquinoline by methoxide.

Table 3. LD_{99} values of compounds **12**–**16** against susceptible and drug-resistant nematodes

Compound	LD_{99} (μg/mL)					
	H. contortus susceptible	*H. contortus* VSRG, benzimidazole resistant	*H. contortus* Lawes, levamisole and benzimidazole resistant	*H. contortus* CAVR, ivermectin resistant	*T. colubriformis*	*O. circumcincta*
12	13	13	8.8	6.3	25	13
13	6.3	4.4	6.3	3.1	50	6.3
14	6.3	6.3	3.1	3.1	6.3	3.1
15	3.1	3.1	3.1	3.1	6.3	3.1
16	3.1	2.2	1.6	1.6	3.1	3.1
1	0.16	5	5	0.16	nt	nt
2	1.6	1.6	>100	0.78	nt	nt

nt, not tested.

Compounds **12**–**16** were tested against susceptible strains of *H. contortus*, strains resistant to benzothiazoles (VSRG strain), ivermectin (CAVR strain) or both benzothiazoles and levamisole (Lawes strain) plus susceptible strains of *Trichostrongylus colubriformis* and *Ostertagia circumcincta*. Results are shown in Table 3, with activities of thiabendazole **1** and levamisole **2** for comparison.

Of these compounds, **15** and **16** exhibited the greatest activity against susceptible strains of *H. contortus* (3.1 μg/mL), comparable in potency to levamisole. Compounds **15** and **16** were also active against the various drug-resistant strains of *H. contortus*, with **16** proving to be even more potent (LD_{99} 1.6 μg/mL) against both the multiple-resistant Lawes strain and the ivermectin-resistant CAVR strain. There is also evidence of activity against the important parasitic nematodes *T. colubriformis* and *O. circumcincta*.

In summary, we have prepared novel arylquinolines in good yield via Suzuki coupling of substituted bromoquinolines. We have demonstrated that a number of these quinolines, in particular the 6-arylquinolines **15** and **16**, show promising potency against susceptible and drug-resistant strains of an important nematode target and represent a new class of anthelmintic compounds. There is obvious potential for lead optimization and further development to offer a new line of defence against drug-resistant parasitic nematode infections.

Acknowledgments

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8. Synthesis of arylquinolines: typical procedure: 8-bromo-2,4-dimethoxyquinoline (0.4 g, 1.5 mmol) was dissolved in toluene (10 mL) under argon. Tetrakis-(triphenylphosphine)palladium (0) (52 mg, 3 mol%) and aqueous sodium carbonate (2 mL of a 2 M solution) were added, and the mixture was stirred for 5 min. Benzeneboronic acid (0.20 g, 1.7 mmol) in ethanol (1 mL) was added, and the mixture was then heated under reflux for 48 h. After cooling, the mixture was poured into a separating funnel, and the reaction flask was washed with water (20 mL) and ether (20 mL); the washings being added to the separating funnel. The aqueous layer was extracted with ether (3×20 mL), and the combined organic layers were dried over magnesium sulfate before removal of the solvent under reduced pressure. The crude product was purified by column chromatography (9:1 hexane–EtOAc) to yield 90% of 2,4-dimethoxy-8-phenylquinoline as white plates, mp (CH_2Cl_2/MeOH) 110–112 °C; found M^+: 265.1105, $C_{17}H_{15}NO_2$ requires 265.1103; ^1H NMR ($CDCl_3$): δ 8.16 (1H, dd, J 8.2, 1.5 Hz, H5), 7.90 (2H, dd, J 8.3, 1.5 Hz, H2′, H6′), 7.77 (1H, dd, J 7.2, 1.5 Hz, H7), 7.54 (2H, m, H6 and H4′), 7.47 (2H, dd, J 8.3, 7.2 Hz, H3′, H5′), 6.29 (1H, s, H3), 4.01 (3H, s, OMe), 3.99 (3H, s, OMe); ^{13}C NMR ($CDCl_3$): δ 164.5, 163.4 (C2, C4), 144.7, 140.4, 138.5 (C1′, C8, C8a), 131.3, 131.1, 127.9, 127.2, 123.5, 121.8 (C5, C6, C7, C2′–6′), 120.1 (C4a), 90.7 (C3), 56.2 (OMe), 53.8 (OMe); Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.91; H, 5.65; N, 5.19.
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