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2-Phenylimidazo[1,2-*b*]pyridazine derivatives highly active against *Haemonchus contortus*

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ABSTRACT

A series of 2-phenylimidazo[1,2-*b*]pyridazine derivatives were synthesized and evaluated for their in vitro anthelmintic activity against *Haemonchus contortus*. The most active compounds had in vitro LD_{99} values of 30 nM, which is comparable to that of the benchmark commercial nematocide, Ivermectin.

In many parts of the world the viability of small-ruminant production is under threat because of growing resistance to the limited number of current drugs used to treat infection by endoparasites, for example control of *Haemonchus contortus* in sheep.[1] Two recently introduced anthelmintics, Monepantel[2] and Derquantel,[3] are welcome, but new drugs are still urgently needed.[4]

In the course of our search for new anthelmintics based upon high-throughput screening of compounds in the commercial NemaTox *H. contortus* (McMaster strain) larval development assay,[5] we obtained the hit compound, 2-(3,4-methylenedioxyphenyl)-6-propoxy-imidazo[1,2-*b*]pyridazine **1**[6,7] (Fig. 1) which afforded an LD_{99} comparable to the commercial nematocide Levamisole (Table 1).

Importantly, compound **1** maintained activity against resistant strains of *H. contortus*: LD_{99} = 0.94 μM for the benzimidazole-resistant VRSG[8] strain, LD_{99} = 0.67 μM for the benzimidazole- and Levamisole-resistant Lawes strain, and LD_{99} = 1.85 μM for the Ivermectin-resistant CAVR[9] strain. Furthermore, compound **1** showed good activity against the McMaster strains of *Trichostrongylus colubriformis*, LD_{99} = 0.67 μM, and *Ostertagia circumcincta*, LD_{99} = 0.33 μM.

Exploration of SAR associated with compound **1** was aided by well-established synthetic routes to the imidazo[1,2-*b*]pyridazine template.[10] As outlined in Scheme 1, key steps in the preparation of compounds of this type involved reaction of 3-amino-6-chloropyridazine **2**[11] with a sodium alkoxide[4] or a sodium alkanethiolate salt[12] to give 3-amino-6-alkoxypyridazines **3** and 3-amino-6-alkylthio-pyridazines **4**, respectively. Reaction of these aminopyridazines with 2-bromoethanones **5** afforded the target 6-substituted imidazo[1,2-*b*]pyridazines **6** and **7**. Analogous reactions of **3** and **4** with 2-bromopropan-1-ones **8** provided the 3-methyl derivatives **9** and **10**.

The C-6 amino derivatives **13a–d** were obtained by heating 6-chloroimidazo[1,2-*b*]pyridazine **12**, prepared[6] from **2** and 2-bromo-1-[4-(2-methoxyethoxy)phenyl]-ethanone **11**,[13] with the appropriate amine.[14,15] The 6-*n*-butyl substituted compound **14** was obtained from **12** by a Ni-catalyzed coupling reaction with *n*-BuMgBr. The 6-aryl substituted derivatives **15** were prepared via Suzuki-coupling of aryl boronic acids with **12** using a published procedure.[16,17]

Compounds **6** and **7** were brominated with NBS in chloroform[18] to produce 3-bromo-substituted imidazo[1,2-*b*]pyridazine derivatives **16**. We also prepared 3-chloro derivatives **17** and 3-iodo derivatives **18**[17] using similar chemistry. The 3-iodo compounds were converted to the corresponding 3-cyanoimidazo[1,2-*b*]pyridazines **19** by treatment with cuprous cyanide in hot DMF.[19]

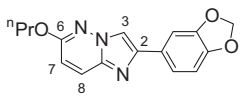

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Figure 1.

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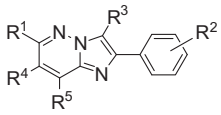
Table 1
In vitro anthelmintic activity of 2-phenylimidazo[1,2-*b*]pyridazines **1**, **6**, **7**, **9**, **10**, **13**–**22**, **24** against *H. contortus*



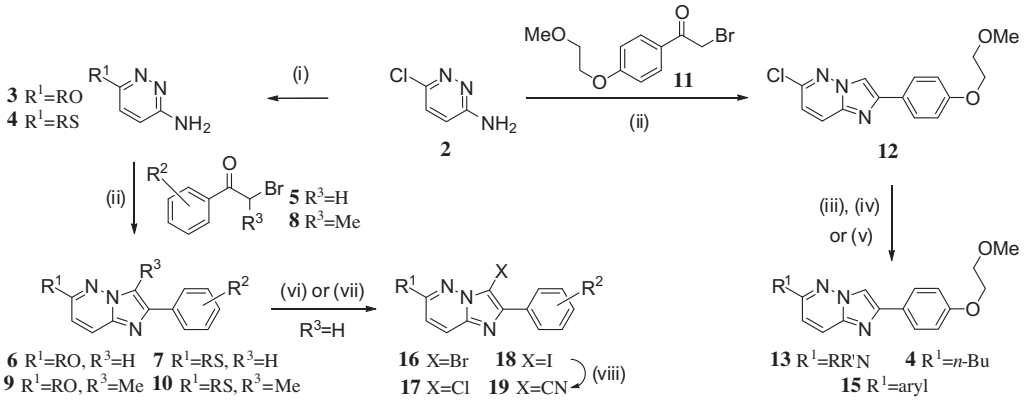
Compound	R^1	R^2	R^3	R^4	R^5	LD_{99}[a] (μM)
1	*n*-PrO	3,4-Methylenedioxy	H	H	H	0.77
6a	*n*-PrO	H	H	H	H	na
6b	*n*-PrO	4-Cl	H	H	H	13.03
6c	*n*-PrO	3-OMe	H	H	H	0.81
6d	*n*-PrO	3,4-diOMe	H	H	H	4.15
6e	*n*-PrO	3,4-Ethylenedioxy	H	H	H	2.60
6f	*n*-PrO	4-OCH_2CH_2OMe	H	H	H	0.29
6g	*n*-PrO	4-OCH_2CH_2OEt	H	H	H	0.32
6h	*n*-PrO	3-OMe–4-OCH_2CH_2OMe	H	H	H	2.27
6i	EtO	4-OCH_2CH_2OMe	H	H	H	1.30
6j	*n*-BuO	4-OCH_2CH_2OMe	H	H	H	0.64
6k	Cyclopropylmethoxy	4-OCH_2CH_2OMe	H	H	H	0.11
6l	Cyclopropylmethoxy	4-OCH_2CH_2OEt	H	H	H	0.11
6m	Cyclopropylmethoxy	4-OEt	H	H	H	0.09
6n	Cyclopropylmethoxy	4-CF_3	H	H	H	na
6o	Cyclopropylmethoxy	2,4-diCl	H	H	H	na
6p	Cyclopropylmethoxy	4-Et	H	H	H	0.27
6q	Cyclopentyloxy	4-OCH_2CH_2OMe	H	H	H	5.31
6r	*i*-PrO	4-OCH_2CH_2OMe	H	H	H	4.96
6s	$MeOCH_2CH_2O$	4-OCH_2CH_2OMe	H	H	H	17.47
7a	*n*-PrS	4-OEt	H	H	H	1.21
7b	*n*-PrS	3-OMe	H	H	H	2.10
7c	*n*-PrS	4-OCH_2CH_2OMe	H	H	H	2.36
7d	*n*-PrS	3-OMe-4-OCH_2CH_2OMe	H	H	H	2.17
7e	*n*-BuS	4-OCH_2CH_2OMe	H	H	H	0.26
7f	*n*-BuS	4-OCH_2CH_2OEt	H	H	H	0.59
7g	*i*-PrS	4-OCH_2CH_2OMe	H	H	H	0.59
7h	*i*-BuS	4-OCH_2CH_2OMe	H	H	H	0.87
7i	*n*-BuS	4-CF_3	H	H	H	na
7j	*n*-PrS	2,4-diCl	H	H	H	na
9a	*n*-PrO	4-OCH_2CH_2OMe	Me	H	H	0.32
9b	*n*-PrO	3-OCH_2CH_2OMe	Me	H	H	5.49
9c	*i*-PrO	3-OCH_2CH_2OMe	Me	H	H	14.65
10	*i*-PrS	3-OCH_2CH_2OMe	Me	H	H	19.58
13a	Pyrrolidino	4-OCH_2CH_2OMe	H	H	H	9.60
13b	*n*-PrNH	4-OCH_2CH_2OMe	H	H	H	2.11
13c	*n*-Bu(Me)N	4-OCH_2CH_2OMe	H	H	H	2.29
14	*n*-Bu	4-OCH_2CH_2OMe	H	H	H	1.92
15a	Ph	4-OCH_2CH_2OMe	H	H	H	8.11
15b	3-Thienyl	4-OCH_2CH_2OMe	H	H	H	1.96
16a	*n*-PrO	4-OCH_2CH_2OMe	Br	H	H	0.03
16b	Cyclopropylmethoxy	4-OCH_2CH_2OMe	Br	H	H	0.10
16c	*n*-PrS	3-OMe-4-OCH_2CH_2OMe	Br	H	H	1.66
17a	*n*-PrO	4-OCH_2CH_2OMe	Cl	H	H	0.06
17b	BnO	4-OCH_2CH_2OMe	Cl	H	H	na
18a	*n*-PrO	4-OCH_2CH_2OMe	I	H	H	0.03
18b	*n*-PrO	3-OMe–4-OCH_2CH_2OMe	I	H	H	10.35
19a	*n*-PrO	4-OCH_2CH_2OMe	CN	H	H	0.11
19b	*n*-PrO	3-OMe–4-OCH_2CH_2OMe	CN	H	H	na
20a	*n*-PrO	4-OCH_2CH_2OMe	H	Me	H	0.32
20b	*n*-PrO	4-OEt	H	Me	H	0.60
21a	*n*-PrO	4-OCH_2CH_2OMe	H	Fused	Phenyl	0.91
21b	*n*-PrO	4-OEt	H	Fused	Phenyl	1.80
22	*n*-PrO	4-OCH_2CH_2OMe	Ph	H	H	9.29
24	H	4-OCH_2CH_2OMe	H	H	H	na
Levamisole						0.66–2.00
Ivermectin						0.006–0.031

[a] na = not active (LD_{99} >15 μg/mL).

The 7-methyl compounds **20** (Fig. 2) were synthesized by reaction of 3-amino-5-methyl-6-propoxypyridazine (prepared from 3-amino-6-chloro-5-methylpyridazine[20]) with the appropriate 2-bromo-1-(4-alkoxyphenyl)ethanone. Analogous chemistry with 1-amino-4-chlorophthalazine[20] gave compounds **21** (Fig. 2).

The 3-phenyl derivative **22** (Fig. 2) was obtained from the corresponding 3-iodo compound **18a** by a Suzuki-coupling reaction.[16,17]

The results from the screening of compound **1** and a range of examples of compounds of type **6**, **7**, **9**, **10**, **13**–**22**, and **24** in the



Scheme 1. Reagents and conditions: (i) ROH, Na, 130 °C or RSH, NaOH, H_2O, 130 °C; (ii) $NaHCO_3$, EtOH, reflux; (iii) R^4R^5NH, heat; (iv) *n*-BuMgBr, cat. $[Ph_2P(CH_2)_3PPh_2{\cdot}NiCl_2]$, THF, rt; (v) $R^1B(OH)_2$, cat. $Pd(PPh_3)_4$, NaOH, DME, H_2O, 75 °C; (vi) NBS or NCS, $CHCl_3$, reflux; (vii) NIS, CH_3CN, rt; (viii) CuCN, DMF, 100 °C.

NemaTox *H. contortus* larval development assay are shown in Table 1. Removal of the 3,4-methylenedioxyphenyl substituent at position 2 in **1** led to loss of activity, since compound **23** (Fig. 2), prepared from reaction of 3-amino-6-propoxypyridazine[6] and bromoacetaldehyde diethyl acetal,[21] was inactive. Replacement of the 3,4-methylenedioxyphenyl substituent by unsubstituted phenyl (compound **6a**) or 4-chlorophenyl (**6b**) or 4-trifluoromethylphenyl (**6n**) likewise led to striking loss of activity, indicating that an electron-rich C-2 phenyl substituent was desirable. Removal of the propoxy substituent at position 6 led to dramatic loss of activity (compound **24**, Table 1).

Replacement of the potentially metabolically- and chemically-labile methylenedioxy moiety of compound **1** by 3,4-dimethoxy substitution (**6d**) or an ethylenedioxy moiety (**6e**) resulted in weaker activity; however, replacement of the methylenedioxy moiety by non-classical isosteric alkoxyethoxy substituents[22,23] (compounds **6f** and **6g**) or an ethoxy group (**6m**) led to a significant improvement in activity.

Further improvement in activity was observed when the propoxy substituent at C-6 was replaced by a cyclopropylmethoxy group (**6k**). Shortening or lengthening the C-6 alkoxy group resulted in lesser activity (**6i**, **6j**) and incorporation of secondary alkoxy groups (**6q**, **6r**) led to poor activity. The activity of the 6-alkylthio-imidazo[1,2-*b*]pyridazines **7** followed a similar trend (though generally slightly less potent) to that of the 6-alkoxy analogues.

The relatively good activity of the 3-methyl imidazo[1,2-*b*]pyridazine derivative **9a** compared with analogues **9b**, **9c** and **10** indicated that having the 2-methoxyethoxy substituent at the 4-position of the C-2 phenyl moiety generally resulted in better activity than when the substituent is at the 3-position.

The 6-amino derivatives **13** showed reasonable activity (though less potent than the 6-alkoxy or 6-alkylthio compounds), with the *n*-propylamino derivative **13b** being the most active.

The 6-butyl compound **14**, the direct C-linked analogue of the highly active propoxy derivative **6f**, showed good activity against *H. contortus*, as did the 6-(3-thienyl) substituted derivative **15b**. The 6-phenyl analogue **15a** was much less potent, suggesting that the presence of the heteroatom may be significant.

Compounds **20** and **21** also showed good activity with the 7-methyl compounds **20** being superior to the corresponding phthalazine derivatives **21**, indicating that in order to maintain high activity, minimal steric bulk should be incorporated at positions 7 and 8 of the imidazo[1,2-*b*]pyridazine core.

The 3-substituted imidazo[1,2-*b*]pyridazine derivatives **16–19** showed very potent activity. The LD_{99} value of 30 nM for each of

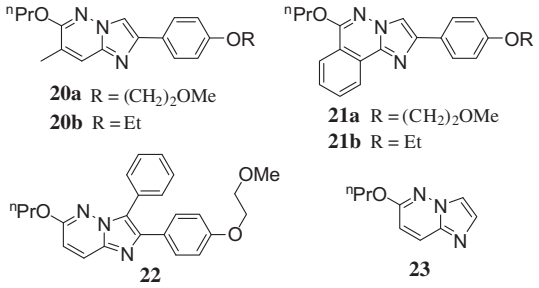


Figure 2.

the 3-bromo compound **16a** and the 3-iodo derivative **18a** is comparable to the level of activity associated with the Ivermectin class of commercial endoparasiticides.

The 3-cyano derivative **19a** also showed good activity while the activity of 3-phenyl derivative **22** was relatively poor. The results from compounds **16–19** and **22** indicate that for strong activity the 3-substituent should be electron-withdrawing and not too large.

In conclusion, we have discovered a class of compounds that are highly active in a *H. contortus* larval development assay. For high activity, 6-*n*-propoxy or 6-cyclopropylmethoxy, and 2-(4-[2-methoxyethoxy])phenyl substituents appear preferable: see (in Table 1) compounds **6f**, **6k**, **9a**, **16a**, **16b**, **17a**, **18a** and **20a**, which show a level of activity superior to Levamisole. The potent activity of the 3-halo derivatives **16a** and **18a** is comparable to that of the benchmark commercial product, the macrocyclic lactone Ivermectin.

There remains scope for further exploration of the imidazo[1,2-*b*]pyridazine template which may lead to compounds useful for treatment of helminth infections in animals.

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Supplementary data

Supplementary data (representative synthetic procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.05.096.

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