Synthesis and structure–activity relationships for anticipated molluscicidal activity of some 2-amino-5-substituted pyridine derivatives

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Abstract: A series of 2-amino-5-substituted pyridine derivatives was synthesized and their molluscicidal activity against white garden, *Theba pisana* (Müller), and brown garden, *Helix aspersa* (Müller), snails was investigated by two methods of application. Some of these compounds showed strong activity under laboratory conditions against the two types of snail. *T pisana* was more sensitive to the tested compounds than *H aspersa*. The most effective compounds were 2-amino-5-(benzotriazole-1-ylmethyl)-3-methylpyridine, 2-amino-5-[1-(benzotriazole-1-yl)nonyl]-3-methylpyridine and 2-[(1,2,4-triazole-1-ylmethyl)amino]-3-methylpyridine which exhibited high molluscicidal activity. The toxicity results are discussed in relation to the chemical structures.

Keywords: 2-amino-5-substituted pyridines; molluscicidal activity; structure–activity relationship; *Theba pisana*; *Helix aspersa*

1 INTRODUCTION

Terrestrial gastropod mollusca continue to be serious agricultural pests. Today, control of these pests with chemical substances is still regarded as the most successful method, particularly over large areas. Of the many substances which have been officially tested for the control of land gastropods, metaldehyde and methiocarb are the most useful and form the active ingredients of many commercial formulations.[1] However, the problems associated with the use of metaldehyde have not yet been solved, and so many commercial pesticides and experimental compounds have been investigated for their molluscicidal effects under laboratory and field conditions to try to identify a potential replacement.[2–4]

The high insecticidal activity of pyridine alkaloids, nicotine, nornicotine and anabasine,[5] has led to the synthesis and examination of many analogues and in particular to a study of the effects of nuclear and side-chain substitution on biological activity. The patent literature contains an enormous number of pyridine derivatives that have diverse pesticidal activity, including insecticides,[6] fungicides,[7] bactericides,[8] herbicides,[9] nematicides,[10] acaricides[11] and algicides.[12] No trials on the molluscicidal activity of pyridines against land gastropods have been reported, and only 4-aminopyridine has been tested on the freshwater snail, *Limnaea stagnalis* (L) for blocking of the fast potassium current.[13] However, no other pyridine derivatives have been screened and/or developed as commercial molluscicides. Thus, we have synthesized a series of 2-amino-5-substituted pyridine derivatives according to our recently reported and versatile procedure,[14] in order to evaluate their possible molluscicidal activity under laboratory conditions by two methods of application, discussing aspects of the relationship between chemical structure and molluscicidal activity.

2 EXPERIMENTAL METHODS

2.1 General experimental procedures

[^{1}H] and [^{13}C]NMR spectra were recorded on a Varian spectrometer at 300 MHz and 75 MHz respectively using tetramethylsilane as an internal reference for [^{1}H] spectra in hexadeutero dimethyl sulfoxide; melting points were measured with a Kofler hot-stage apparatus and were uncorrected. A Carlo Erba-1106 instrument (CHN analysis) and a AEL MS-30 mass spectrometer were also used.

2.2. Synthesis

The sequence of the reactions leading to the synthesis of 2-amino-5-substituted pyridine derivatives in this study is outlined in Fig 1. 1-Hydroxymethyl-1*H*-benzotriazole (**1**) was reacted with 2-aminopyridines in presence of acetic acid and a catalytic amount of *p*-toluenesulfonic acid to give the benzotriazole adduct **2**. The methylene group of **2** can be mono- or di-lithiated and subsequently substituted by various

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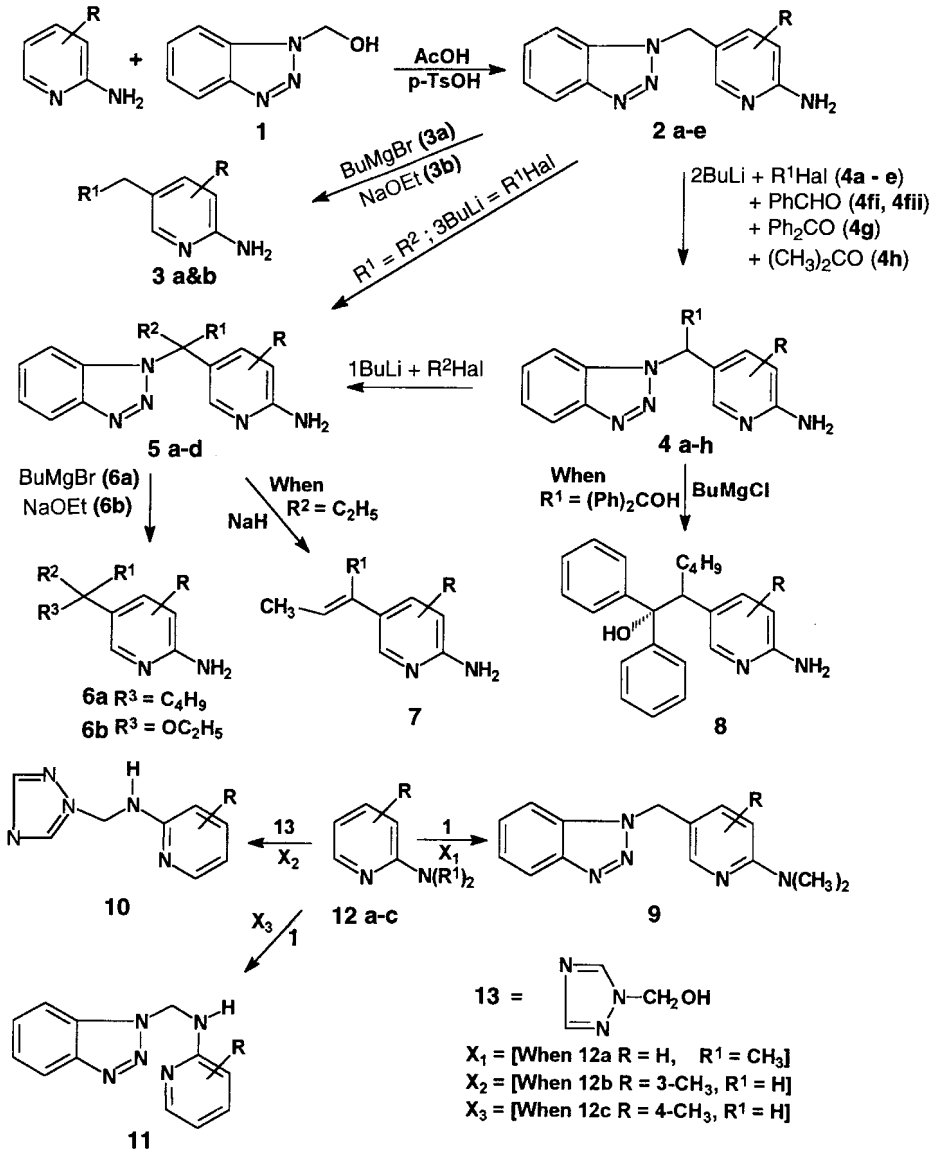

Figure 1. Overall synthetic routes to 2-amino-5-subsituted pyridine derivatives.

electrophiles. The benzotriazole moiety in both the primary products **2** and in their methylene substituted derivatives **4** and **5**, is displaced by alkyl, aryl, and or alkoxy anions, as described in our previous paper.[14]

*2.2.1 General procedure for the synthesis of compounds **2a–e** and **9***

A mixture of 1-(hydroxymethyl)-1*H*-benzotriazole (3.75 g, 25 mmol), the corresponding 2-aminopyridine or 2-(dimethylamino)pyridine (25 mmol) and a catalytic amount of toluene-*p*-sulfonic acid in acetic acid (25 ml) was heated under reflux for 72 h. The acetic acid was removed under reduced pressure, and aqueous sodium carbonate was added to the residue. The product was extracted with ethyl acetate (4 × 80 ml), washed with aqueous sodium hydroxide, then water (80 ml), and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the solid was chromatographed with chloroform + ethyl acetate (10 + 1 by volume) to give the pure compounds.

*2.2.2 General procedure for synthesis of compounds **4a–h** and **5a–d***

To a solution of 2-amino-5-(benzotriazole-1-yl-methyl)pyridine (**2b**, **2c** or **2e**; 5 mmol) in tetrahydrofuran (THF; 100 ml) at −78 °C was added butyl lithium (for **5a–d**, 15 mmol; for compounds **4a–h**, 10 mmol) under nitrogen. The mixture developed an intense greenish–blue colour immediately. The solution was stirred for 15 min at this temperature and the electrophile (for **5a–d**, 10 mmol and for **4a–h**, 5 mmol of the appropriate alkyl halide; for **4fi** and **4fii**, benzaldehyde; **4g** benzophenone, and **4h**, acetone) was added. The mixture was kept at this temperature for a further 15 min. Water (50 ml) was then added to the mixture at −78 °C, and the solution was extracted with diethyl ether (3 × 150 ml), washed with water and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silica gel with methylene chloride + hexane (1 + 1 by volume) as the eluent. In the case of **5b**, lithiation was carried out in a stepwise procedure: 2 equiv of BuLi

were added to the solution of **2b** and 1 equiv of ethyl bromide. After 15 min, a further 1 equiv of BuLi and 1 equiv of propyl bromide were added. The temperature for the whole process was kept at −78 °C and the work-up was as described above.

*2.2.3 General procedure for the synthesis of compounds **3b** and **6b***

To butanol or ethanol (20 ml) was added sodium metal (2.3 g, 100 mmol). On complete dissolution of the metal, the benzotriazole adduct **2d** or **5a** (5 mmol) was added in one portion and the solution was refluxed for 5 h. Evaporation of the solvent gave a residue which was dissolved in water and extracted with ethyl acetate (3 × 60 ml). The organic extracts were washed with water (50 ml) and dried over magnesium sulfate. Evaporation of the solvents gave a residue which was chromatographed with hexane + dichloromethane (1 + 1 by volume) to give the desired product.

*2.2.4 General procedure for the synthesis of compounds **3a, 6a** and **8***

To a solution of benzotriazole adducts **2b**, **5a** or **4g** (5 mmol) in THF (50 ml) under nitrogen was added butyl magnesium bromide (Grignard reagent 40 mmol); in diethyl ether (20 ml). The diethyl ether was distilled off and the mixture was refluxed for 8 h. The reaction was monitored by TLC until the starting material had been consumed. The reaction mixture was then allowed to cool, poured into ice-water (30 ml), acidified to pH 9 with hydrochloric acid (2M) and extracted with diethyl ether (3 × 60 ml). The ether solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml) and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography with hexane + dichloromethane (1 + 1 by volume).

*2.2.5 Synthesis of 2-amino-5-(1-ethylprop-1-enyl)-3-methylpyridine **7***

To a solution of 2-amino-5-[1-(benzotriazol-1-yl)-1-ethylpropyl]-3-methylpyridine **5a** (1.50 g, 5 mmol) in THF (40 ml) was added NaH (0.24 g, 10 mmol) in one portion. The solution was refluxed for 4 h, cooled to room temperature and water (30 ml) added. The solution was extracted with ethyl acetate (3 × 30 ml), washed with aqueous sodium hydrogen carbonate, and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed with hexane + dichloromethane (3 + 1 by volume) to give the desired product as a yellowish oil.

*2.2.6 Synthesis of 2-[(1,2,4-triazole-1-ylmethyl)amino]-3-methylpyridine **10***

A mixture of 1-hydroxymethyl-1,2,4-triazole **13** (2 g, 20 mmol) and 2-amino-3-methylpyridine **12b** (2.70 g, 25 mmol) was heated in ethanol (50 ml) under reflux for 20 h. The solvent was distilled off, and the solid product was recrystallized from ethanol.

*2.2.7 Synthesis of 2-[(benzotriazole-1-ylmethyl)amino]-4-methylpyridine **11***

A mixture of 1-hydroxymethylbenzotriazole **1** (3.75 g, 25 mmol) and 2-amino-4-methylpyridine **12c** (2.70 g, 25 mmol) was heated in ethanol (50 ml) under reflux for 20 h. The solvent was distilled off, and the solid product was recrystallized from ethanol.

The yields and melting points of the above compounds are given in Table 1.

2.3 Molluscicidal tests

2.3.1 Test animals

Specimens of the herbivorous snails, *Theba pisana* (Müller) and *Helix aspersa* (Müller) were collected during autumn 1998, from untreated nursery plants and farms in Alexandria governorate, Egypt. The snail species used in these studies were selected on the basis of their geographical distribution and economy of the crops they damage and identified according to the key given by Godan.[1] Adult animals were chosen and allowed to acclimatize to laboratory conditions for three weeks and were fed on bran bait *ad libitum*.

2.3.2 Test chemicals

Stock solutions of each compound, including methiocarb as a reference, were prepared in dimethyl sulfoxide (DMSO), which causes little distress to slugs and has been shown to be the most appropriate solvent for the topical application,[16] and serially diluted with the same solvent to achieve the desired concentrations.

2.3.3 Bioassay techniques

2.3.3.1 Topical application. (Contact toxicity). The method of Hussein *et al*[17] was used because it is easy, reproducible, and allows rapid screening of large numbers of chemicals that may be used by spray application. Preliminary experiments were carried out to establish the range of dosage of the tested chemicals. Six different concentrations, ranging from 5.0 to 25 g litre^{-1} for each compound were prepared and three replicates (10 animals for each) were kept in 0.5-litre glass jars covered with cloth netting and secured with a rubber band to prevent snails from escaping. Control snails were treated with DMSO. The tested dose was gently applied to the surface of the snail body inside the shell using a micropipet containing 30 µl in the case of *H aspersa* and 5 µl in the case of *T pisana*. Snails were provided with lettuce leaves to feed on 24 h after treatment. Dead animals were detected 24, 48, and 72 h after treatment by loss of response to a thin stainless steel needle according to the WHO procedure.[18] Pure methiocarb (Mesurol, Bayer Co) was used as a standard molluscicide.

2.3.3.2 Toxic baits (Stomach toxicity). Bran baits containing 10 and 20 g kg^{-1} of the tested pyridine derivatives were used for trials, after preliminary tests had revealed that more than 20 g kg^{-1} baits discouraged feeding by snails. The preparation of the bran baits was carried out according to the method of El-Sebae *et al*[19]

Compound	R	R^1	R^2	Yield (%)	mp (°C)
2a	H	–	–	53	183–185
2b	3-CH_3	–	–	73	174–175
2c	4-CH_3	–	–	60	213–214
2d	6-CH_3	–	–	62	208–210
2e	4,6-$(CH_3)_2$	–	–	61	247–249
3a	3-CH_3	C_4H_9		77	Oil
3b	6-CH_3	OC_4H_9		70	45–47
4a	3-CH_3	C_2H_5	–	60	152–153
4b	3-CH_3	iC_3H_9	–	78	192–193
4c	3-CH_3	$(CH_2)_2CH(CH_3)_2$	–	61	136–137
4d	3-CH_3	C_8H_{17}	–	65	106–107
4e	4,6-$(CH_3)_2$	C_2H_5	–	59	183–184
4fi	3-CH_3	$C_6H_5CH(OH)$	–	36	223–225
4fii	3-CH_3	$C_6H_5CH(OH)$	–	17	262–264
4g	3-CH_3	$(C_6H_5)_2COH$	–	72	280–281
4h	3-CH_3	$(CH_3)_2COH$	–	69	227–230
5a	3-CH_3	C_2H_5	C_2H_5	85	161–162
5b	3-CH_3	C_3H_7	C_2H_5	60	78–81
5c	4-CH_3	$(CH_2)_2CH(CH_3)_2$	$(CH_2)_2CH(CH_3)_2$	78	180–181
5d	3-CH_3	C_8H_{17}	C_8H_{17}	81	100–101
6a	3-CH_3	C_2H_5	C_2H_5	83	34–36
6b	3-CH_3	C_2H_5	C_2H_5	72	44–46
7	3-CH_3	C_2H_5	–	58	Oil
8	3-CH_3	–	–	70	168–170
9	H	–	–	56	164–165
10	3-CH_3	–	–	85	157
11	4-CH_3	–	–	90	163[b]

Table 1. Characteristics of 2-amino-5-substituted pyridine derivatives[a]

[a] See Fig 1 for structures.
[b] Literature (Reference 15) 157–158 °C.

and they were tested for molluscicidal activity against *T pisana* snails. For each treatment, three glass jars (0.5 litre) containing 10 adult snails per jar, and tightly covered with cloth netting secured with a rubber band were used. Three jars were also prepared for the control group containing bran bait free of chemicals. Two millilitres of water were added daily into each jar to provide suitable humidity for snail activity. Mortality counts were recorded daily up to 10 days and the dead snails were removed.

2.3.3.3 Statistical procedure. Percentage mortality was corrected by Abbott's formula.[20]

LD_{50} (μg per snail) values with fiducial limits for each treatment were determined by the probit-analysis method of Finney.[21]

3 RESULTS AND DISCUSSION

The performance of molluscicides against terrestrial gastropods is greatly affected by the method of application, which determines their ability to penetrate to the sites of action,[22] and by species-specific differences in the effect of the molluscicidal itself.[23]

The molluscicidal activity of 2-amino-5-substituted pyridine derivatives has been evaluated by a contact method against *H aspersa* and *T pisana* (Table 2) and as toxic baits against *T pisana* (Table 3) and compared with methiocarb as a standard.

The results of tests on 2-amino-5-substituted pyridine derivatives which are presented in Table 2 against the two tested snails by topical application showed that there are some promising compounds which could be developed in this area. Most of the tested compounds showed excellent activity particularly against *T pisana*. The structure–activity relationship studies of pyridine derivatives revealed that methyl substitution on the pyridine ring, particularly at the 3-position **(2b)**, increased the activity against *H aspersa* except for the 4-methyl analogue **(2c)**, but, the activity was decreased against *T pisana* snails, when compared with the unsubstituted compound **(2a)**, apart from **2b**, which showed increased activity over methiocarb in both tests, indicating that the 3-position is necessary for molluscicidal activity. On the other hand, 4,6-dimethyl substitution **(2e)** showed, moderate toxicity, ranking between compounds **2d** and **2c** against *H aspersa* but **2e** was the least effective analogue among compounds of type **2** against *T pisana*. Surprisingly, linkage of methyl to the amino group or linking the benzotriazole at this point reduced molluscicidal activity (**2a** versus **9** & **2c** versus **11**). On the other hand, replacing the benzotriazole in compound **11** with a triazole ring led to a potent compound, **10**, with $LD_{50} = 89.26$ and 260.77 μg per snail against *T pisana* and *H aspersa*, respectively. The corresponding LD_{50} values for methiocarb were 107.34 and 210.27 μg per snail. Substitution with a straight or

Compound	LD_{50} (μg per snail) at 48h with 95% Fiducial Limits[a]			
	H aspersa		*T pisana*	
2a	635.02	(573.95–702.60)	81.14	(73.96–97.52)
2b	118.78	(106.32–132.81)	60.65	(50.22–73.23)
2c	674.70	(600.38–758.26)	106.92	(92.45–145.55)
2d	354.16	(295.16–424.90)	132.47	(116.32–150.17)
2e	539.76	(459.59–633.93)	217.11	(137.48–381.70)
3a	560.32	(509.24–616.52)	58.10	(37.19–76.71)
3b	544.81	(490.91–604.62)	65.74	(59.82–79.49)
4a[b]		>750	47.30	(37.27–59.95)
4b	342.97	(223.79–479.78)	98.06	(81.22–118.34)
4c	136.81	(106.74–230.22)	165.13	(104.46–180.41)
4d	306.50	(266.75–386.31)	81.70	(65.49–89.29)
4e[b]		>750	85.77	(76.04–96.75)
4fi	518.59	(424.67–633.31)	72.53	(54.82–95.86)
4fii[b]		>750	178.93	(137.62–227.61)
4g	629.47	(561.72–705.42)	614.46	(502.83–751.15)
4h	336.68	(289.11–392.04)	104.18	(89.34–130.45)
5a[b]		>750	83.18	(78.13–97.73)
5b	460.72	(418.82–506.79)	109.88	(93.35–112.25)
5c	342.02	(238.68–454.40)	235.89	(202.96–274.13)
5d[b]		>750	330.89	(296.02–481.44)
6a	376.99	(339.26–418.91)	96.77	(79.83–117.25)
6b	524.33	(432.15–637.75)	76.29	(69.10–93.07)
7	317.13	(265.35–473.67)	59.68	(48.22–79.86)
8	582.05	(473.44–615.67)	129.00	(105.50–157.66)
9[b]		>750	121.47	(106.61–150.74)
10	260.77	(216.18–314.54)	89.26	(66.24–103.29)
11[b]		>750	365.79	(337.60–444.55)
Methiocarb	210.72	(189.20–244.90)	107.34	(87.83–124.35)
Control	0% mortality at 48h			

Table 2. Molluscicidal activity of 2-amino-5-substituted pyridine derivatives against *Helix aspersa* and *Theba pisana* by topical application

[a] $n = 30$, in three replicates of 10 each.

[b] LD_{50} values for compounds **4** (**a**, **e** & **fii**), **5** (**a** & **b**); **9** and **11** were not calculated because of the low percentage mortalities, ≤20% at the highest dose against *H aspersa*.

branched carbon chain on the methylene bridge as R^1 reduced activity against *H aspersa* compared to the unsubstituted compound (**4a**–**c** versus **2b** & **4e** versus **2e**). However, lengthening this chain up to C_5 gradually increased the activity against *H aspersa* (**4a**–**c**), but the activity (**4d**) decreased again with chains greater than C_5. Moreover, substitution (R^1) with phenyl ring (s) diminished the activity, as shown in compounds **4fi**, **4fii** versus **2b**, and this activity was highly affected by the orientation of the hydroxy group in the two diastereoisomers **4fi** and **4fii**. On the other hand, when R^1 was converted from two phenyls to methyls (**4g** versus **4h**), the molluscicidal activity, was enhanced.

Additional substituents on the methylene bridge as R^2 with ethyl (**5a** versus **4a**), isopropyl (**5b** versus **4b**), isobutyl (**5c** versus **4c**), and octyl groups (**5d** versus **4d**) continuously reduced activity against *H aspersa*. The activity patterns of the R^1 substituents were reversed in case of *T pisana*, but, additional substituents as R^2 reduced the activity in the same way as with *H aspersa*.

Removing the benzotriazole from the molecule **(5a)** led to an increase in activity **(7)**. However, replacement of the benzotriazole moiety in compounds of type **2** with a butyl or butoxy group (**2b** versus **3a** or **3b**), respectively, led to a reduction in the molluscicidal activity except in compound **2b** versus **3a** against *T pisana*. However, replacing the benzotriazole in compounds of type **5** (R^1, R^2) with the same groups (**5a** versus **6a** or **6b**) increased molluscicidal action. Replacement of benzotriazole in compound **4g** with a butyl group gave compound **8**, which was more active.

Table 3 shows the comparative toxicities after 10 days of the tested chemicals as 10 and 20 g kg^{-1} bran baits against *T pisana*. Interpretation of the structure–activity relationships against *T pisana*, indicated that the addition of a methyl group to the pyridine ring gave the highest level of the activity at position-3 only **(2b)**, and, the other analogues **2c**, **2d** and **2e** were less active against *T pisana*, except compound **2d** as 20 g kg^{-1} bait, which achieved 100% mortality. As in the topical test (Table 2), addition of methyl at the amino group reduced activity (**2a** versus **9**). Nevertheless, adding hydroxymethybenzotriazole instead of methyl gave a slight increase of acivity (**2c** versus **11**) and replacing benzotriazole with a triazole ring (**11** versus **10**) increased the molluscicidal activity above that of methiocarb as 20 g kg^{-1} bait.

Substitution at the methylene bridge with an alkyl

Table 3. Efficacy of 2-amino-5-substituted pyridine derivatives as bran bait against *Theba pisana* snails

Compound	Mortality of snails exposed to bran bait (%) (±SE)[a]	
	10 g kg^{-1} bait	20 g kg^{-1} bait
2a	83.33 (±1.67)	60.00 (±1.29)
2b	86.67 (±1.24)	100
2c	23.33 (±3.16)	53.33 (±2.09)
2d	20.00 (±2.24)	100
2e	0.00	30.00 (±3.65)
3a	NT[b]	NT
3b	0.00	20.00 (±3.87)
4a	40.00 (±2.74)	63.33 (±1.45)
4b	56.67 (±2.03)	23.33 (±3.16)
4c	56.67 (±3.07)	20.00 (±3.87)
4d	73.33 (±1.35)	46.67 (±3.68)
4e	NT	NT
4fi	66.67 (±1.87)	73.33 (±1.78)
4fii	13.33 (±1.58)	20.00 (±2.24)
4g	40.00 (±1.58)	40.00 (±2.74)
4h	46.67 (±0.84)	26.67 (±1.12)
5a	60.00 (±2.24)	83.33 (±1.67)
5b	43.33 (±2.32)	80.00 (±1.12)
5c	NT	NT
5d	40.00 (±1.58)	0.00
6a	0.00	20.00 (±2.24)
6b	0.00	20.00
7	0.00	23.33 (±3.16)
8	NT	NT
9	46.67 (±3.05)	53.33 (±2.85)
10	63.33 (±0.72)	100
11	36.67 (±0.95)	56.67 (±0.77)
Methiocarb	66.67 (±0.71)	53.33 (±1.58)
Control	0.00	3.33 (±3.16)

[a] $n = 30$ in three replicates of 10 each.
[b] NT = Not tested.

group as R^1 reduced the activity in both 10 and 20 g kg^{-1} bran baits compared to the unsubstituted compound (**4a**–**d** versus **2b**), but lengthening this alkyl group increased activity. Furthermore, the phenyl substituents greatly reduced the activity (**4fii** diastereoisomer versus **2b**). Additional substitution at the methylene bridge as R^2 with ethyl increased activity in the 20 g kg^{-1} bran bait over the standard (**4a** versus **5a** & **4b** versus **5b**), but the opposite activity was observed in both bran baits when the octyl group was introduced **(5d)**. Removing or displacing of benzotriazole with butyl or butoxy from the molecule (**2b** versus **3b** and **5a** versus **6a**, **b** & **7**), also reduced activity (Table 3).

Comparing the results of the topical application with those of the bran bait test, compound **4a** was apparently the most effective among the tested chemicals against *T pisana* in topical application (Table 2) and gave relatively satisfactory control in the bait test (Table 3). Also, the results obtained showed that compounds **3b**, **6a**, **6b** and **7**, which are free of benzotriazole, were more active than methiocarb in topical application, but showed unimpressive effects in the bait test (Tables 2 and 3). These results may suggest that compounds such as **3b**, **6a**, **6b** and **7** were more effective as a contact poison than a stomach poison under laboratory conditions.

In conclusion, the comparative study of the activity of the different compounds in relation to their structures against *T pisana* snails showed that the introduction of the methyl group at pyridine ring at position 3 seems to be necessary for activity in the two tests used. Introducing the ethyl group as R^1 increased toxicity in topical application but decreased it in the bran bait test (**4a** versus **2b**), while the opposite was found with the additional introduction of another ethyl group as R^2 (**4a** versus **5a**). Replacement of the ethyl group by isopropyl, isobutyl or octyl as R^1 reduced activity (**4b**, **4c**, or **4d** versus **2b**) as did an octyl group at R^2 (**4d** versus **5b**) in both tests. The results obtained in the present study show a number of promising compounds, e g **2b**, **4d** and **10**, that could replace methiocarb for land snail control when administered topically or as a bran bait.

Our efforts are now directed towards optimizing the molluscicidal activity of the most promising compounds and some structural modifications are under investigation that will be described in a future publication.

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REFERENCES

1 Godan D, *Pest slugs and snails, biology and control* Springer-Verlag, Berlin. pp 191–192 (1983).
2 Radwan MA, El-Wakil HB and Osman KA, Toxicity and biochemical impact of certain oxime carbamate pesticides against terrestrial snail, *Theba pisana* (Müller). *J Environ Sci Health* **B 27**:759–773 (1992).
3 Miller E, Swails D, Olson F and Staten RT, White garden snail (*Theba pisana* Müller): Efficacy of selected bait and sprayable molluscicides. *J Agric Entomol* **5**:189–197 (1988).
4 Schuytema GS, Nebeker AV and Griffis WL, Effects of dietary exposure to forest pesticides on the brown garden snail, *Helix aspersa* (Müller). *Arch Environ Contam Toxicol* **26**:23–28 (1994).
5 Yamamoto I, Kamimura H and Yamamoto R, Nicotinoids as an insecticide. *Reprinted from the Memoirs of the Tokyo Univ of Agric*, **VII**:67–90 (1963).
6 Alig B, Stendel W and Londershausen M, Preparation of substituted pyridines as insecticides. (Bayer A.-G) EP 356,797 (Cl. C07d213/64), DE Appl. 3,828,820 (1988); *CA*, **113**: 58954g, (1990).
7 Nakajima T, Komyoji T, Akagi T, Nagatani K, Haga T, Matsuo N and Suzuki K, Synthesis and fungicidal activity of *N*-phenylpyridinamines. *ACS Symp Ser* **584**:443–448 (1995).
8 Yazaki A, Niino Y, Ohshita Y, Hirao Y, Amano H, Hayashi N and Kuramoto Y. Preparation of novel pyridonecarboxylic acid derivatives as antibacterial agents. (Wakunaga Pharm Co Ltd) PCT Int Appl WO 97 11,068 (Cl. C07D401/04) JP Appl 96/178,462 (1996); *CA* **126**: 305587g (1997).
9 Kleemann A., Preparation of heterocyclic-substituted pyridine

selective herbicides. (Shell Int Res) PCT Int Appl WO 94 22,833 (Cl. C07D213/69), EP Appl 93/105,006 (1993); *CA* **122**:31337g (1995).

10 Huebl D and Pieroh EA, A method for combating nematodes with 2-(2-pyridylimino)-1,3-dithietane or its salts. EP 310, 540 (Cl. C07D409/12), 05 DE Appl 3,733,806 (1987); *CA* **111**: 134128s (1989).

11 Salmon R, Pearson DPJ, Parry DR and Kozakiewicz AM Acaricidal and insecticidal pentafluoro(phenyl)sulfur or pentafluoro-(pyridinyl)sulfur compounds. (Zeneca Ltd) PCT Int Appl WO 94 21,606 (Cl. C07D207/36) GB Appl. 93/6, 184 (1993); *CA* **122**: 31333c (1995).

12 Oishi Y, So K, Watanabe T and Konya K, Preparation of anilinopyridine derivatives as algicides and fouling control agents. (Ihara Chemical Industry Co Ltd) JP 62 169,767 [87,169,767] (Cl. C07D213/74) (1987), Appl 86/11,731 (1986); *CA* **108**:150315u (1988).

13 Alekseev SI, Blocking of the fast potassium current in *Limnaea stagnalis* neurons by pyridine and its derivatives. *Biol Membr* **10**:272–286 (1993).

14 Katritzky AR, El-Zemity S and Lang H, Conversions of 2-aminopyridines into 5-substituted derivatives mediated by 1-hydroxymethylbenzotriazole. *J Chem Soc Perkin Trans 1* 3129–3133 (1995).

15 Katritzky AR, Rachwal S and Rachwal B, The chemistry of benzotriazole Part 3. The aminoalkylation of benzotriazole. *J Chem Soc Perkin Trans 1* 799–804 (1987).

16 Young AG and Wilkins RM, A new technique for assessing the contact toxicity of molluscicides to slugs. *J Moll Stud* **55**:533–536 (1989).

17 Hussein HI, Kamel A, Abou-Zeid M, El-Sebae AH and Salah MA, Uscharin, the most potent molluscicidal compound tested against land snails. *J Chem Ecol* **20**:135–140 (1994).

18 Anon, Molluscicidal screening and evaluation. *WHO Bull* **38**:507–581 (1965).

19 El-Sebae AH, El-Okda MMK and Marei AS, Local formulation of three carbamoylated oximes as terrestrial molluscicides. *Agric Res Rev* **60**:85–91 (1982).

20 Abbott WS, A method of computing the effectiveness of an insecticide. *J. Econ Entomol* **18**:265–267 (1925).

21 Finney DJ, *Probit Analysis*, 3rd edn, Cambridge Univ Press, London. p 318 (1971).

22 Henderson IF and Martin AP, Control of slugs with contact action molluscicides. *Ann Appl Biol* **116**:273–278 (1990).

23 Radwan MA, A technique for testing the efficacy of molluscicidal baits against land snails. *Com In Sci.* & *Dev. Res* **651**:17–26 (1993).