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Synthesis and molluscicidal structure–activity relationships of some novel 1,2,4-triazole *N*-methyl carbamates

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Abstract: A new series of 1,2,4-triazole derivatives and their corresponding carbamates have been synthesized and screened for their molluscicidal activity against two types of terrestrial snail, *Helix aspersa* and *Theba pisana*, by two methods of application, either as contact or as bran baits. Several of the tested compounds exhibited good molluscicidal activity, and *T pisana* was more sensitive than *H aspersa*. Substitution at the *o*- and/or *p*-positions of the phenyl ring with chlorine or bromine gave higher molluscicidal activity than the unsubstituted compound, with *o,p*-dichloro substitution being optimum. In addition, compounds containing two triazole moieties showed higher molluscicidal activity, particularly as stomach poisons, than the contact toxic effect of the corresponding compound with one triazole ring. In general, carbamate derivatives were more active than their corresponding 1,2,4-triazole derivatives.

Keywords: carbamates; molluscicidal activity; structure-activity relationship; *Theba pisana*; *Helix aspersa*

1 INTRODUCTION

Terrestrial snails are destructive agricultural pests causing economic damage to a wide variety of plants including vegetables, forage crops, tree fruits, shrubs, flowers, ground green cover and newly sown lawn-grasses. Moreover, they play an important role in transmitting and spreading diseases to cultivated plants.[1]

The use of specific molluscicides is considered to be one of the most effective measures for terrestrial mollusc control. Carbamates are a potent class of molluscicide.[2–5] The activity of carbamates against terrestrial molluscs has been evaluated for aromatic *N*-methyl carbamates, eg carbaryl, mexacarbate and methiocarb.[6–8] Methiocarb has been considered more effective than the long-established molluscicide, metaldehyde, because methiocarb is little affected by environmental conditions and its toxicity increases in humid conditions which are favourable for terrestrial gastropods.[8]

1,2,4-Triazoles constitute an important group of heterocylic nitrogen derivatives showing a broad spectrum of biological activity as herbicides, cotton defoliants, growth regulators,[9] insecticides[10] and fungicides.[11] In our recent research, 2-[(1,2,4-triazol-1-ylmethyl)amino]-3-methylpyridine, as well as (1*H*-1,2,4-triazol-1-ylmethyl)anilines, *N*-alkylanilines and *N,N*-dialkylanilines exhibited promising molluscicidal activity.[12,13] In an extension of these studies, a new series of 1,2,4-triazole-based *N*-methyl carbamates has been synthesized and tested in two laboratory-based bioassays to evaluate their molluscicidal potency. The molluscicidal structure-activity relationships are discussed here.

2 EXPERIMENTAL METHODS

2.1 General experimental procedures

^{1}H NMR spectra were recorded on a Varian spectrometer at 200 MHz using tetramethylsilane as an internal reference in hexadeuterodimethyl sulfoxide; melting points were measured with a Kofler hot-stage apparatus and were uncorrected. High resolution mass measurements were performed on an AEL MS-30 mass spectrometer.

2.2 Synthesis

The sequence of the reactions leading to the synthesis of *o*-(1*H*-1,2,4-triazol-ylmethyl)substituted phenols and their corresponding *N*-methyl carbamate derivatives is outlined in Fig 1. 1-Hydroxymethyl-1*H*-1,2,4-triazole is readily obtained either by stirring a mixture of 1,2,4-triazole with formalin in water at room temperature for 5 h or, preferably, by refluxing 1,2,4-triazole with paraformaldehyde in the presence of a catalytic amount of triethylamine.[14] In the latter case, a yield of 98% was achieved. The required compounds were all prepared by heating under reflux a mixture of the phenol or naphthol with one or two equivalent of

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1-hydroxymethyl-1*H*-1,2,4-triazole in acetic acid for 4–72 h (see Table 1).

This reaction can be considered as an extention of the Mannich reaction, in which the primary or secondary amine is replaced by hydroxymethyl-1,2,4-triazole and the phenol or naphthol provides the activated proton. Compounds **1** and **3** were easily converted into their corresponding carbamate derivatives, **2** and **4**, respectively, by reaction with methyl isocyanate in the presence of a catalytic amount of triethylamine.[15]

2.2.1 General procedure for the synthesis of o-*(1*H*-1,2,4-triazol-1-ylmethyl)phenols (**1a–k**),* o,p-*di-(1*H*-1,2,4-triazol-1-ylmethyl)phenols (**3a–b**) and (1*H*-1,2,4-triazol-1-ylmethyl)naphthols (**5a–b**)*

A mixture of 1-hydroxymethyl-1*H*-1,2,4-triazole[14] (25 mmol, in the case of compounds **1a–k**, **5a–b** and 50 mmol in the case of compounds **3a–b**) and the corresponding phenol or naphthol (25 mmol) in acetic acid (25 ml) was heated under reflux for 4–72 h (12 h in the case of compounds **1a–k**, 72 h in the case of compounds **3a–b** and 4 h in the case of compounds **5a–b**). The solvent was then removed under reduced pressure, and to the residue was added aqueous sodium hydrogen carbonate solution (10 M, 30 ml). The solution was extracted with diethyl ether (3 × 100 ml), washed with water (50 ml) and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography using hexane + ethyl acetate (5+1 by volume) as eluent. The physical properties of the products are given in Tables 1, 2 and 3.

2.2.2 General procedure for the synthesis of o-*(1*H*-1,2,4-triazol-l-ylmethyl)phenyl* N*-methyl carbamate (**2a–h**) and* o,p-*di-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl* N*-methyl carbamate (**4a–b**)*

A mixture of methyl isocyanate (1.3 ml, 0.023 mol) in anhydrous diethyl ether (10 ml) with the corresponding *o*-(1*H*-1,2,4-triazol-1-ylmethyl)phenol (**1a** and **1d–j** in the case of compounds **2a–h**) or *o,p*-di-(1*H*-1,2,4-triazol-1-ylmethyl)phenol (0.02 mol) (**3a–b** in the case of compounds **4a–b**) and three drops of

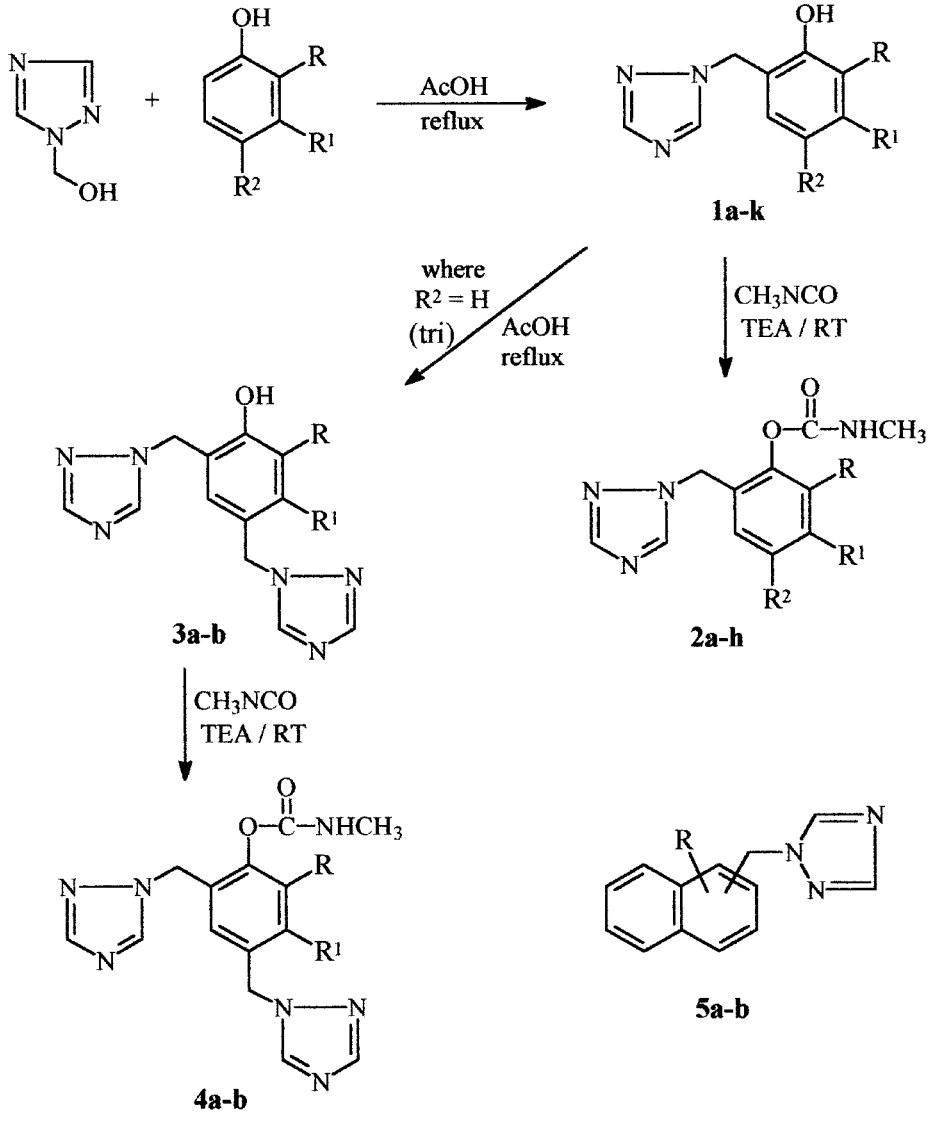
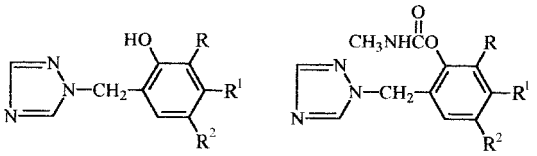


Figure 1. Overall synthetic routes to *o*-(1*H*-1,2,4-triazol-1-ylmethyl) substituted phenols and their corresponding *N*-methyl carbamate derivatives. (tri) = hydroxymethy-1*H*-1,2,4-triazole.

Table 1. Physical data for 1*H*-1,2,4-triazoles and their corresponding *N*-methyl carbamate derivatives



1 2

Compound	*R*	*R*^{1}	*R*^{2}	*Yield (%)*	*mp (°C)*
1a	H	H	H	65	140–141
1b	CH_3	H	H	66	110–112
1c	H	H	CH_3	68	160–161
1d	Cl	H	H	75	122–123
1e	H	Cl	H	70	196–198
1f	H	H	Cl	67	185–186
1g	Cl	H	Cl	80	200–203
1h	Br	H	H	63	179–180
1i	H	H	Br	66	180–183
1j	Br	H	Br	72	173–175
1k	H	H	NO_2	55	205–206
2a	H	H	H	81	140–141
2b	Cl	H	H	93	124–125
2c	H	Cl	H	90	100–101
2d	H	H	Cl	95	122–123
2e	Cl	H	Cl	95	132–133
2f	Br	H	H	80	112–113
2g	H	H	Br	81	163–164
2h	Br	H	Br	89	156–157

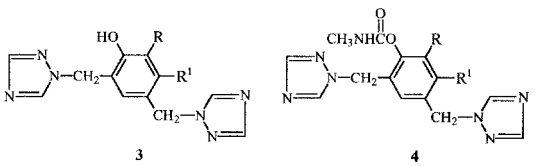
triethylamine, in a small glass-stoppered flask was allowed to stand for 1 week at room temperature. The solvent was removed under reduced pressure and the desired product obtained as white needles after recrystallization. The yield and melting points are presented in Tables 1 and 2.

2.3 Molluscicidal tests

2.3.1 Test animals

Specimens of the herbivorous snails, *Theba pisana* (Muller) and *Helix aspersa* (Muller) were collected during autumn 1999 from untreated nursery plants and farms in Alexandria Governorate, Egypt. The snail species used in these studies were selected on the basis of their wide geographical distribution and the economic importance of the crops they damage, and were identified according to the key given by Godan.[1] Adult animals were fed on bran bait *ad libitum* and allowed to acclimatize to the laboratory conditions for 3 weeks.

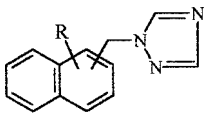
Table 2. Physical data for 1*H*-1,2,4-triazoles and their corresponding *N*-methyl carbamate derivatives



3 4

Compound	*R*	*R*^{1}	*Yield (%)*	*mp (°C)*
3a	Cl	H	53	179–180
3b	H	Cl	60	230–231
4a	Cl	H	80	130–131
4b	H	Cl	71	145–146

Table 3. Physical data for 1- and 2-(1*H*-1,2,4-triazol-1-ylmethyl) substituted naphthol derivatives



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Compound	*R*	*Tri (position)*[a]	*Yield (%)*	*mp (°C)*
5a	2-OH	1	70	226–227
5b	1-OH	2	68	222–223

[a] Tri = hydroxymethyl-*1H*,1,2,4-triazole.

2.3.2 Test chemicals

Stock solutions of each tested compound, including methiocarb (4-methylthio-3,5-dimethylphenyl *N*-methylcarbamate) 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 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 as spray application. Preliminary experiments were carried out to establish the effective range of the tested chemicals. Six different concentrations, ranging from 2.5 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. The tested dose was gently applied on the surface of the snail body inside the shell using a micropipette 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] Methiocarb (Mesurol, Bayer Co) and DMSO were included as standards for comparison.

2.3.3.2 Toxic baits (stomach toxicity). Bran baits containing 5 and 10 g kg^{-1} of the tested compounds were used for trials, after preliminary tests had revealed that more than 10 g kg^{-1} baits discouraged snails feeding. The preparation of bran baits was

carried out according to the method of El-Sebae *et al*,[19] and they were tested for their 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 from 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 7 days, and 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 molluscicidal properties for the new series of 1,2,4-triazole derivatives and their corresponding carbamates against two tested snails by the topical application method are shown in Table 4. Many of the tested compounds exhibited good molluscicidal activity, particularly against *T pisana*. Mono-substitution of the 1,2,4-triazole moiety with a methyl (**1b** and **1c**), nitro (**1k**) or chloro (**1d**–**f**) group did not improve the activity over the unsubstituted compound (**1a**) against the two tested snails. However, conversion of these 1,2,4-triazole derivatives into *N*-methyl carbamates (**2b**–**d**) led to an obvious increase in their molluscicidal activity. Furthermore, the position of chlorine substituent in carbamate derivatives played an important positive role in their potency in the order *meta* > *ortho* > *para*. Moreover, it was found that disubstitution of chlorine in *o,p*-positions resulted in a further increase in molluscicidal activity (**1g** *versus* **1a** or **2e** *versus* **2a**). Thus, molluscicidal activity reached the highest level in compound **2e**, which is superior to methiocarb against *T pisana* snails.

Table 4. Molluscicidal activity of the test compounds against *Helix aspersa* and *Theba pisana* snails by topical application method

	LD_{50} (μg per snail) at 48h with 95% fiducial limits[a]	
Compound	H aspersa	T pisana
1a	>750	>750
1b	>750	>750
1c	>750	701 (506–862)
1d	>750	>750
1e	>750	>750
1f	>750	695 (534–805)
1g	432 (279–668)	251 (302–407)
1h	716 (493–941)	601 (399–730)
1i	>750	>750
1j	675 (513–889)	420 (239–756)
1k	688 (387–926)	592 (492–701)
2a	>750	495 (436–562)
2b	374 (267–407)	245 (205–288)
2c	331 (299–367)	221 (194–251)
2d	412 (285–684)	248 (177–294)
2e	212 (170–271)	101 (83–123)
2f	392 (354–435)	235 (186–293)
2g	>750	555 (487–632)
2h	308 (277–401)	125 (97–146)
3a	>750	>750
3b	716 (578–873)	625 (337–963)
4a	216 (177–260)	143 (110–185)
4b	436 (388–661)	384 (329–448)
5a	414 (381–578)	276 (217–350)
5b	>750	>750
Methiocarb	211 (189–245)	107 (88–124)
Control	0.0	0.0

[a] Average based on three replicates ($n = 3$), 10 animals each.

Although chloro-substitution in the synthesized carbamates containing two 1,2,4-triazole moieties in their structure increased the molluscicidal action, the *ortho*-substituted compound (**4a**) was more active than the *meta*-substituted one (**4b**) against the two tested snails. A fact which demonstrates the steriospecificity of action of the carbamates was seen in that compounds containing two triazole moieties in their structure (**4a**–**b**) proved to be more potent than those containing one triazole moiety (**2b**–**c**).

Substitution with bromine on the aryl ring (**1h**–**i**) had little effect on molluscicidal activity, but an effect was obtained with the *ortho*-bromo-substituted carbamate derivative (**2f**). However, the 2,4-dichloro compound (**2e**) was more active than the 2,4-dibromo compound (**2h**) and both of these were more active than the unsubstituted compound.

The results of 7 days of screening in the bait test against *T pisana*, presented in Table 5, indicate that methyl substitution at the *ortho*-position (**1b**) displays better activity than that at the *para* position (**1c**). Interestingly, compound **1b** was superior to the standard (methiocarb) at a concentration of $5\,g\,kg^{-1}$ in the bait. In contrast, chloro-substituted derivatives (**1d**–**f** and **2b**–**d**) were inactive as bran baits. However, the 2,4-dichlorosubstituted compound (**2e**) gave high molluscicidal activity compared with the standard in the $5\,g\,kg^{-1}$ bran baits. Conversion of compounds **1h** and **1j** into their carbamates increased the activity above that of the standard in a $5\,g\,kg^{-1}$ bait (**2f** and **2h**). The 2,4-dibromo compound (**2h**) was more active than the 2,4-dichloro compound (**2e**) as a $5\,g\,kg^{-1}$ bait, which is the opposite trend to that found in the topical test (Table 4). *Ortho*-chloro substitution in a compound containing two 1,2,4-triazole moieties (**3a**) and its corresponding carbamate compound (**4a**) showed higher activity than in their *meta* analogues (**3b** and **4b**). Compound **4a** was the most active in the series, including the standard, achieving 78% and 94% mortality in 5 and $10\,g\,kg^{-1}$ bran baits, respectively.

The β-naphthol derivative (**5a**) showed superior activity to the α-naphthol derivative (**5b**), indicating that replacing the phenol in 1,2,4-triazole derivatives with naphthol enhanced the molluscicidal activity

Table 5. Molluscicidal activity of the test compounds against *Theba pisana* snails by ingestion assays

	Mortality of snails exposed to bran bait (%) (± SE)[a]	
Compound	*5 g kg^{-1} bait*	*10 g kg^{-1} bait*
1a	0.00	16 (±0.84)
1b	79 (±0.76)	47 (±1.2)
1c	37 (±0.19)	18 (±1.2)
1d	0.00	13 (±0.43)
1e	13 (±0.58)	18 (±1.0)
1f	0.00	18 (±1.0)
1g	13 (±0.63)	33 (±0.51)
1h	0.00	13 (±0.47)
1i	0.00	0.00
1j	0.00	0.00
1k	0.00	30 (±0.89)
2a	0.00	20 (±0.56)
2b	0.00	0.00
2c	30 (±0.82)	0.00
2d	13 (±1.9)	37 (±0.86)
2e	63 (±0.56)	27 (±0.33)
2f	53 (±3.5)	20 (±1.8)
2g	13 (±1.9)	0.00
2h	67 (±0.34)	37 (±0.23)
3a	43 (±0.83)	80 (±1.1)
3b	37 (±1.9)	73 (±0.40)
4a	78 (±0.50)	94 (±0.48)
4b	53 (±2.0)	87 (±1.2)
5a	57 (±2.2)	33 (±2.1)
5b	13 (±0.82)	0.00
Methiocarb	43 (±0.56)	67 (±0.71)
Control	0.00	0.00

[a] Average based on three replicates ($n = 3$), 10 animals each.

(**1a** *versus* **5a**–**b**). This finding suggests that the site of action of these compounds may require or favour the specific configuration of the naphthol precursor. The higher mortalities which have resulted from some of the tested compounds against *T pisana* at the lower dose (5 g kg^{-1}) than at the higher dose (10 g kg^{-1}) is due to the repellent effect of the higher dose.[1,7]

In conclusion, comparing the results of the topical application test with those of the bran bait test, compounds **1b**, **3a**–**b** and **5a** were superior in bran bait tests rather than in topical tests, indicating that these compounds were more effective as stomach poisons than as contact poisons under laboratory conditions. These results suggest that the molecular mass of the tested compounds plays an important role in their lipophilicities and consequently in the stomach toxicity. Also, compounds **4a** and **4b** were apparently the most effective among the tested compounds against *T pisana*, both in topical and in bran bait tests. These results are consistent with those reported in the literature, indicating that the molluscicidal activity of the different compounds against terrestrial snails is greatly affected by the chemical structure, species specificity and application method.[7,12,22]

Finally, the derivatives of 1,2,4-triazole linked with aryl *N*-methyl carbamate represent a new class of potent compounds against terrestrial snails, which were comparable or superior to methiocarb in both topical and bran bait tests.

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