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RESEARCH

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Novel synthesis of some heterocycles and their molluscicidal activity against the destructive land snail, *Theba pisana*

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Abstract

Background Terrestrial snails, specifically *Theba pisana*, represent significant agricultural pests in the Mediterranean region, particularly in Egypt. They are gastropods that cause substantial damage to a variety of vegetation, rendering them important agricultural pests that result in economic losses. In response, we have developed unique and non-toxic molluscicides. The study assessed nine novel heterocycles compared with methomyl as a reference compound, to study their molluscicidal effects on *T. pisana*. These heterocycles include 2-pyrazolines, 2-oxocyclohex-3-ene, and 3-cyano-2-ethoxypyridine.

Results The obtained data revealed that the majority of the produced chemicals were remarkably effective against *T. pisana* snails, exhibiting different degrees of toxicity seven days post-treatment. Methomyl exhibited the highest toxicity, followed by prop-2-en-1-one and 1-thiocarbamoyl-2-pyrazoline derivatives, with LC_{50} values of 44.14, 59.54, and 72.00 ppm, respectively.

Conclusions These findings will inform the potential of these synthetic compounds as one of the sources for molluscicide development and their integration into pest management strategies.

Keywords 2-Pyrazoline, Pyridine, Molluscicides, *Theba pisana*, Methomyl

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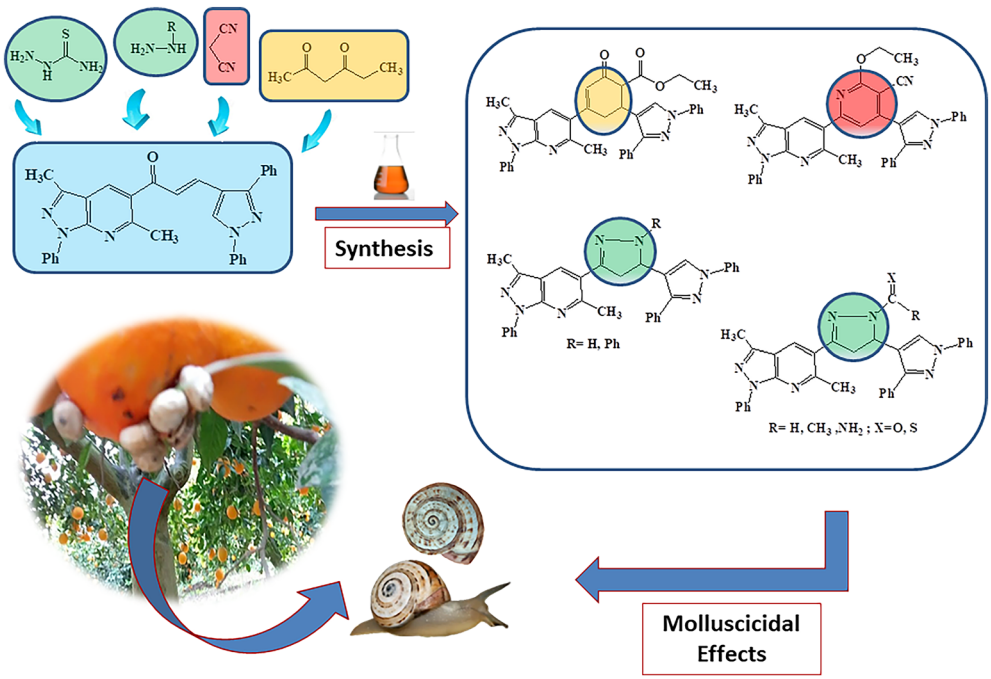
Graphical Abstract



Background

The land snails are creatures known as gastropods that seriously harm a variety of vegetation, making them important agricultural pests. They target buds, roots, leaves, flowers, and tree trunks, resulting in significant harm to growing plants [1]. These pests harm plants at different stages of growth, resulting in decreased yields [2] and posing a danger to sustainable agriculture [3]. Land snails cause economic loss because of their eating habits and their contamination of crops with their bodies, excrement, or slime. This not only reduces product quality but also causes major financial losses [4]. Furthermore, land snails act as intermediary hosts, indirectly spreading infections to humans and domestic animals through infected plants and fruits [5, 6].

Land snails have grown to be a major agricultural pest in several Egyptian regions, with reported attacks on diverse plant components [7–11]. Of these pests, the terrestrial snail species *Theba pisana*, is one of the most common and dangerous land snails in the area known as the Mediterranean, especially in Egypt, due to its small size, climbing inclination, ability to cause plant damage, and high reproductive rate [12].

The excessive use of conventional pesticides has a harmful influence on both human beings and non-target wildlife. It also aids insects in developing tolerance to these toxins. As a result, it was important to find new, ecologically friendly molluscicides for use in ongoing control strategies. Studies show that 2-pyrazolines have a vital function in organic and biological chemistry [13–16], as well as being effective insecticides [17–20]. Furthermore, the pyridine ring appears in a wide range of synthetic chemistry [21, 22], including agrochemicals and insecticides [23–28]. As a result of the aforementioned and continuing teamwork [29–36], we are interested in developing novel 2-pyrazoline or pyridine analogs combining pyrazolopyridine and pyrazole nuclei having molluscicidal activity against the land snail, *T. pisana*. (Fig. 1).

Results and discussion

Chemistry

The building blocks for the production of different heterocycles are acetyl pyrazolopyridine **1** [37] and pyrazole-4-carboxaldehyde, which reacted by Claisen—Schmidt condensation to produce 1-propen-2-one derivative **2** (Scheme 1). Different 2-pyrazoline derivatives **3–5** can be obtained through cycloaddition of **2** using hydrazine hydrate 80% at different reaction conditions. If the cycloaddition occurred in ethanol, unsubstituted 2-pyrazoline **3** was formed. Conversely, the use of formic or

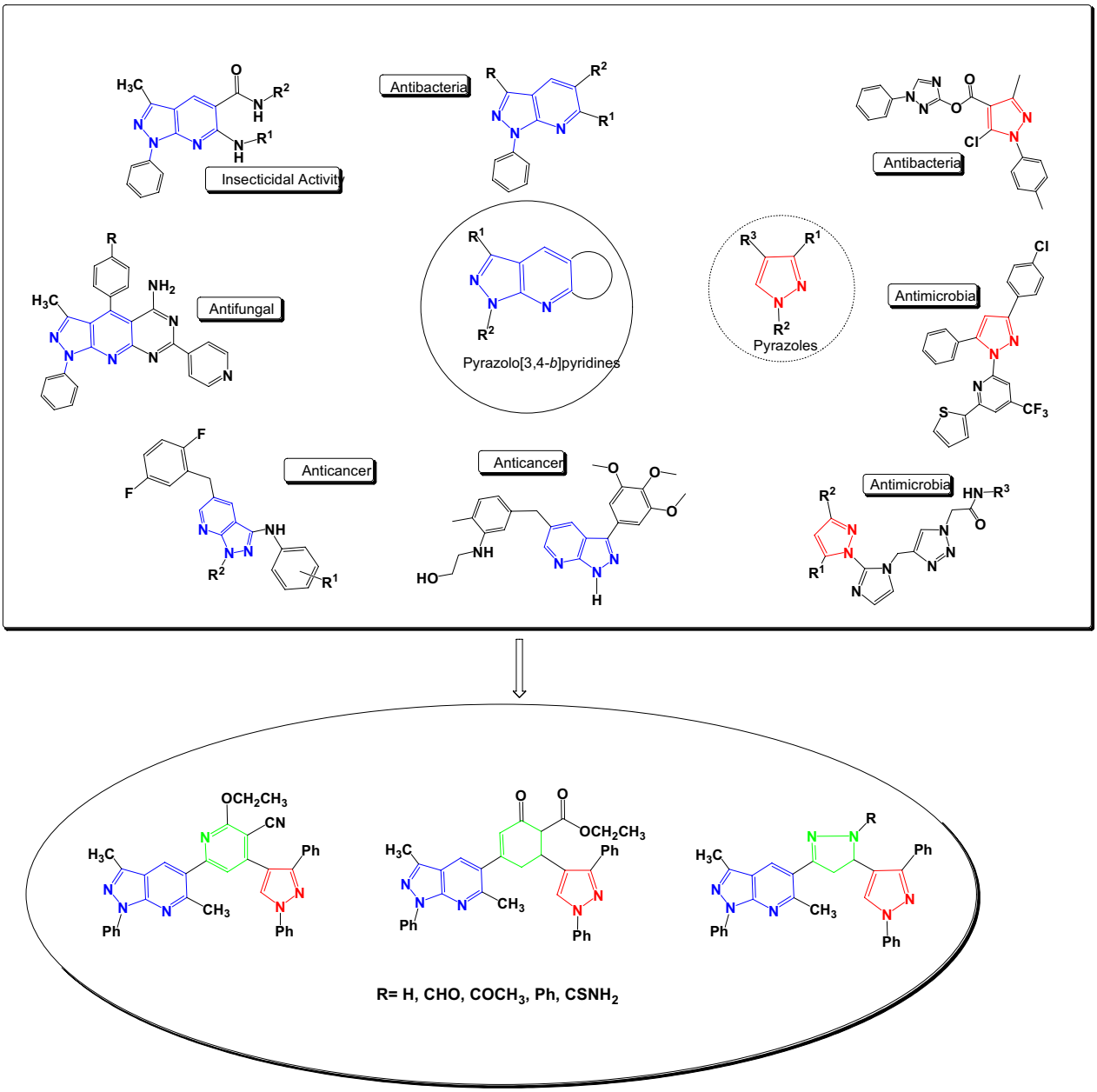
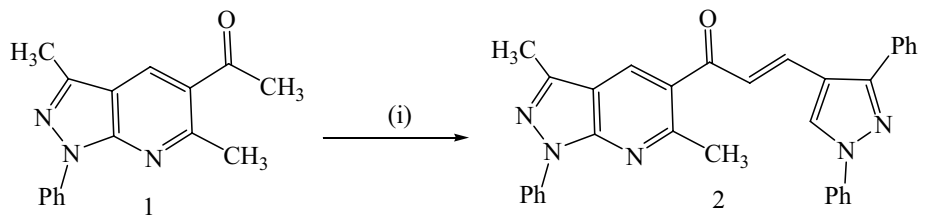
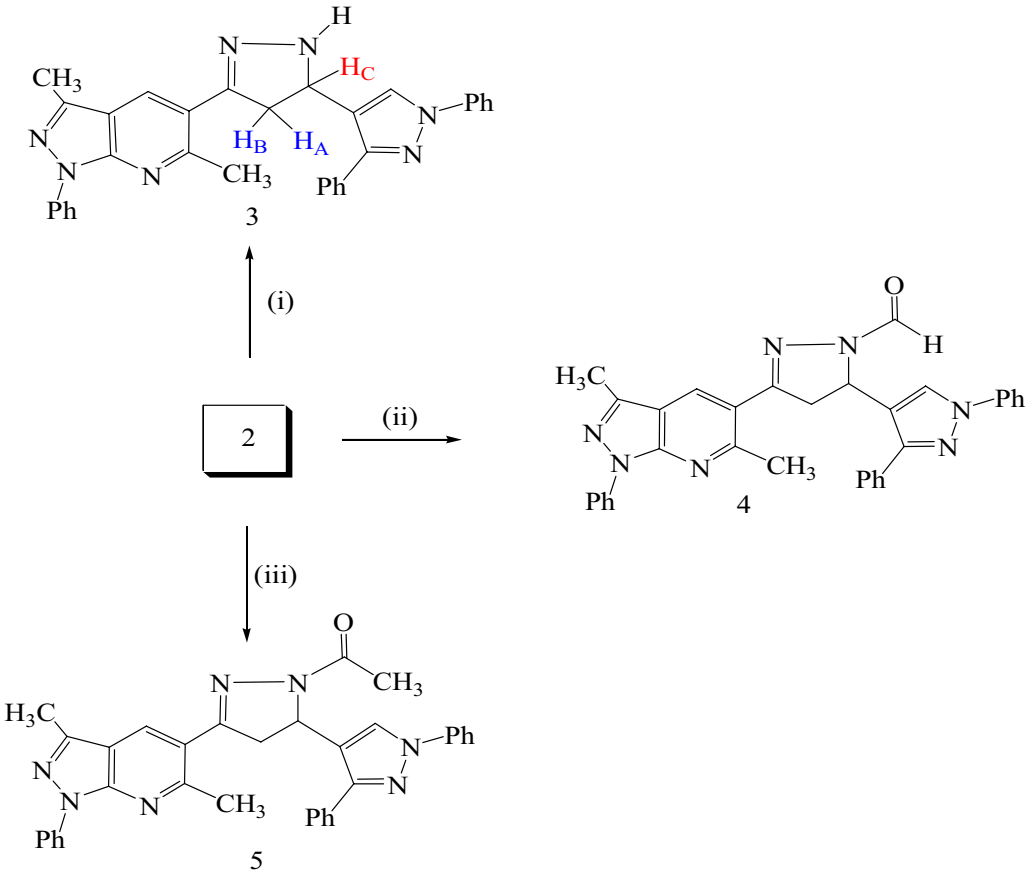


Fig. 1 Examples of reported and newly synthesized heterocycles



Scheme 1 (i) Pyrazole-4-carbaldehyde, EtOH, NaOH, stirring 6 h



Scheme 2 (i) Hydrazine hydrate 80%, EtOH, reflux 6 h, (ii) Hydrazine hydrate 80%, HCOOH, reflux 8 h; (iii) Hydrazine hydrate 80%, CH_3COOH, reflux 8 h

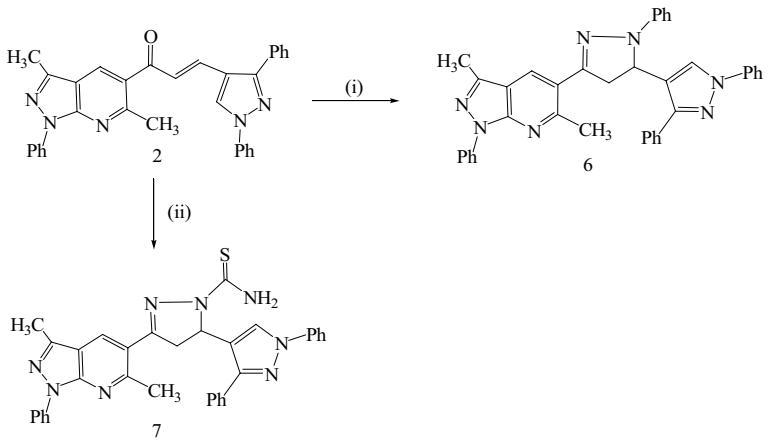
acetic acid led to 1-formyl- or 1-acetyl-2-pyrazoline derivatives **4** and **5**, respectively (Scheme 2).

Spectral data and elemental analysis confirmed the structures of products **3–5**. For instance, the ^{1}H-NMR spectra of **3** exhibited three doublets of doublets caused by the two methylene protons in the 2-pyrazoline ring. The two methylene protons form an ABC structure, with H_A, H_B, and H_C appearing as double doublets at δ = 3.11–3.16, 3.40–3.46, and 6.06–6.09 ppm, with J_{AB} = 18 Hz, J_{AC} = 12 Hz, and J_{BC} = 5.5 Hz, respectively. The NH proton of **3** appeared as a signal at δ = 8.43 ppm. Similarly, the ^{13}C-NMR exhibited two signals at δ = 44.6 and 57.0 ppm referring to pyrazoline-$\underline{C}H_2$, and pyrazoline-$\underline{C}H$.

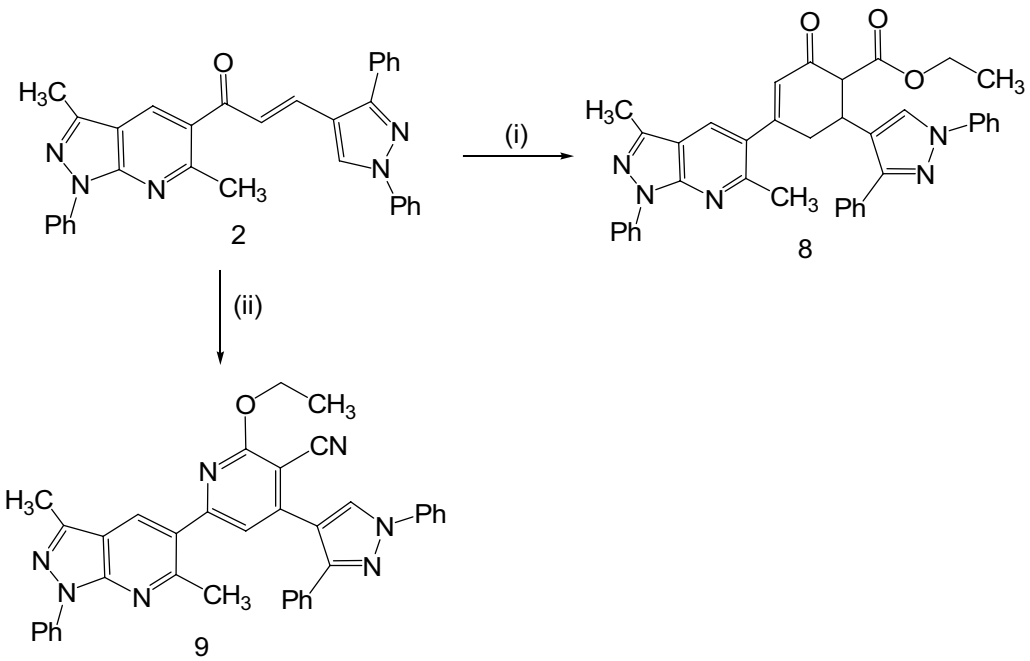
The reaction of **2** with phenylhydrazine resulted in 1-phenyl-2-pyrazoline **6**. Furthermore, 1-thiocarbamoyl-5-aryl-2-pyrazoline **7** was obtained by heating **2** with thiosemicarbazide in ethanol as a solvent (Scheme 3).

The spectral data indicated the structures of 1-phenyl-2-pyrazoline **6** and 1-thiocarbamoyl-2-pyrazoline **7**, and their infrared spectra confirmed the lack of carbonyl bond absorption bands. In addition, compound **7** showed new absorption bands from the amino group at ν = 3431 and 3230 cm^{-1}, and a new signal from the C = S group at δ = 176.5 ppm, according to the ^{13}C-NMR spectra.

For additional reactions of 1-propen-2-one **2** functionality, it undergoes treatment with ethyl acetoacetate or malononitrile to produce ethyl 2-oxocyclohexene carboxylate **8** or 3-cyano-2-ethoxypyridine derivative **9**, separately (Scheme 4). FT-IR spectra of **8** exhibited the appearance of two C = O at υ = 1665 with 1712 cm^{-1}. Moreover, the ^{1}H-NMR spectra confirmed the existence of the ethyl group, a signal (triplet) at δ = 1.20–1.27 ppm for CH_3, and a signal (quartet) at δ = 4.58–4.63 ppm due to CH_2. The cyclohexene ring protons gave three signals at δ = 3.05–3.20 due to cyclohexene-C$\underline{H_2}$, 3.65–3.78 due to two protons of cyclohexene-CH, and at 6.50 due to the other proton of cyclohexene-H. Additional signals were found on the ^{13}C-NMR spectra of compound **8** at δ = 13.9 ppm due to carbon of methyl ester, 29.7 ppm due to cyclohexene-CH_2, 39.6 ppm due to carbon of methylene ester, 169.9 ppm of cyclohexyl-CO, and 193.7 ppm of ester-CO.



Scheme 3 (i) Phenyl hydrazine, EtOH, reflux 6 h; (ii) Thiosemicarbazide, EtOH, NaOH, reflux 8 h



Scheme 4 (i) Ethyl acetoacetate, EtOH, piperidine, reflux 8 h; (ii) Malononitrile, EtOH, EtONa, reflux 3 h

On the other hand, spectroscopic analyses supported the structure of **9**, the IR spectra indicating a CN stretching peak at $\nu = 2217$ cm^{-1}. The ^{1}H-NMR spectra, which are in line with ^{13}C-NMR spectroscopy, revealed the signal (triplet) at $\delta = 1.51–1.54$ ppm due to -$CH_2\underline{C}H_3$, and quartet signal at $\delta = 4.55–4.61$ ppm of -$C\underline{H}_2CH_3$. In addition, ^{13}C-NMR (DEPT) distinguished the negative signal of methylene (CH_2) of **9** at $\delta = 34.2$ ppm and the others, CH_3, CH or quaternary C have positive signals.

Biological activity

The molluscicidal activity of investigated compounds on *Theba pisana* applying the residual film assay

The residual film treatment was performed to evaluate the molluscicidal effects of pyridine derivatives on the terrestrial snail *Theba pisana* when compared to methomyl, the recommended compound (Tables 1 and 2). Results listed in Table 1 showed that the majority of the produced chemicals had remarkable effectiveness against *T. pisana* snails, with different levels of toxicity 7

Table 1 Mortalities of *Theba pisana* adult snails exposed to different concentrations of certain compounds using residual film technique under laboratory conditions

Tested compounds	Conc. (ppm)	Corrected mortality percentages (days post-exposure)		
		1 day	3 days	7days
1	50	0.0^{b}	13.33^{def}	13.33^{gh}
	100	0.0^{b}	33.33^{bcd}	53.33^{bcde}
	200	0.0^{b}	33.33^{bcd}	60.0^{abcd}
2	50	0.0^{b}	6.67^{ef}	46.67^{bcdef}
	100	0.0^{b}	26.67^{bcde}	60.0^{abcd}
	200	0.0^{b}	46.67^{ab}	73.33^{ab}
3	50	0.0^{b}	0.0^{f}	6.67^{h}
	100	0.0^{b}	0.0^{f}	6.67^{h}
	200	0.0^{b}	13.33^{def}	33.33^{defgh}
4	50	0.0^{b}	0.0^{f}	20.0^{fgh}
	100	0.0^{b}	20.0^{cdef}	40^{cdefg}
	200	0.0^{b}	26.67^{bcde}	46.67^{bcdef}
5	50	0.0^{b}	0.0^{f}	26.67^{efgh}
	100	0.0^{b}	20.0^{cdef}	26.67^{efgh}
	200	0.0^{b}	20.0^{cdef}	53.33^{bcde}
6	50	0.0^{b}	6.67^{ef}	33.33^{defgh}
	100	0.0^{b}	13.33^{def}	46.67^{bcdef}
	200	0.0^{b}	33.33^{bcd}	73.33^{ab}
7	50	0.0^{b}	6.67^{ef}	40.0^{cdefg}
	100	0.0^{b}	26.67^{bcde}	60.0^{abcd}
	200	0.0^{b}	40.0^{abc}	73.33^{ab}
8	50	0.0^{b}	0.0^{f}	13.33^{gh}
	100	0.0^{b}	0.0^{f}	26.67^{efgh}
	200	0.0^{b}	26.67^{bcde}	46.67^{bcdef}
9	50	0.0^{b}	6.67^{ef}	20.0^{fgh}
	100	0.0^{b}	20.0^{cdef}	53.33^{bcde}
	200	0.0^{b}	46.67^{ab}	66.67^{abc}
Methomyl	50	6.67^{b}	40.0^{abc}	53.33^{bcde}
	100	6.67^{b}	46.67^{ab}	73.33^{ab}
	200	20.0^{a}	60.0^{a}	86.67^{a}
LSD (0.05)		4.31	16.45	20.24
$P < 0.05$		.0000 ***	.0001 ***	.0000 ***

The identical letters within the same column means that they are not significant

LSD least significant difference (for tested compounds)

days after treatment. The highest mortality rates for the tested snails were recorded by methomyl, followed by prop-2-en-1-one **2**, and 1-thiocarbamoyl-2-pyrazoline **7** with values of (53.33, 73.33 and 86.67%), (46.67, 60.0 and 73.33%) and (40.0, 60.0 and 73.33%) at 50, 100 and 200 ppm concentrations, respectively. On the other hand, the synthesized compounds examined in this work did not cause death after the first day of treatment compared to methomyl, which showed a mortality rate of (6.67, 6.67, and 20.0%) at the same concentrations one-day post-treatment. After the third day, mortality percentages started to show up and progressively rose as treatment times and concentrations increased. The Median Lethal Concentration value (LC_{50} in ppm) of each compound was estimated and is displayed in Table 2

In comparison to the methomyl reference compound, two of the tested compounds, **2** and **7**, exhibited high molluscicidal efficacy towards *T. pisana* having LC_{50} rates of 59.54 and 72.0 ppm, respectively, whereas that of methomyl was 44.14 ppm. Meanwhile, the least effective compounds, 2-pyrazoline **5**, cyclohexanone **8**, and 1-formyl-2-pyrazoline **3**, had LC_{50} values of (0.0, 0.0, and 0.0) and (212.56, 226.50, and 431.65 ppm) after 3 and 7 days of treatment.

Thus, the current findings demonstrated the molluscicidal efficacy of several pyrazole derivatives against the land snails *Theba pisana*, supporting their inclusion in pest control programs. In the same vein, many studies have shown the efficacy of some synthetic compounds as molluscicides. Synthesized pyrano [2,3-*c*]pyrazole derivatives demonstrated moderate molluscicidal activity against Biomphalaria alexandrina snails [38]. Novel thiophene, thiadiazole, and pyrazole derivatives having molluscicidal activity against *B. alexandrina* snails [39]. El Shehry [40] tested novel derivatives of pyrazole, isoxazole, pyridine, pyrimidine, 1,4-thiazine, and 1,3,4-thiadiazine containing a benzofuran moiety against

Table 2 Toxicity effect of certain compounds against *Theba pisana* snails using residual film technique under laboratory condition

Tested compounds	After 24 h LC_{50} (ppm) with CL	After 3 days LC_{50} (ppm) with CL	After 7 days LC_{50} (ppm) with CL	Regression equation	R^2
1	—	378.78 (139.34–1029.67)	129.70 (79.73–210.98)	y = 2.265x + 0.210	0.84
2	—	205.15 (123.90–339.68)	59.54 (24.11–147.07)	y = 1.173x + 2.917	0.99
3	—	—	431.65 (204.77–909.90)	y = 1.777x + 0.3	0.75
4	—	1440.37 (283.44–7319.56)	204.81 (86.92–482.61)	y = 1.259x + 2.089	0.90
5	—	—	212.56 (84.97–531.70)	y = 1.1736x + 2.2654	0.75
6	—	371.38 (182.29–756.61)	95.34 (51.79–175.51)	y = 1.750x + 1.536	0.96
7	—	240.43 (135.21–427.52)	72.00 (34.65–149.63)	y = 1.455x + 2.296	0.99
8	—	—	226.50 (116.64–439.81)	y = 1.706x + 0.982	0.99
9	—	220.54 (132.07–368.27)	112.59 (67.36–188.21)	y = 2.113x + 0.664	0.93
Methomyl	1457.47 (403.98—5258.14)	107.92 (31.33–371.73)	44.14 (22.73–85.72)	y = 1.706x + 2.193	0.99

LC_{50} 50% lethal concentration, *CL* Confidence limits

B. alexandrina and found that these compounds had promising molluscicidal activity. In addition, synthesized heterocyclic compounds have shown insecticidal activity [41–43].

Materials and methods

Instrumentation and chemicals

The materials used in the current experiment were of analytical grade. The melting points that were not adjusted were estimated utilizing an APP Digital ST 15 melting point instrument. The Shimadzu-408 infrared spectrophotometer was applied to record the IR spectra that are presented in cm^{-1}. Using a Bruker AV-400 and JEOL ECA II 500 MHz spectrometer, the NMR spectra were acquired. Parts per million, or ppm, of chemical shifts, were determined with TMS as an internal reference. With System GmbH vario EL V2.3 1998 CHNS Mode, analysis of elements was carried out.

1-(3,6-Dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (2) A solution of ethanol (20 ml) containing sodium hydroxide (2 ml, 40%) was mixed with pyrazole-4-carboxaldehyde (1.24 g, 5 mmol) and acetyl pyrazolopyridine **1** (1.33 g, 5 mmol). For 6 h, the solution was stirred at room temperature. After cooling and pouring crushed ice to the reaction mixture, the solid result was filtered out, dried, and crystallized using toluene. Yield: (72%, pale yellow crystals), mp 169–171 °C. IR (KBr): υ 306**8** (Aromatic-H), 16**45** (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.56 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 7.18–7.90 (m, 17 H, Ar-H, pyridine-H, and ethylenic-H), 8.03–8.19 (m, 2H, pyrazole-H and ethylenic-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ=12.1 (pyrazole-CH_3), 2**5.0** (pyridine-CH_3), 114.7, 118.3, 119.0, 120.6, 123.0, 123.2, 123.5, 125.4, 125.6, 127.2, 128.3, 128.9, 129.1, 129.7, 131.1, 132.9, 135.0, 135.2, 135.5, 139.6, 140.4, 143.8, 149.3, 149.6, 149.9, 153.5, 158.6, 192.3 (C=O) ppm. Anal. Calcd. for $C_{32}H_{25}N_5O$ (495.57): C, 77.56; H, 5.08; N, 14.13%. Found: C, 77.51; H, 5.02; N, 14.20%.

5-(5-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-pyrazolin-3-yl)-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (3) A solution containing **2** (0.99 g, 2 mmol) and hydrazine hydrate 80% (0.16 ml, 5 mmol) was refluxed in ethanol (10 ml) for 6 h. The mixture was cooled, and then the solid precipitate was separated and crystallized using the ethanol. Yield: (70%, yellow powder), mp 184–185 °C. IR (KBr): υ 3398 (NH), 3056 (Ar-H), 2914 (Aliph-H) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ=2.62 (s, 3H, pyrazole-CH_3), 2.75 (s, 3H, pyridine-CH_3), 3.11–3.16 (dd, *J*=18, 5.5 Hz, 1H, 4-H_A), 3.40–3.46 (dd, *J*=18, 12 Hz, 1H, 4-H_B), 6.06–6.09 (dd, *J*=12.0, 5.5 Hz, 1H, 5-H_C), 7.10–7.81 (m, 10H, Ar-H and pyridine-H), 8.18–8.32 (m, 7H, Ar-H and pyrazole-H), 8.43 (s, 1H, NH, D_2O exchangeable) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=12.5 (pyrazole-CH_3), 25.3 (pyridine-CH_3), 44.6 (pyrazoline-CH_2), 57.0 (pyrazoline-CH), 116.1, 119.3, 120.7, 122.5, 125.2, 125.7, 128.5, 128.6, 128.7, 128.8, 129.0, 129.6, 150.2, 152.8, 153.8, 158.0, 158.4 ppm. Anal. Calcd. for $C_{32}H_{27}N_7$ (509.60): C, 75.42; H, 5.34; N, 19.24%. Found: C, 75.36; H, 4.81; N, 19.25%.

3,6-Dimethyl-1-phenyl-5-(1-formyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-2-pyrazolin-3-yl)-1H-pyrazolo[3,4-b]pyridine (4) Compound **2** (0.99 g, 2 mmol) was dissolved in the solution of formic acid (15 ml) containing hydrazine hydrate 80% (0.16 ml, 5 mmol). The mixture was refluxed for 8 h, and the solid product formed after cooling was filtered out and crystallized with ethanol. Yield: (65%, pale yellow powder), mp 199–200 °C. IR (KBr): υ 3057 (Ar-H), 2916 (aliphatic-H), 1684 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ=2.65 (s, 3H, pyrazole-CH_3), 2.80 (s, 3H, pyridine-CH_3), 3.44–3.49 (dd, *J*=20, 5 Hz, H_A), 3.91–3.97 (dd, *J*=17, 10.5 Hz, H_B), 5.80–5.84 (dd, *J*=10.5, 5 Hz, H_X), 7.12–7.78 (m, 10H, Ar-H and pyridine-H), 7.85–8.49 (m, 7H, Ar-H and pyrazole-H), 8.93 (s, 1H, –CHO) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=12.6 (pyrazole-CH_3), 22.5 (pyridine-CH_3), 44.3 (pyrazoline-CH_2), 52.9 (pyrazoline-CH), 118.9, 121.9, 123.8, 125.9, 127.8, 128.4, 128.8, 128.9, 129.1, 129.3, 129.4, 129.7, 130.6, 131.2, 134.9, 137.8, 141.8, 150.5, 173.0 (CO) ppm. Anal. Calcd. for $C_{33}H_{27}N_7O$ (537.61): C, 73.72; H, 5.06; N, 18.24%. Found: C, 73.61; H, 4.97; N, 18.13%.

3,6-Dimethyl-1-phenyl-5-(1-acetyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-2-pyrazolin-3-yl)-1H-pyrazolo[3,4-b]pyridine (5) Hydrazine hydrate 80% (0.16 ml, 5 mmol) was added onto **2** (0.99 g, 2 mmol) in acetic acid (10 ml) and then refluxed for 8 h. During cooling, the separated material was separated and recrystallized with ethanol. Yield: (69%, white crystals), mp 180–181 °C. IR (KBr): υ 3072 (Ar-H), 2999 (Alip-H), 1664 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ=2.47 (s, 3H, pyrazole-CH_3), 2.59 (s, 3H, pyridine-CH_3), 3.01 (s, 3H, –$COCH_3$), 3.24–3.28 (dd, *J*=17.5, 5.0 Hz, H_A), 3.72–3.76 (dd, *J*=11, 9.0 Hz, H_B), 5.87–5.90 (dd, *J*=8.0, 5.0 Hz, H_X), 7.26–7.86 (m, 15H, Ar-H, pyrazole-H and pyridine-H), 8.30–8.32 (m, 2H, Ar–H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ=12.5 (pyrazole-CH_3), 22.2 (pyridine-CH_3), 27.7 (-CO$\underline{C}H_3$), 43.9 (pyrazoline-CH_2), 51.4 (pyrazoline-CH), 119.1, 120.0, 120.6, 122.2, 125.7, 126.0, 126.5, 128.1, 128.4, 128.6, 129.0, 129.3, 129.8, 133.1, 139.2, 139.9, 142.9, 153.3, 169.0 (CO) ppm. Anal. Calcd. for $C_{34}H_{29}N_7O$ (551.64): C, 74.03; H, 5.30; N, 17.77%. Found: C, 73.94; H, 5.20; N, 17.68%.

3,6-Dimethyl-1-phenyl-5-(1-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-2-pyrazolin-3-yl)-1H-pyrazolo[3,4-b]pyridine (6) Phenyl hydrazine (3 mmol) was added to

ethanol (15 ml) solution containing chalcone **2** (3 mmol), and heated for 6 h. Following cooling, 50 ml of water was added, and the resulting precipitate was filtered, dried, and purified with ethanol. Yield: (72%, orange powder), mp 300–302 °C. IR (KBr): υ 3062 (Ar–H), 2922 (Aliph-H) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 2.62 (s, 3H, pyrazole-CH_3), 3.16 (s, 3H, pyridine-CH_3), 3.40–3.46 (dd, *J* = 21.0, 8.0 Hz, H_A), 3.94–3.99 (dd, *J* = 15.0, 10.0 Hz, H_B), 5.53–5.57 (dd, *J* = 10.0, 8.0 Hz, H_C), 7.16–7.65 (m, 13H, Ar-H and pyridine-H), 7.66–8.31 (m, 9H, Ar-H and pyrazole-H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 12.5 (pyrazole-CH_3), 25.2 (pyridine-CH_3), 45.0 (pyrazoline-CH_2), 56.0 (pyrazoline-CH), 109.3, 111.1, 113.5, 114.8, 118.8, 121.9, 122.6, 128.8, 128.9, 129.3, 129.4, 130.4, 139.6, 144.6, 146.2, 149.9, 157.0, 158.2 ppm. Anal. Calcd. for $C_{38}H_{31}N_7$ (585.70): C, 77.93; H, 5.33; N, 16.74%. Found: C, 77.84; H, 5.24; N, 16.62%.

3,6-Dimethyl-1-phenyl-5-(1-thiocarbamoyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-2-pyrazolin-3-yl)-1H-pyrazolo[3,4-b] pyridine (7) Thiosemicarbazide (0.18 g, 3 mmol) and chalcone **2** (0.99 g, 3 mmol) dissolved in ethanol (20 ml) including sodium hydroxide (0.20 g, 5 mmol) and heated for 8 h. The mixture was cooled, put over crushed ice to be separated, and recrystallized from the ethanol. Yield: (69%, white crystals), mp 200–201 °C. IR (KBr): υ 3431, 3230 (NH_2), 3030 (Ar-H) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): *δ* = 2.63 (s, 3H, pyrazole-CH_3), 3.00 (s, 3H, pyridine-CH_3), 3.47–3.51 (dd, *J* = 15.0, 7.0 Hz, H_A), 3.94–3.97 (dd, *J* = 10.0, 8.5 Hz, H_B), 6.39–6.41 (dd, *J* = 8.5, 7.0 Hz, H_X), 6.92–7.54 (m, 10H, Ar-H and pyridine-H), 7.70–8.32 (m, 9H, Ar-H, pyrazole-H and NH_2) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 12.5 (pyrazole-CH_3), 27.7 (pyridine-CH_3), 45.0 (pyrazoline-CH_2), 58.3 (pyrazoline-CH), 114.9, 119.4, 120.6, 122.7, 124.6, 125.0, 125.7, 126.8, 129.0, 130.4, 139.1, 143.1, 143.7, 149.5, 155.5, 158.1, 176.5 (C = S) ppm. Anal. Calcd. for $C_{33}H_{28}N_8S$ (568.69): C, 69.70; H, 4.96; N, 19.70; S, 5.64%. Found: C, 69.60; H, 4.89; N, 19.60; S, 5.52%.

Ethyl 4-(3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-6-(1,3-diphenyl-1H-pyrazol-4-yl)-2-oxocyclohex-3-ene carboxylate (8) Compound **2** (0.99 g, 2 mmol) and ethyl acetoacetate (0.26 ml, 2 mmol) were dissolved with ethanol (10 ml) with piperidine (5 drops) and refluxed for 8 h. The precipitate generated after cooling was purified with toluene. Yield: (74%, pale yellow powder), mp 190–191 °C. IR (KBr): υ 3058 (Ar–H), 2924 (Aliph-H), 1712 (CO ester), 1665 (CO) cm^{-1}; ^{1}H-NMR ((pyridine-d_5, 400 MHz)): *δ* = 1.05–1.08 (t, *J* = 17.5 Hz, 3H, –$CH_2C\underline{H}_3$), 2.52 (s, 3H, pyrazole-$C\underline{H}_3$), 2.61 (s, 3H, pyridine-$C\underline{H}_3$), 3.05–3.20 (d, 2H, J = 17.5 Hz, cyclohexene-$C\underline{H}_2$), 3.65–3.78 (dd, 2H, 2 cyclohexene-CH), 4.58–4.63 (q, 2H, *J* = 17.5, 5.0 Hz, –$C\underline{H}_2CH_3$), 6.50 (s, 1H, cyclohexene-H), 7.12–7.78 (m, 12H, Ar-H, pyrazole-H and pyridine-H), 8.06–8.51 (m, 5H, Ar-H) ppm; ^{13}C-NMR (pyridine-d_5, 100 MHz): δ = 12.2 (pyrazole-$\underline{C}H_3$), 13.9 (-$CH_2\underline{C}H_3$), 23.9 (pyridine-$\underline{C}H_3$), 29.7 (cyclohexene-$\underline{C}H_2$), 39.6 ($\underline{C}H_2CH_3$), 115.1, 118.5, 120.3, 122.7, 123.0, 123.2, 123.5, 123.7, 125.3, 126.3, 126.6, 128.4, 129.1, 129.6, 133.9, 135.0, 140.1, 143.0, 149.6, 150.3, 151.8, 154.9, 161.2, 169.9 (CO), 193.7 (CO ester) ppm. Anal. Calcd. for $C_{38}H_{33}N_5O_3$ (607.70): C, 75.10; H, 5.47; N, 11.52; %. Found: C, 75.00; H, 5.38; N, 11.41%.

3-Cyano-2-ethoxy-6-(3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl) pyridine (9) A freshly prepared sodium ethoxide solution (2 mmol) in ethanol (10 ml) was mixed with **2** (0.99 g, 2 mmol) and malononitrile (0.13 g, 2 mmol) and stirred at r.t. Then the resulting mixture was refluxed for 3 h; the solid that was produced upon cooling was separated and purified with ethanol. Yield: (70%, pale orange powder), mp 193–194 °C. IR (KBr): υ 3047 (Ar–H), 2853 (aliphatic-H), 2217 (CN) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 1.51–1.54 (t, 3H, *J* = 18 Hz, –$CH_2C\underline{H}_3$), 2.58 (s, 3H, pyrazole-$C\underline{H}_3$), 2.66 (s, 3H, pyridine-$C\underline{H}_3$), 4.55–4.61 (q, 2H, *J* = 19.5, 11 Hz, -$C\underline{H}_2CH_3$), 6.85–7.72 (m, 10H, Ar-H and pyridine-H), 7.82–8.59 (m, 8H, Ar-H, pyridine-H and pyrazole-H) ppm; ^{13}C-NMR ($CDCl_3$, DEPT, 100 MHz): δ = 12.2 (pyrazole-$\underline{C}H_3$), 15.2 (-$CH_2\underline{C}H_3$), 26.9 (pyridine-$\underline{C}H_3$), 33.8 ($\underline{C}H_2CH_3$), 91.5, 117.8, 119.5, 120.2, 121.6, 122.1, 128.6, 128.7, 128.9, 129.0, 129.5, 131.5, 139.6, 139.9, 143.2, 147.9, 148.0, 152.0, 157.8, 159.8. 164.9 (CN) ppm. Anal. Calcd. for $C_{37}H_{29}N_7O$ (587.67): C, 75.62; H, 4.97; N, 16.68%. Found: C, 75.55; H, 4.90; N, 16.60%.

Biological activity

Collection of snails for testing

Adult white garden snails, *Theba pisana*, of approximately similar age and size, were obtained from infested citrus orchards in the Faisal region of the Suez Governorate, Egypt. The obtained samples were brought straight to the lab and placed in a glass terrarium containing moist clay soil and were covered using fabric netting. The snails were provided with fresh green lettuce (*Lactuca sativa* L.) leaves for about two weeks before treatment to allow for acclimatization until the commencement of the experiment. The rearing terrarium was cleaned regularly, and sick or dead snails were quickly removed.

Molluscicidal activity bioassays

Residual film technique

Bioactivity experiments were carried out using the contact-based (residual film) technique described by Ascher and Mirian [44], to assess the obtained compounds toward the white garden land snail, *T. pisana*,

in comparison with methomyl, the recommended pesticide, at different concentrations (50, 100, and 200 ppm) for each compound. Each compound was prepared as a stock solution in dimethyl sulfoxide (DMSO) before being diluted using distilled water to achieve the required concentrations. Two milliliters for each concentration of the compounds were added and then spread across the bottom of a petri dish, and then the dish was gently rotated in a circular motion. Within a few minutes, under room conditions, the water evaporated, leaving behind a thin layer of the compounds at the applied concentrations. Following that, five adult, healthy snails from the examined species were brought in and introduced to the specified concentration of the investigated materials. Each treatment, involving an untreated check, was carried out three times. The mortality percentages were computed and adjusted using the Abbott formula [45] after dead snail counts were conducted every day for seven days.

Data analysis

Mortality results from the molluscicidal test on *T. pisana* were analyzed using Costat software with one-way analysis of variance (ANOVA) and the least significant difference at 0.05 (LSD). Finney's probit analysis was utilized to determine the LC_{50} and confidence intervals of 95% corresponding to the (upper and lower) confidence limits [46].

Conclusions

The novel chalcone 2-propen-1-one **2** was synthesized and reacted with different nucleophiles, binucleophiles, and active methylene reagents. The structures of the new heterocyclic compounds, 2-pyrazolines, and pyridine derivatives, were determined using elemental analysis with spectroscopic techniques including FT-IR and nuclear magnetic resonance spectroscopy. Our results indicate that the two compounds, prop-2-en-1-one **2**, and 1-thiocarbamoyl pyrazoline derivative **7**, exhibit a promising molluscicidal effect compared with the traditional chemical pesticide methomyl. Therefore, these compounds can be developed for use as molluscicides in control programs for these animals.

Supplementary Information

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Supplementary material 1.

Supplementary material 2.

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Author contributions
All authors of this research contributed to the conception of the study; AOA, TIE, and HAM performed the experiments; AAOA, and TIE made the chemical synthesis sections; HAM carried out the toxicity assay on snails; AAOA, MSY, and IH contributed significantly to analysis and manuscript preparation and MSY, IH revised and edited it. All the authors have read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Assiut University, Egypt.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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