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Original article

Synthesis and molluscicidal evaluation of some new pyrazole, isoxazole, pyridine, pyrimidine, 1,4-thiazine and 1,3,4-thiadiazine derivatives incorporating benzofuran moiety

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ABSTRACT

Chalcone derivative **3** was synthesized *via* the base catalyzed Claisen–Schmidt condensation and was used as a precursor for synthesizing pyrazoline **11**, isoxazoline **12**, pyrazoline carbothioamide **13**, 5,6-dihydropyrimidine-2-(1*H*)-thione **14** and aminopyridinecarbonitrile derivative **15**. Bromination of **3** afforded the dibromo derivative **4**. Monobromo derivative **5** obtained by boiling **4** in dry benzene in the presence of triethylamine. Fused thiadiazines **9a**,**b** and 1,4-thiazine **9c** derivatives were synthesized upon treatment of α-bromopropenone derivative **5** with 4-amino-4*H*-1,2,4-triazole-3-thiol (**6**) or 1-amino-2-mercapto-5-methylpyrimidin-4(1*H*)-one (**7**) or with 2-aminothiophenol (**8**) in ethanolic potassium hydroxide solution. The newly synthesized compounds were screened for their molluscicidal activities, whereas compounds **3**, **4**, **9a**, **11** and **15** exhibited promising molluscicidal activities. On the other hand compounds **5**, **9b**, **9c**, **12**, **13** and **14** showed a moderate effect as compared to the standard molluscicidal agent (Bayluscide).

1. Introduction

Schistosomiasis (bilharziasis) is an endemic disease caused by helminthes belonging to the genus schistosoma. This disease affects more than 200 million people and places with more than 600 million inhabitants are at risk of infection in more than 70 countries in the tropics WHO [1]. In view of its prevalence and morbidity this disease is a serious public health problem in many countries especially Egypt and one of the great efforts made to combat this disease is combating the water snails *Biomphlaria alexandrina*, the intermediate host of the infective phase of schistosoma mansoni, through molluscicides to control the vector snails with easy and cheap procedures.

Chalcones are natural biocides [2] and well known as intermediates for synthesizing of various heterocycles which have impressive array of biological activities [3–5]. In addition, benzofuran derivatives are nowadays an important class of organic compounds that occur in a great number of natural products [6], used in cosmetics [7] and as synthetic pharmaceuticals [8,9]. Benzo[*b*]furans build blocks for fluorescent sensors [10], and are used as optical brighteners. Moreover, many of the natural benzo[*b*]furans have physiological, pharmacological and toxic properties [11].

In the present study we are just making the so called preliminary blind screening until we find the suitable effective lead compounds, then we can modifying its properties, evaluate its biodegradability stability as well as its effect on the other water living organisms.

2. Results and discussion

2.1. Chemistry

2-Acetylbenzofuran (**1**) and 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**2**) [12] reacted in the presence of aqueous sodium hydroxide yielded the 1,3-disubstituted prop-2-en-1-one derivative **3**. Bromonation of **3** with bromine in chloroform yielded 2,3-dibromo-1,3-disubstituted propan-1-one **4** in good yield. Compound **4** undergoes dehydrobromonation by using triethylamine in dry benzene yielded 2-bromo-1,3-disubstituted prop-2-en-1-one **5**. The ^{1}H, ^{13}C NMR and mass spectrum of **5** supported the structure. (cf. Scheme 1).

In a one pot reaction between **4** and **6** or **7** or with **8** in the presence of triethylamine in absolute ethanol, there are three possibilities for that reaction. The first is the attack at C_2 to give

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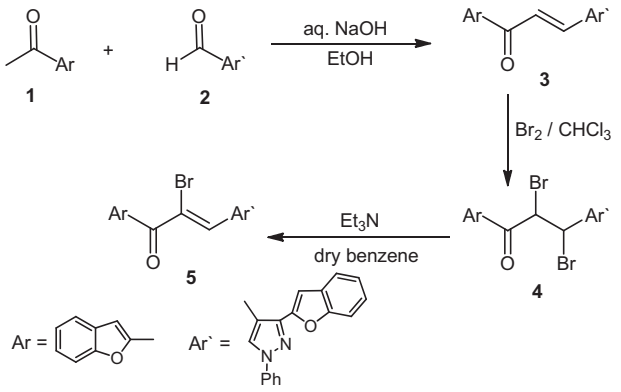
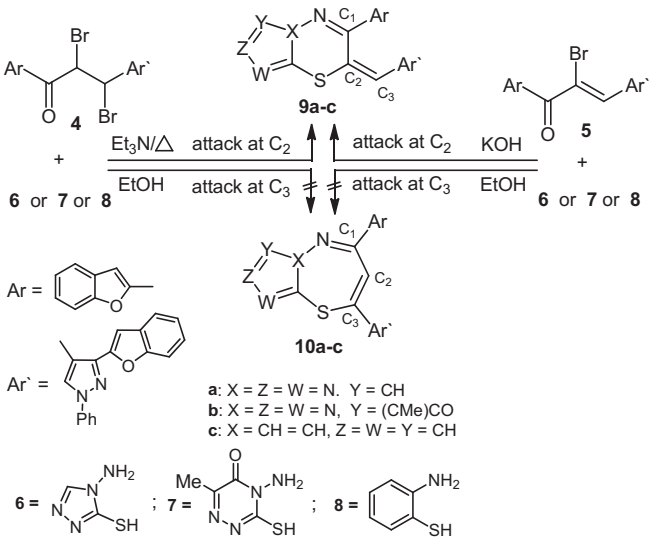


Scheme 1. The reaction sequences of the formation of α-bromopropenone derivative **5**.

thiadiazines **9a**,**b** and thiazine **9c** derivatives, the second is the attack at C_3 to yield the fused thiadiazepines **10a**,**b** and thiazepine **10c** derivatives, finally dehydrobromonation may take place to afford **5**. On the other hand, the unexpected chalcone derivative **3** obtained as the major product, which was confirmed by spectroscopic and analytical data. This could be attributed to dehydrobromination of two molecules of hydrogen bromide under mild basic condition.

It worthily mentioned that, the above reaction was carried out in two steps. Initially, triethylamine was added to dibromo derivative **4** in absolute ethanol and refluxed for 1 h. To this reaction mixture compound **6** or **7** or **8** was added and refluxed for further 6 h, which yielded **9a**–**c** rather than **10a**–**c**, respectively. Compounds **9a**–**c** were also synthesized by an alternate route to confirm their formation, when α-bromopropenone derivative **5** was treated with **6** or **7** or with **8** in the presence of potassium hydroxide in ethanol, compounds **9a**–**c** were obtained as a sole products rather than **10a**–**c**. (cf. Scheme 2).

A mechanism for the formation of **9a**–**c** involves the formation of **5** at first by refluxing **4** with triethylamine in absolute ethanol. When compounds **6**, **7** or **8** were added to the reaction mixture Schiff base was formed, further nucleophlic attack at C_2 resulted in cyclization and subsequent dehydrobromonation yielding fused thiadiazines **9a**,**b** and thiazine **9c** derivatives rather than fused thiadiazepines **10a**,**b** or thiazepine **10c** derivatives. Compounds



Scheme 2. Synthesis of thiadiazines and thiazine derivatives **9a**–**c**.

9a–**c** were confirmed by ^{1}H NMR, mass and elemental analysis (cf. Scheme 3).

Various interesting heterocycle skeletons were synthesized via reaction of **3** with hydrazine hydrate or with hydroxylamine hydrochloride in refluxing ethanol afforded the corresponding 4,5-dihydropyrazole derivative **11** and 4,5-dihydroisoxazole derivative **12** respectively. On the other hand, when compound **3** was condensed with thiosemicarbazide or with thiourea in boiling ethanolic alkaline medium yielded 4,5-dihydropyrazole carbothioamide derivative **13** and 5,6-dihydropyrimidine-2-(1*H*)-thione derivative **14** respectively. Moreover, when compound **3** reacted with malononitrile in boiling ethanol in the presence of a catalytic amount of ammonium acetate yielded aminopyridinecarbonitrile derivative **15**. Spectral data (^{1}H, ^{13}C NMR, mass and elemental analysis) of all the newly synthesized compounds were in full agreement with the proposed structures (cf. experimental and Scheme 4).

2.2. Molluscicidal activity

The mortality of compounds **3**, **4**, **5**, **9a**–**c**, **11**, **12**, **13**, **14** and **15** toward *B. alexandrina* snails was screened. An insight inspection of the results listed in Table 1 shows that compounds **3**, **9a**, **11** and **15** have high effect but all the other compounds have moderate to low effect, they all showed very weak activity below 5 ppm. The data obtained showed promising result especially the compounds that possess triazolo and pyrazolo residues, this data was in a good agreement with our previous reports [13,14]. The comparison of the molluscicidal activity of the tested compounds reported here with the international standard 2′,5-dichloro-4-nitrosalicylanilide (Bayluscide) [15,16] showed that our compounds are still far inferior as molluscicidal agents.

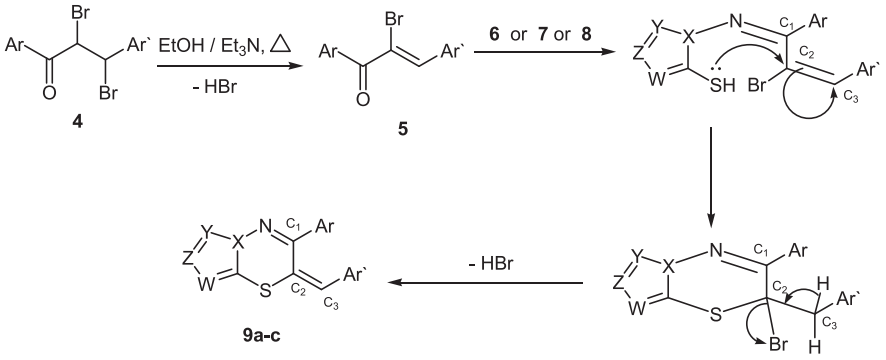
3. Material and methods

3.1. General

All melting points were determined on an Electrothermal 9100 digital melting point apparatus. NMR and mass spectra were recorded on: ^{1}H, ^{13}C NMR spectra were determined using Jeol JMS-AX 500 MHz, Jeol GLM EX 270 MHz FT NMR spectrophotometer, DMSO-d_6, TMS as internal standard, chemical shift in δ (ppm). Mass spectra were recorded on Varian MAT 311 A at 70 ev. Elemental analysis (in accord with the calculated values) was carried out in the microanalytical unit, Faculty of Science, Cairo University. Precoated silica gel 60 F_{254} plats with a layer thickness 0.25 nm from Merck were used for thin layer chromatography. Yields are not optimized.

3.2. 1-(Benzofuran-2-yl)-3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one (3)

To a solution of **1** (10 mmol) in absolute ethanol (20 mL) and aqueous solution of 10% NaOH (10 mL) the aldehyde **2** (10 mmol) was added with constant stirring and the resulting solution was heated to 80 °C for 4 h, cooled to room temperature, and was stand overnight. The solid obtained was separated, collected by filtration, dried and recrystallized from ethanol. Yield, 80%; m.p. 190–192 °C; ^{1}H NMR (DMSO-d_6) δ: 7.10 (d, 1H, J = 12.5 Hz, olefinic CH=), 7.15 (s, 1H, furan H-3), 7.25–8.10 (m, 15H, Ar-H, furan H-3 and olefinic –CH=), 9.50 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 98.5, 107.0, 111.5, 115.9, 119.3, 121.1, 123.3, 123.5, 123.7, 126.2, 127.5, 128.8, 129.4, 129.5, 131.1, 139.5, 141.0, 145.2, 150.0, 155.0, 161.7, 177.4. MS, m/z (%): 430 [M$^+$] (25.8), 353 (1.2), 313 (1.42), 285 (100), 145 (10.9),



Scheme 3. A plausible mechanism for the formation of **9a**–**c**.

117 (4.1), 89 (60.3), 77 (67.7). Anal. Calcd. For $C_{28}H_{18}N_2O_3$ (430.46): C, 78.13; H, 4.21; N, 6.51. Found: C, 78.23; H, 4.15; N, 6.46.

3.3. 1-(Benzofuran-2-yl)-3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dibromopropan-1-one (*4*)

Bromine (10 mmol) was added dropwise with vigorous stirring to a solution of **3** (10 mmol) in (30 mL) chloroform at room temperature over 30 min. After complete addition, the reaction mixture was allowed to stand for an hour. The precipitate formed was filtered off, washed with ether to remove the excess of bromine and recrystallized from ethanol. Yield, 85%; m.p. 170–172 °C; ^{1}H NMR (DMSO-d_6) δ: 5.40 (d, 1H, –CH–CH–, $J = 9.2$ Hz), 5.80 (d, 1H, –CH–CH–, $J = 8.3$ Hz), 7.20–7.90 (m, 13H, Ar-H), 8.00, 8.10 (2s, 2H, benzofuran H-3), 9.00 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 48.8, 54.7, 98.4, 110.8, 113.4, 119.4, 120.3, 121.1, 121.6, 122.3, 123.4, 123.5, 124.6, 127.5, 129.4, 135.6, 143.1, 150.9, 153.5, 156.7, 158.9, 179.1. MS, *m*/*z* (%): 589 [M^+] (37), 509 (12.5), 470 (24.5), 259 (100), 236 (45), 145 (3.6), 117 (5.9), 77 (85). Anal. Calcd. For $C_{28}H_{18}Br_2N_2O_3$ (590.26): C, 56.97; H, 3.07; N, 4.75. Found: C, 56.88; H, 3.13; N, 4.66.

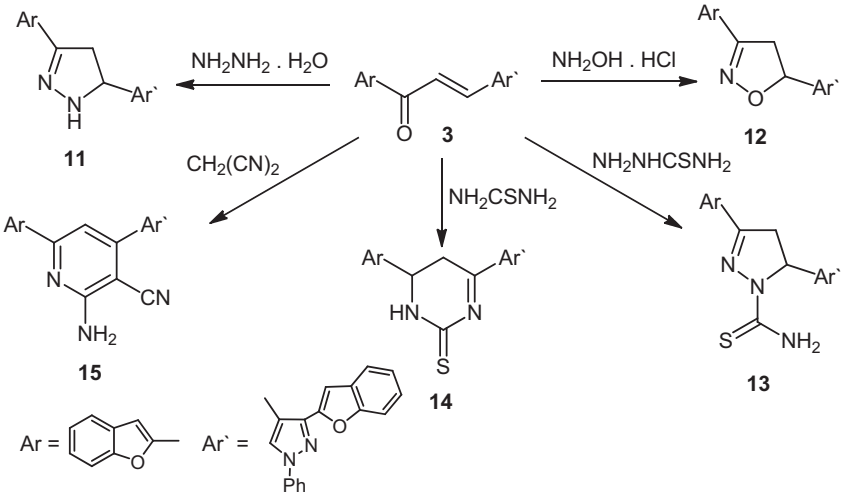
3.4. 1-(Benzofuran-2-yl)-3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2-bromoprop-2-en-1-one (*5*)

Triethylamine (40 mmol) in dry benzene (30 mL) was added to a solution of **4** (10 mmol) in dry benzene (50 mL) with stirring at room temperature for 24 h. After removal of the separated triethylamine hydrobromide, the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethanol. Yield, 65%; m.p. 204–206 °C; ^{1}H NMR (DMSO-d_6) δ: 7.10–7.90 (m, 14H, Ar-H and olefinic –CH=C–), 8.50, 8.80 (2s, 2H, benzofuran H-3), 9.60 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 98.7, 113.4, 118.2, 120.3, 121.1, 121.3, 122.3, 122.9, 123.1, 124.1, 126.8, 127.5, 129.4, 130.3, 131.8, 134.3, 135.6, 141.1, 152.9, 156.2, 158.1, 172.5. MS, *m*/*z* (%): 508 [M^+] (12.5), 431 (35), 428 (12.9), 363 (17.8), 259 (45), 248 (18.9), 145 (12.6), 117 (64.6), 77 (100). Anal. Calcd. For $C_{28}H_{17}BrN_2O_3$ (509.35): C, 66.03; H, 3.36; N, 5.50. Found: C, 66.10; H, 3.28; N, 5.46.

3.5. General procedure for synthesis of thiadiazines (*9a*,*b*) and thiazine (*9c*)

Method A: A mixture of compound **4** (10 mmol) and triethylamine (20 mmol) in absolute ethanol (50 mL) was refluxed for 1 h. To the resulting reaction mixture (10 mmol) compounds **6**, **7** and **8** were added individually and refluxed for 6 h. The resulting solid was filtered off, washed with water and recrystallized to give **9a**, **9b** and **9c** respectively.

Method B: A mixture of compound **5** (10 mmol) and compounds **6**, **7**, **8** (10 mmol) were added individually in alcoholic potassium hydroxide solution (15 mmol) and refluxed in absolute ethanol (30 mL) for 6 h. The precipitated solid was filtered off, washed with water and recrystallized to yield **9a**–**c**.



Scheme 4. 1,3-Addition to chalcone derivative **3** to form compounds **11**–**15.**

Table 1
Molluscicidal activity of compounds **3**–**15** on *Biomphlaria alexandrina* snails (10 snails by concentrations) under laboratory conditions and after 24 h exposure.

Compd. no.	Different concentration used in (ppm)		
	1	5	10
3	0	7	10
4	0	5	8
5	0	2	5
9a	0	6	9
9b	0	1	4
9c	0	0	3
11	0	3	7
12	0	0	3
13	0	1	4
14	0	0	3
15	0	3	8
Bayluscide	10	10	10

*3.5.1. 6-(Benzofuran-2-yl)-7-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7H-[1,2,4] triazolo [3,4-b][1,3,4] thiadiazine (**9a**)*

The compound **9a** was obtained from the reaction of 4-amino-4*H*-1,2,4-triazole-3-thiol (**6**) (10 mmol), recrystallized from (EtOH/DMF). Yield, 55%; m.p. 257–259 °C; ^{1}H NMR (DMSO-d_6) δ: 6.80 (s, 1H, =CH–), 7.10–7.90 (m, 14H, Ar-H and triazole H-3), 8.40, 8.80 (2s, 2H, benzofuran H-3), 9.00 (s,1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 97.1, 111.7, 113.4, 118.8, 119.9, 120.3, 120.6, 122.3, 123.1, 123.5, 123.8, 125.1, 125.9, 127.5, 129.4, 134.1, 140.5, 143.3, 147.7, 152.9, 154.4, 155.2, 157.2, 159.5, 159.9. MS, *m*/*z* (%): 526 [M$^+$] (12.5), 411 (43.4), 407 (11.8), 267 (21.4), 260 (13), 117 (14.2), 113 (7.7), 77 (100). Anal. Calcd. For $C_{30}H_{18}N_6O_2S$ (526.51): C, 68.43; H, 3.45; N, 15.96. Found: C, 68.36; H, 3.51; N, 15.83.

*3.5.2. 3-(Benzofuran-2-yl)-2-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7-methylpyrimido[2,1-b][1,3,4]thiadiazin-8(2H)-one (**9b**)*

The compound **9b** was obtained from the reaction of 1-amino-2-mercapto-5-methylpyrimidin-4(1*H*)-one (**7**) (10 mmol), recrystallized from (EtOH/DMF). Yield, 45%; m.p. 200–202 °C; ^{1}H NMR (DMSO-d_6) δ: 1.60 (s, 3H, CH_3), 6.40 (s, 1H, =CH–), 7.20–7.90 (m, 13H, Ar-H), 8.00, 8.20 (2s, 2H, benzofuran H-3), 8.80 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 97.4, 109.3, 110.8, 112.1, 113.4, 118.8, 119.5, 120.1, 120.3, 120.5, 120.6, 123.1, 125.1, 127.6, 129.4, 129.5, 140.5, 145.2, 147.7, 152.9, 155.7, 158.3, 159.9, 165.5, 170.3. Anal. Calcd. For $C_{32}H_{20}N_6O_3S$ (568.55): C, 67.59; H, 3.55; N, 14.78. Found: C, 67.66; H, 3.62; N, 14.87.

*3.5.3. 3-(Benzofuran-2-yl)-2-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2H-benzo[b][1,4] thiazine (**9c**)*

The compound **9c** was obtained from the reaction of 2-aminothiophenol (**8**) (10 mmol), recrystallized from (EtOH/DMF). Yield, 60%; m.p. 218–220 °C; ^{1}H NMR (DMSO-d_6) δ: 5.80 (s, 1H, CH), 7.10–7.90 (m, 19H, Ar-H and benzofuran H-3), 8.80 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 97.9, 110.6, 113.4, 118.8, 120.3, 120.4, 122.3, 123.1,123.5, 123.8, 124.4, 125.1, 127.7, 129.4, 130.3, 130.7, 132.2, 141.7, 145.3, 147.7, 153.2, 155.6, 158.5, 159.3, 183.8. Anal. Calcd. For $C_{34}H_{21}N_3O_2S$ (535.56): C, 76.24; H, 3.95; N, 7.85. Found: C, 76.31; H, 3.88; N, 7.76.

*3.6. 3-(Benzofuran-2-yl)-4-(3-(benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole (**11**)*

To an ethanolic solution of **3** (10 mmol), hydrazine hydrate (15 mmol) was added dropwisely. The reaction mixture was heated under reflux for 6 h and then cooled and poured onto crushed ice. The solid product was filtered off and recrystallized from ethanol. Yield, 70%; m.p. 180–182 °C; ^{1}H NMR (DMSO-d_6) δ: 3.10 (dd, 1H, CH_2 pyrazoline, J = 16.3, 12.3 Hz), 3.70 (dd, 1H, CH_2 pyrazoline, J = 10.7, 8.7 Hz), 5.30 (dd, 1H, CH pyrazoline, J = 12.4, 9.6 Hz), 6.80 (br s, 1H, NH), 7.10–7.90 (m, 13H, Ar-H), 8.10, 8.70 (2s, 2H, benzofuran H-3), 8.80 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 39.4, 55.2, 97.9, 105.3, 111.3, 111.5, 115.1, 118.0, 119.2, 119.4, 122.1, 123.0, 123.6, 124.2, 124.5, 126.3, 128.5, 129.4, 139.5, 140.0, 145.2, 150.0, 155.4, 156.1. Anal. Calcd. For $C_{28}H_{20}N_4O_2$ (444.49): C, 75.66; H, 4.54; N, 12.60. Found: C, 75.58; H, 4.47; N, 12.67.

*3.7. 3-(Benzofuran-2-yl)-4-(3-(benzofuran-2-yl)-4,5-dihydroisoxazol-5-yl)-1-phenyl-1H-pyrazole (**12**)*

To a solution of **3** (5 mmol) in absolute ethanol (15 mL), hydroxylamine hydrochloride (0.3 g) and freshly fused anhydrous sodium acetate (3.0 g) were added and the reaction mixture was heated under reflux for 7 h on a water bath. The content of the flask was poured onto ice water with stirring. The separated solid was filtered off, washed with water and dried. Further purification was done by recrystallization from ethanol. Yield, 55%; m.p. 175–177 °C; ^{1}H NMR (DMSO-d_6) δ: 3.80 (dd, 1H, CH_2 isoxazoline, J = 13.1, 10.3 Hz), 4.00 (dd, 1H, CH_2 isoxazoline, J = 9.2, 7.8 Hz), 6.20 (dd, 1H, isoxazoline H-5, J = 13.4, 8.5 Hz), 7.10–7.80 (m, 13H, Ar-H), 7.90, 8.30 (2s, 2H, benzofuran H-3), 8.90 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 38.7, 59.8, 98.7, 105.1, 111.2, 111.5, 114.3, 118.4, 119.2, 119.3, 122.3, 122.6, 123.6, 124.4, 125.0, 128.5, 129.4, 129.5, 139.7, 140.1, 145.2, 155.1, 156.3, 164.2. MS, *m*/*z* (%): 445 [M$^+$] (31.7), 428 (14.6), 337 (31.4), 321 (40.6), 295 (11.6), 257 (13.2), 285 (59.8), 115 (23.8), 89 (26.5), 77 (100). Anal. Calcd. For $C_{28}H_{19}N_3O_3$ (445.48): C, 75.49; H, 4.30; N, 9.43. Found: C, 75.40; H, 4.38; N, 9.37.

*3.8. 3-(Benzofuran-2-yl)-5-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydropyrazole-1-carbothioamide (**13**)*

To a mixture of compound **3** (10 mmol) and thiosemicarbazide (10 mmol) in ethanol (50 mL), NaOH (20 mmol) in 5 mL of water was added and refluxed for 10 h. The reaction mixture was poured onto crushed ice, the resulting solid was filtered, dried and recrystallized from DMF. Yield, 45%; m.p. 228–230 °C; ^{1}H NMR (DMSO-d_6) δ: 3.80 (dd, 1H, CH_2 pyrazoline, J = 14.7, 9.6 Hz), 4.20 (dd, 1H, CH_2 pyrazoline, J = 10.1, 8.8 Hz), 6.20 (dd, 1H, pyrazoline H-5, J = 13.4, 9.4 Hz), 7.10–7.90 (m, 13H, Ar-H), 8.10, 8.60 (2s, 2H, benzofuran H-3), 8.80 (s, 2H, thioamide NH_2), 9.60 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 32.6, 52.5, 95.1, 104.2, 107.6, 109.5, 113.4, 118.3, 119.2, 119.3, 122.3, 123.1, 123.8, 125.1, 127.5, 127.9, 129.4, 137.4, 140.6, 150.4, 151.8, 151.9, 154.5, 161.7. Anal. Calcd. For $C_{29}H_{21}N_5O_2S$ (503.52): C, 69.17; H, 4.20; N, 13.91. Found: C, 69.23; H, 4.28; N, 13.85.

*3.9. 6-(Benzofuran-2-yl)-4-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-5,6-dihydropyrimidine-2(1H)-thione (**14**)*

To a solution of **3** (10 mmol) and thiourea (30 mmol) in ethanol (20 mL), ethanolic KOH (20 mmol, 5 mL) was added. The reaction mixture was refluxed. TLC (EtOAc:Pet-ether, 2:1) showed that the reaction was completed in 5 h. The reaction mixture was poured in cold solution of 10% HCl (50 mL) and the precipitate was filtered off, washed with water and recrystallized from C_6H_6/EtOH. Yield, 45%; m.p. 249–251 °C; ^{1}H NMR (DMSO-d_6) δ: 3.40 (dd, 1H, CH_2 pyrimidine), 4.00 (dd, 1H, CH_2 pyrimidine), 5.80 (dd, 1H, pyrimidine H-5), 7.10–7.80 (m, 13H, Ar-H), 8.00, 8.70 (2s, 2H, benzofuran H-3), 9.20 (s, 1H, pyrazole H-5), 10.30 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.1, 59.7, 98.8, 104.7, 112.0, 119.1, 119.3, 122.2, 123.8, 125.3, 125.4, 125.9, 126.5, 127.4, 128.4, 128.7, 129.0, 130.2, 139.5, 141.0, 148.7,

149.7, 154.4, 154.6, 175.7. Anal. Calcd. For $C_{29}H_{20}N_4O_2S$ (488.50): C, 71.29; H, 4.13; N, 11.47. Found: C, 71.21; H, 3.06; N, 11.39.

*3.10. 2-Amino-6-(benzofuran-2-yl)-4-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) pyridine-3-carbonitrile (**15**)*

A solution of **3** (10 mmol) in absolute ethanol (40 mL) containing excess of ammonium acetate and malononitrile (10 mmol) was heated under reflux for 5 h. The reaction mixture was then cooled, poured onto crushed ice and the resulting solid was filtered off, washed with water, dried and recrystallized from EtOH. Yield, 65%; m.p. 305–307 °C; ^{1}H NMR (DMSO-d_6) δ: 5.10 (br s, 2H, NH_2), 7.20–8.20 (m, 16H, Ar-H, pyridyl H-5 and benzofuran H-3), 9.20 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6) δ: 92.5, 98.4, 104.1, 106.2, 112.2, 113.1, 120.5, 120.9, 121.4,122.3, 122.9, 123.5, 124.7, 125.2, 127.5, 128.9, 129.2, 135.2, 136.7, 139.3, 144.4, 154.4, 155.1, 159.2,168.2, 171.4. Anal. Calcd. For $C_{31}H_{19}N_5O_2$ (493.52): C, 75.44; H, 3.88; N, 14.19. Found: C, 75.51; H, 3.93; N, 14.11.

4. Molluscicidal activity tests

The molluscicidal activity tests were carried out for each compound under investigation. *B. alexandrina* snails (ca. 7 mm shell diameter) were collected from the field (water canals) and maintained under laboratory conditions for a period of 10 days before the test and fed daily by lettuce leaves. Three concentrations of each compound under investigation were prepared ranging from 1 to 10 ppm. The required amount of the compound under investigation was mixed thoroughly with two drops of Tween 20 and 2 mL of DMSO to render the compounds completely soluble, followed by addition of the appropriate volume of untreated raw water (taken directly from the Nile River or its subsidiary branches/canals) to get a homogeneous suspension with the requisite concentration and placed in glass jar vessels 15 × 25 × 20 cm dimensions fitted with air bubblers. Ten snails were used in each experiment and maintained in the test solution under laboratory conditions at 25 °C for 24 h. Each experiment was repeated three times, and the mean number of killed snails was taken for each concentration (Table 1). A control group was taken by placing 10 snails in water containing two drops of Tween 20 and 2 mL of DMSO. Bayluscide was used as a reference molluscicidal agent. These bioassays are in accordance with the WHO guidelines [17] slightly modified by using two mixed solvents to dissolve the compounds.

5. Conclusions

In summary, an interesting fused ring systems containing benzofuran residue were synthesized and evaluated for their molluscicidal activities. All the screened compounds did not exhibit any effect bellow 5 ppm concentration. Compounds **3**, **4**, **9a**, **11** and **15** showed potent molluscidal activities while compounds **5**, **9b**, **9c**, **12**, **13** and **14** showed a moderate effect as compared to the standard molluscicidal agent (Bayluscide). This obtained results, showed that our compounds are still far inferior as molluscicidal agents.

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