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Original article

Synthesis and molluscicidal activity of some new thiophene, thiadiazole and pyrazole derivatives

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ABSTRACT

The base-catalyzed reaction of benzoyl acetone **1** with phenyl isothiocyanate yields the non-isolable intermediate **2**. Treatment of **2** with dilute HCl afforded the corresponding thiocarbamoyl derivative **3**. Reaction of the intermediate **2** with phenacyl bromide, ethyl bromoacetate, chloroacetonitrile, chloroacetyl chloride, bromodiethyl malonate and chloroacetone afforded the corresponding thiophene derivatives **5**, **8**, **15** and **17**. The thiocarbamoyl derivative **3** reacts with arylazophenacyl bromide and/or hydrazine hydrate to afford the corresponding thiadiazole and pyrazole derivatives **20a–c** and **22**, respectively. These new synthesized compounds show generally a moderate molluscicidal activity to *Biomphalaria alexandrina* snails.

1. Introduction

Schistosomiasis is an endomic disease in tropical and subtropical regions that affects over 200 million humans worldwide. Control of snail intermediate hosts is an effective means of reducing the disease transmission. The early use of molluscicides in schistosomiasis control has been reviewed by Duncan et al. [1,2] and Bayluscide [3], the ethanol amine salt of niclosamide is considered the compound of choice in many parts of the world. A major disadvantage of Bayluscide as a chemical molluscicide is related to its toxicity to fish. Interests of medicinal chemists on this compound continued and, as a result, other aryl [4,5] and heterocycles [6–9] have been prepared and tested as molluscicides.

We have found it mandatory to participate in these efforts and directed a part of our research towards the synthesis of heterocyclic compounds that can be used as molluscicides [10,11]. Pyrazoles and their fused derivatives are known to exhibit diverse biological activities and important applications in pharmaceutical industries [7,8]. Thiophene, in particular, has been investigated by Royer and his co-workers [12]; they reported the effectiveness of some mono- and polyhalogenated thiophene carboxanilides against *Biomphalaria glabrata*. Other thiophene containing compounds have been also evaluated [13]. In continuation of our search for some effective synthetic molluscicides, phenylaminothiophene, thiadiazole and pyrazole derivatives seemed promising for molluscicidal evaluation. In spite of the fact that, the synthetic compounds in this paper may have more hazardous effect to the environment, however, we are just making the so-called preliminary blind screening until we find the suitable effective lead compounds, then we can study modifying its properties and expand this study to evaluation of its biodegradability/stability as well as its effect on other water-living organisms.

2. Chemistry

2.1. Synthesis of some new thiophene derivatives

Previously, we investigated the reaction of phenyl isothiocyanate with active methylene compounds in alkaline medium, which has proved to be a convenient route for the synthesis of thiazole, pyrazole, oxazine and pyrimidine ring systems [14–17]. Now, we have extended our synthetic program to the synthesis of otherwise inaccessible heterocyclic ring system, utilizing phenyl isothiocyanate as a key starting material. It is known that a great variety of reactants bearing the N=C=S fragment undergo cyclization on reaction with α-halocarbonyl compounds to afford thiazoles, 2,3-dihydrothiazoles and thiazolidines [18], which have been shown to exhibit antiprotozoal [19] and fungicidal properties [20]. In this paper, we describe a generally applicable extension of this synthetic approach, first reported by Hantzch and Weber [21]. Thus, the base-catalyzed reaction of the acidic methylene compound **1** with phenyl isothiocyanate in dry DMF at room temperature yields

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the non-isolable intermediate **2**. Treatment of **2** with dilute HCl afforded the corresponding thiocarbamoyl derivative **3**. Assignment of the product **3** was based on elemental analysis, IR, and ^{1}H NMR spectral data. The IR spectrum showed absorption bands at 3229, 3125, 1595 and 1293 cm^{-1} attributable to the enolic OH, NH, C═O and C═S, functions, respectively. ^{1}H NMR spectrum of **3** displayed multiplet signals at δ 7.1–7.5 ppm for NH proton. Its mass spectrum showed the molecular ion peak $m/z = 297$ (M^+, 14%) The non-isolable potassium salt **2** was allowed to react with phenacyl bromide in stirring dry DMF at room temperature to give thiophene derivative **5**. The structure **5** was inferred from its spectral data. Thus, the IR spectrum showed absorption bands at $\bar{\nu}$ 3330 and 1626 cm^{-1} corresponding to NH and carbonyl groups. Its ^{1}H NMR spectrum showed a broad singlet at δ 11.6 ppm, singlet at δ 1.7 ppm and multiplet signals integrated for (15H) centered at 7.4 (aromatic protons). On shaking the compound with D_2O, the broad band signal at δ 11.6 ppm disappeared. Based on the foregoing data, structure **5** was further confirmed by Indirect method. Thus, it was found that, refluxing of **3** with phenacyl bromide in dry acetone and dry potassium carbonate produced the acyclic intermediate **4**. Structure **4** was suggested for the reaction on the basis of both elemental and spectral analyses. The IR spectrum showed the presence of a carbonyl absorption bands at $\bar{\nu}$ 1741 and 1627 cm^{-1} respectively, while the NH appeared at 3422 cm^{-1}. The ^{1}H NMR spectrum of **4** revealed three singlet signals at δ 1.62, 6.15 and 11.6 ppm due to the protons of CH_3, SCH_2 and NH groups, besides multiplet signals at δ 7.01–7.8 ppm attributable to the aromatic protons.

Refluxing **4** in a mixture of DMF/EtOH containing catalytic amounts of TEA led to the formation of a product identical in all respects (m.p., mixed m.p., IR and ^{1}H NMR) to **5** (Scheme 1).

In a similar manner, treatment of the non-isolable intermediate **2** with ethyl bromoacetate in situ gave a single product which analyzed correctly for $C_{19}H_{15}NSO_3$. The structure of **8** was inferred from its spectral and elemental analyses. Thus, the infrared spectrum of **8** showed a band near 3421 cm^{-1} corresponding to an NH function, and two bands at 1727 and 1662 cm^{-1} due to the two carbonyl groups. The mass spectrum of **8** showed the molecular ion peak at $m/z = 337$ (9%) indicating that the reaction proceeds *via* the proposed intermediates **6** and **7**, in addition to the presence of fragment at $m/z = 294$ (63%) due to the loss of carbon dioxide from the molecular ion.

All attempts to prepare the acyclic intermediate **6** under different reaction conditions were failed and instead, in all cases, the reaction always afforded the cyclic thiophene derivative **8**.

In a similar manner to the behaviour of ethyl bromoacetate with the non-isolable intermediate **2**, chloroacetonitrile reacted with **2** under the same reaction conditions to yield the same product **8**.

However, the product obtained had molecular formula $C_{19}H_{15}NSO_2$ which did not correspond to those of the expected product **10**. We deduced that the compound was identical in all respects with product **8** (m.p., mixed m.p., IR, ^{1}H NMR).

The derivative **8** in this case is expected to be formed *via* an initial elimination of KCl molecule with the formation of the intermediate **9** that cyclizes into the product **10**. It was found that, the cyano group was hydrolyzed under the reaction conditions to give the carboxylic acid group and yielded product **8**. The structure of **8** which obtained in this case was established by spectral data. The IR spectrum showed no absorption band of cyano group around the region 2150–2300 cm^{-1} indicating that the cyano group was disappeared during the reaction course. On the other hand, the IR spectrum showed two bands at 1731 and 1639 cm^{-1} due to the carboxylic and ketonic carbonyl groups. Moreover, the ^{1}H NMR spectrum revealed three singlet signals at δ 1.8, 10.8 and 11.79 ppm attributable to methyl, COOH and NH protons, respectively.

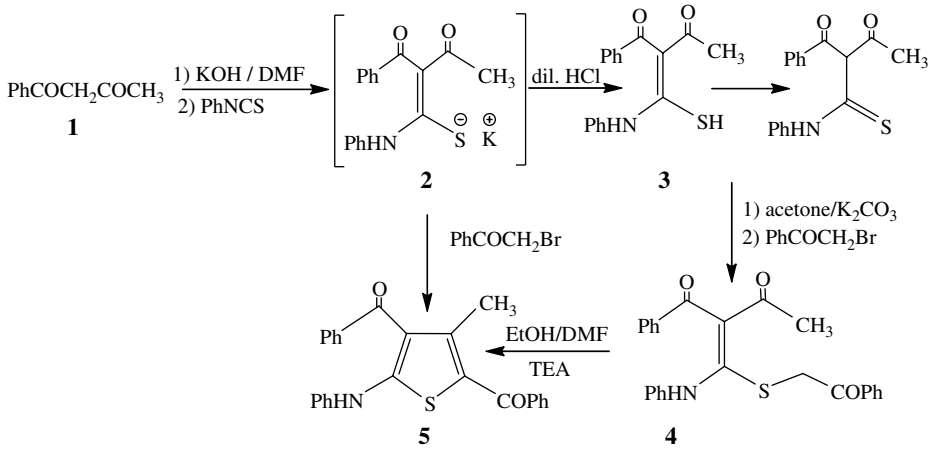
All attempts to prepare the intermediate **9** by stirring at room temperature compound **2** with chloroacetonitriles in the presence of different bases to subject it for cyclization to obtain **10** were failed, and instead gave almost compound **8**.

In a similar way, it has been found that reaction of chloroacetyl chloride with **2** in the presence of DMF gave exclusively the unexpected product **8** instead of compound **12** (Scheme 2).

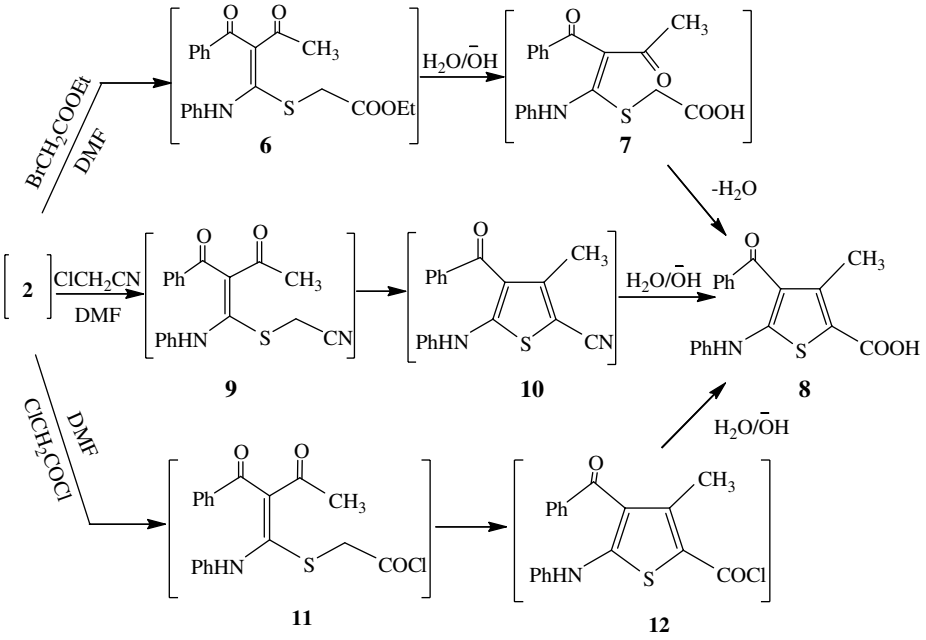
In continuation of our work on the synthesis of biologically interesting heterocyclic molecules containing thiophene moiety *via* multicomponent one-flask reaction, we reported here in our results for the synthesis of thiophene derivatives **15**.

As an application, stirring equimolar amounts of bromodiethyl malonate with the non-isolable intermediate **2** in the presence of potassium hydroxide and DMF gave a solid product **15**. The formation of compound **15** can be explained according to the following proposed mechanism (Scheme 3).

Bromodiethyl malonate reacted with the non-isolable intermediate potassium salt **2** to give the intermediate **13** which hydrolyzes and decarboxylates one of the carbethoxy groups under the reaction condition to give compound **14** which cyclized directly to give 2-carboethoxy-3-methyl-4-benzoyl-5-phenylaminothiophene **15**. The structure of **15** was established on the basis of both elemental and spectral data. The IR spectrum showed absorption bands at 3448, 1710 and 1670 cm^{-1} corresponding to NH and two carbonyl



Scheme 1.



Scheme 2.

groups, respectively. Moreover, the mass spectrum showed the molecular ion peak at $m/z = 365$ (100%, as base peak). All attempts to isolate the intermediates **13** and **14** were failed.

We thought to extend this synthetic approach by allowing **2** to react with chloroacetone under the same previous reaction conditions. It was found that, the reaction yielded a single product which analyzed correctly for $C_{20}H_{17}NSO_2$. This product was formulated as 2-acetyl-3-methyl-4-benzoyl-5-phenylamino thiophene **17**.

The structure of **17** was proved by IR and ^{1}H NMR spectra. Its ^{1}H NMR spectrum revealed three singlet signals at δ 2.2, 2.5 and 10.24 ppm due to the CH_3, $COCH_3$ and NH protons, in addition to multiplet bands at 7.1–7.7 ppm for aromatic protons. Moreover, the mass spectrum give an additional conformation for the correct structure which showed the molecular ion peak $m/z = 335$ (M^+, 22%) (Scheme 4).

2.2. Synthesis of new thiadiazole derivatives

On the other hand, it has been found that the arylazophenacyl bromides **18a–c** behaved differently towards the non-isolable intermediate **2** when compared with the reaction of phenacyl bromide itself.

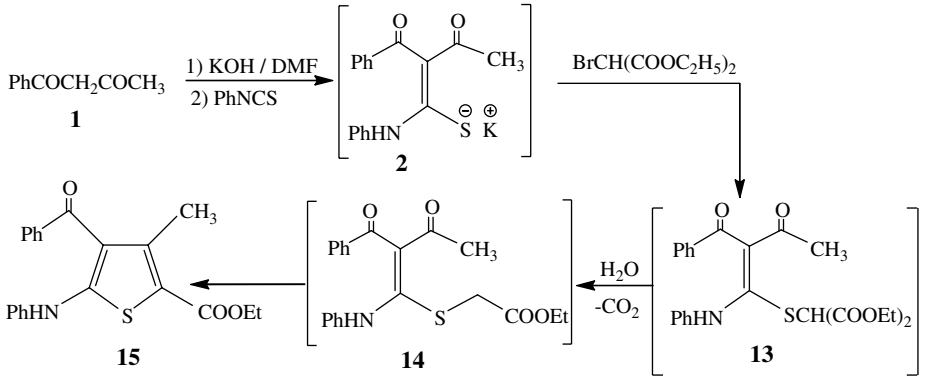
Thus, when **18a–c** reacted with **3** in boiling ethanol containing a catalytic amount of triethylamine afforded the final product **20**. The formation of **20** is assumed to proceed *via* first elimination of HBr to give the open acyclic intermediate **19** which then cyclized by loss of aniline moiety affording the final product **20** (Scheme 5).

This result finds parallelism with previously reported work [17]. Structures **20a–c** was proposed for the reaction product based on IR spectrum which revealed the absence of any absorption band for the NH function group and showed bands at 1670, 1665 and 1660 cm^{-1} due to the three carbonyl groups and C=N function group, respectively.

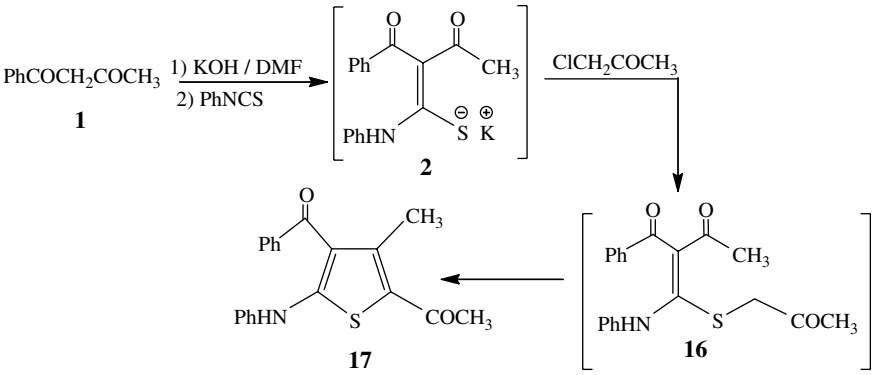
The mass spectroscopy measurements of **20a** showed the molecular ion peak at $m/z = 426$ (M^+, 12%).

2.3. Synthesis of new substituted pyrazole derivative

Finally, in continuation of our interest in pyrazole chemistry, and with a view directed towards preparing biological active heterocycles, we wish to broaden the scope of the reaction of hydrazine with compound **3** as candidates for facile synthetic route of heterocyclic pyrazoles. The work resulted in the formation of unexpected pyrazole derivative. Thus, it has been found that treatment of **3** with hydrazine hydrate in boiling ethanol containing



Scheme 3.



Scheme 4.

a catalytic amount of triethylamine afforded 3-methyl-4-benzoyl-5-phenylaminopyrazole **22** and not the expected β-hydrazino-β-phenylamino derivative **21**.

Structure **22** was proved by IR spectrum which showed stretching frequencies at 3405 and 3286 cm^{-1} for two (NH) function groups while the carbonyl group showed absorption band at 1665 cm^{-1}.

Moreover, structure **22** was also proved by mass spectroscopy which give molecular ion peak at $m/z = 277$ (M^+, 42%) (Scheme 6).

3. Conclusion

We report a facile route for the formation of thiophene based on benzoyl α-phenylthiocarbamoylacetone.

4. Biological evaluation

4.1. Molluscicidal activity

The toxicity of compounds (**5**, **8**, **15**, **17**, **20a–c** and **22**) to *Biomphalaria alexandrina* snails was evaluated as shown in Table 1. The half lethal dose (LC_{50}) and sublethal dose (LC_{90}) in ppm for each compound were determined and are shown in Table 2. Compounds **20b** and **c** exhibited the highest toxic action and were nearly similar in their (LC_{50}) values (5.5 and 6 ppm), respectively. Compounds **20a** and **22** were also active with (LC_{50}) values of (8 and 13 ppm), respectively, where compounds (**5**, **8**, **15** and **17**) were the least toxic (15–19 ppm) among the interesting compounds. The thiadiazole derivatives (**20a–c**) are superior to the thiophene derivatives (**5**, **8**, **15** and **17**) apparently due to the high basicity of the thiadiazole ring. Compound **20b** shows the highest activity may be due to the presence of methyl substituent in the phenyl group. It seems that the presence of methyl group in the phenyl group activates the biological activity more than the methoxy or the unsubstituted phenyl group itself. Also, the presence of methyl group in the pyrazole ring showed moderate activity. The thiophene carrying compound showed lower activity as observed previously [8]. The available results indicate some important points regarding structure–activity correlation. Variation in the type of heterocyclic ring showed a marked difference in activity. During the exposure period, it was noticed an effusion of the gelatinous material from snails under the influence of the tested compounds. This fact may reveal that the mode of their toxic action is through a physical interference with cell membranes, resulting in hindering their functions and leading to hemolysis and subsequent death.

A comparison of the *molluscicidal* activity of our compounds with an international standard, 2,5-dichloro-4-nitrosalicylanilide which is reported to posses $LC_{100} = 1$ ppm [22,23] showed that our compounds are far inferior as *molluscicidal* agents. Compound **20b** seems promising after some modifications which will be considered in a future study.

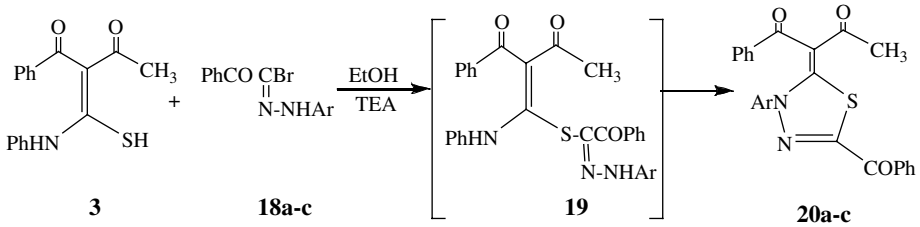
The *B. alexandrina* snails had been recently considered as one of the most serious pests in Egypt. It increases year after one. Therefore, control measures are necessary. The effectiveness of pesticides on *mollusca pests* was studied by many investigators. These synthetic chemical compounds are expensive and in addition, may lead to problems of toxicity to non-target organisms and deleterious long term effect in the environment. Therefore, our interest must be directed to evaluate some anti-snails which can be easily synthesized, economic and are safe in use.

5. Experimental

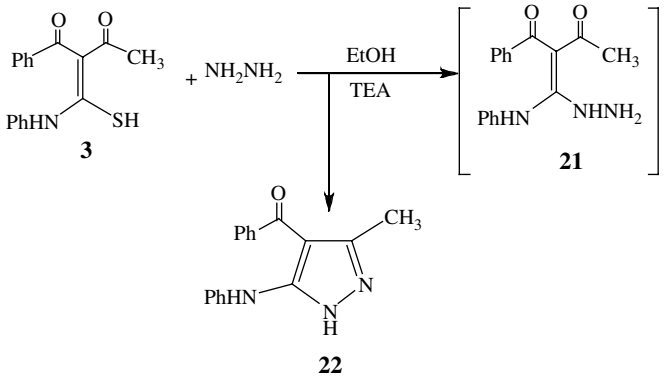
5.1. Chemistry

5.1.1. General methods

All melting points are uncorrected. FTIR spectra (KBr disk) were recorded on a Nicolet Magna. IR model 550 spectrophotometers, ^1H NMR spectra in DMSO-d_6, were determined on Brucker Wpsy 200 MHZ spectrometer with TMS as internal standard and the chemical shifts are in σ ppm. Mass spectra were recorded at 70 eV with



Scheme 5.



Scheme 6.

a varian MAT 311. Microanalyses were performed at the micro-analytical center of Cairo University.

*5.1.2. Benzoyl α-phenyl thiocarbamoyl acetone (**3**)*

A cold suspension of potassium hydroxide (1.4 g, 25 mmol), in DMF (30 ml) was added the benzoyl acetone (4.05 g, 25 mmol), followed by phenyl isothiocyanate (3.37 g, 25 mmol). The mixture was stirred overnight at room temperature and then poured onto ice-cold water. Acidification using dilute HCl until the medium becomes acidic gave solid product **3** which was filtered off, washed with water, dried and crystallized from aqueous ethanol to give compound **3**.

Yellow crystal (Yield 55%), m.p. 140 °C; IR (KBr): $\bar{\nu}/cm^{-1} = 3229$ (OH), 3125 (NH), 1595 (C=O), 1293 (C=S); ^1H NMR (DMSO-d_6), δ 2.5 (s, 3H, CH_3), 7.1–7.5 (m, 10H, Ar), 11.9 (s, 1H, NH); MS: (*m*/*z*) (%) 297 (M^+, 14), 255 (17), 222 (25); Anal. Calcd for $C_{17}H_{15}NO_2S$ (297): C, 68.69; H, 5.05; N, 4.71; Found: C, 68.33; H, 5,00; N, 4.40.

*5.1.3. 2-((2-Oxo-2-phenylethylthio)(phenylamino)methyl)-1-phenyl-butane-1,3-dione (**4**)*

Equimolecular quantities of **3** (2.97 g, 10 mmol) in acetone containing potassium carbonate (1.39 g, 10 mmol) and phenacyl bromide (1.99 g, 10 mmol) were refluxed for 2 h, then left to stand at the room temperature. The crude product was filtered off, dried and recrystallized from ethanol to give **4**.

Yellow crystal (Yield 55%), m.p. 175 °C; IR (KBr): $\bar{\nu}/cm^{-1} = 3422$ (NH), 1741 and 1627 for two (C=O); ^1H NMR: (DMSO-d_6), δ 1.62 (s, 3H, CH_3), 6.15 (s, 2H, CH_2), 7.01–7.80 (m, 15H, Ar), 11.6 (s, 1H, NH); Anal. Calcd for $C_{25}H_{21}NO_3S$ (415.5): C, 72.27; H, 5.09; N, 3.36; Found: C, 72.20; H, 5.00; N, 3.10.

*5.1.4. (3-Methyl-5-(phenylamino)thiophene-2,4-diyl)bis(phenyl-methanone) (**5**)*

5.1.4.1. Pathway (1). To a cold suspension of potassium hydroxide (0.56 g, 10 mmol) in DMF (30 ml), benzoyl acetone was added (1.62 g, 10 mmol) and followed by phenyl isothiocyanate (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature and treated with the phenacyl bromide (1.99 g, 10 mmol); stirring was continued for 4 h. The reaction mixture was poured onto ice-cold water. Acidification using dilute HCl until the medium becomes acidic gave solid product **5** which was filtered off, washed with water, dried and recrystallized from aqueous ethanol to give compound **5**.

5.1.4.2. Pathway (2). Refluxing of acyclic intermediate **4** (4.07 g, 1 mmol) for 2 h in the presence of ethanol (10 ml)/DMF (10 ml) and TEA (4 drops) the reaction mixture was left to cool, and collected the solid product which dried well and recrystallized from ethanol to give compound **5**.

Yellow crystal (Yield 45%), m.p. 127 °C; IR (KBr): $\bar{\nu}/cm^{-1} = 3422$ (NH), 1741 and 1627 for two (C=O); ^1H NMR: (DMSO-d_6), δ 1.62 (s, 3H, CH_3), 7.1–7.5 (m, 15H, Ar), 11.59 (s, 1H, NH); Anal. Calcd for $C_{25}H_{19}NO_2S$ (397): C, 75.54; H, 4.82; N, 3.52; Found: C, 75.20; H, 4.62; N, 3.29.

*5.1.5. 4-Benzoyl-3-methyl-5-(phenylamino)thiophene-2-carboxylic acid (**8**)*

To a cold suspension of potassium hydroxide (0.56 g, 10 mmol) in DMF (30 ml), benzoyl acetone was added (1.62 g, 10 mmol) and followed by phenyl isothiocyanate (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature and treated with the ethyl bromoacetate and/or chloroacetonitrile and/or chloroacetyl chloride (10 mmol); stirring was continued for 4 h. The reaction mixture was poured onto ice-cold water. Acidification using dilute HCl until the medium becomes acidic gave solid product **8** which was filtered off, washed with water, dried and recrystallized from aqueous ethanol to give compound **8**.

Yellow crystal (Yield 65%), m.p. 230 °C; IR (KBr): $\bar{\nu}/cm^{-1} = 3421$ (NH), 1727 and 1662 for two (C=O); ^1H NMR: (DMSO-d_6), δ 1.8 (s, 3H, CH_3), 7.1–7.5 (m, 10H, Ar), 10.8 (s, 1H, COOH), 11.79 (s, 1H, NH); MS: *m*/*z* (%) 337 (M^+, 9), 294 (62.95), 232 (27.78), 221 (33.99), 190 (32.78), 144 (13.15), 105 (100), 77 (98.80); Anal. Calcd for $C_{19}H_{15}NO_3S$ (337): C, 67.65; H, 4.45; N, 4.15; Found: C, 67.35; H, 4.15; N, 3.85.

Table 2
Molluscicidal activity of compounds (**5**, **8**, **15**, **17**, **20a–c** and **22**) expressed as LC_{50} and LC_{90} in ppm

Compound number	LC_{50} (C.L.)[a]	LC_{90} (C.L.)[a]
5	15.6 [11–80]	20 [15–78]
8	19 [15–33]	23 [22–65]
15	18 [16–61]	20 [15–60]
17	16 [14–85]	22 [18–85]
20a	8 [7–65]	10 [9–60]
20b	5.5 [4–12]	9 [8–32]
20c	6 [5–20]	11 [10–15]
22	13 [12–63]	18 [16–65]

[a] Confidence limit.

Table 1
The mean number of snails killed ±1 after an exposure time of 24 h at concentrations in ppm

Compound number	**4** (ppm)	**6** (ppm)	**8** (ppm)	**10** (ppm)	**12** (ppm)	**14** (ppm)	**16** (ppm)
5	1	4	5	6	9	10	10
8	1	2	3	5	6	8	10
15	0	1	1	2	2	4	10
17	1	3	5	8	8	10	10
20a	2	2	4	6	9	10	10
20b	2	3	5	8	10	10	10
20c	1	3	4	7	10	10	10
22	1	3	4	8	9	10	10

*5.1.6. Ethyl-4-benzoyl-3-methyl-5-(phenylamino)thiophene-2-carboxylate (**15**)*

To a cold suspension of potassium hydroxide (0.56 g, 10 mmol) in DMF (30 ml), benzoyl acetone was added (1.62 g, 10 mmol) and followed by phenyl isothiocyanate (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature and treated with the bromodiethyl malonate (2.39, 10 mmol), stirring was continued for 4 h. The reaction mixture was poured onto ice-cold water. Acidification using dilute HCl until the medium becomes acidic gave solid product **15** which was filtered off, washed with water, dried and recrystallized from aqueous ethanol to give compound **15**.

Yellow crystal (Yield 70%), m.p. 162 °C; IR (KBr): $\overline{\nu}/cm^{-1} = 3448$ (NH), 1710 and 1670 for two (C=O); MS: *m/z* (%) 365 (M^+, 100), 304 (20.54), 260 (10.69), 246 (12.32), 147 (11.70), 128 (6.79), 77 (31.43); Anal. Calcd for $C_{21}H_{19}NO_3S$ (365): C, 69.02; H, 5.24; N, 3.83; Found: C, 68.72; H, 4.94; N, 3.53.

*5.1.7. 1-4-Benzoyl-3-methyl-5-(phenylamino)thiophene-2-ethanone (**17**)*

To a cold suspension of potassium hydroxide (0.56 g, 10 mmol) in DMF (30 ml), benzoyl acetone was added (1.62 g, 10 mmol) and followed by phenyl isothiocyanate (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature and treated with the chloroacetone (0.925, 10 mmol), stirring was continued for 4 h. The reaction mixture was poured onto ice-cold water. Acidification using dilute HCl until the medium becomes acidic gave solid product **17** which was filtered off, washed with water, dried and recrystallized from aqueous ethanol to give compound **17**.

Yellow crystal (Yield 59%), m.p. 230 °C; IR (KBr): $\overline{\nu}/cm^{-1} = 3444$ (NH), 1710 and 1665 for two (C=O); ^{1}H NMR: (DMSO-d_6), δ 2.2 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.1–7.7 (m, 10H, Ar), 10.24 (s, 1H, NH); MS: *m/z* (%) 335 (M^+, 22), 304 (20.54), 260 (10.69), 246 (12.32), 147(21); Anal. Calcd for $C_{20}H_{17}NO_2S$ (335): C, 71.62; H, 5.11; N, 4.17; Found: C, 71.321; H, 4.81; N, 3.77.

*5.1.8. (Z)-1-Phenyl-2-(3-phenyl-1,3,4-thiadiazol-2-(3H)-ylidene)butane-1,3-dione (**20a**)*

A mixture of **3** (2.97 g, 10 mmol) and phenylazophenacyl bromide (3.03 g, 10 mmol) in the presence of boiling ethanol (20 ml) and TEA (4 drops) was heated for 2 h. The solid product that separated while hot was precipitated on hot then filtered off, dried and recrystallized from DMF:EtOH (1:1) to give compound **20a**.

Yellow crystal (Yield 87%), m.p. 188 °C; IR (KBr): $\overline{\nu}/cm^{-1} = 3060$ (CH_3), 1670 and 1665–1660 for three (C=O); MS: *m/z* (%) 426 (M^+, 12); Anal. Calcd for $C_{25}H_{18}N_2O_3S$ (426): C, 70.40; H, 4.25; N, 5.63; Found: C, 70.40; H, 4.00; N, 5.33.

*5.1.9. (Z)-2-(3-(p-Tolyl)-1,3,4-thiadiazol-2-(3H)-ylidene)-1-phenyl-butane-1,3-dione (**20b**)*

A mixture of **3** (2.97 g, 10 mmol) and *p*-tolylazo phenacyl bromide (3.17 g, 10 mmol) in the presence of boiling ethanol and TEA (4 drops) was heated for 2 h. The reaction mixture precipitated on hot then filtered off dried and recrystallized from DMF:EtOH (1:1) to give compound **20b**.

Yellow crystal (Yield 74%), m.p. 226 °C; IR (KBr): $\overline{\nu}/cm^{-1} = 3060$ and 3065 for two (CH_3), 1675 and 1660–1670 for three (C=O); ^{1}H NMR: (DMSO-d_6), δ 1.97 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.1–7.8 (m, 14H, Ar); MS: *m/z* (%) 440 (M^+, 26). Anal. Calcd for $C_{26}H_{20}N_2O_3S$ (440): C, 70.89; H, 4.58; N, 6.36; Found: C, 70.88; H, 4.50; N, 3.00.

*5.1.10. (Z)-2-(3-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-(3H)-ylidene)-1-phenylbutane-1,3-dione (**20c**)*

A mixture of **3** (2.97 g, 10 mmol) and 4-methoxyphenylazo-phenacyl bromide (3.33 g, 10 mmol) in the presence of boiling ethanol and TEA (4 drops) was heated for 2 h. The reaction mixture precipitated on hot then filtered off dried and recrystallized from DMF:EtOH (1:1) to give compound **20c**.

Yellow crystal (Yield 35%), m.p. 210 °C; IR (KBr): $\overline{\nu}/cm^{-1} = 3060$ and 3100 for two (CH_3), 1670 and 1660–1670 for three (C=O); ^{1}H NMR: (DMSO-d_6), δ 2.3 (s, 3H, CH_3), 4.0 (s, 3H, CH_3), 7.1–7.8 (m, 14H, Ar), 10.24 (s, 1H, NH); MS: *m/z* (%) 456 (M^+, 85); Anal. Calcd for $C_{26}H_{20}N_2O_4S$ (456): C, 68.41; H, 4.42; N, 5.26; Found: C, 68.40; H, 4.42; N, 5.00.

*5.1.11. (3-Methyl-5-(phenylamino)-1H-pyrazol-4-yl)(phenyl)methanone (**22**)*

A mixture of equimolecular amounts of **3** (2.97 g, 10 mmol) and hydrazine hydrate (0.32 g, 10 mmol) was refluxed in ethanol (20 ml) and TEA (4 drops) for 2 h. The reaction mixture was poured onto ice-cold water, filtered off and recrystallized from ethanol to give the corresponding pyrazole **22**.

Yellow crystal (Yield 76%), m.p. 160 °C; IR (KBr): $\overline{\nu}/cm^{-1} = 3405$ and 3286 (two NH), 1665 (C=O); MS: *m/z* (%) 277 (M^+, 42); Anal. Calcd for $C_{17}H_{15}N_3O$ (277): C, 73.63; H, 5.45; N, 15.16; Found: C, 73.33; H, 5.15; N, 14.86.

5.2. Molluscicidal activity tests

The molluscicidal activity tests were carried out by determination of the half lethal dose LC_{50} and sublethal dose LC_{90} of each compound under investigation. *B. alexandrina* snails were collected from the field (water canals) and maintained under laboratory conditions for a period of 45 days before the tested and fed daily with lettuce leaves. Then, the snails were examined to ensure that they were free from parasitic infection. A series of concentrations (seven) ranging from 4 to 16 ppm of each compound under investigation were prepared. The required amount of the compound under investigation was mixed thoroughly with few drops of Tween 20 followed by addition of the appropriate volume of untreated raw water (taken directly from the River Nile) to get a homogeneous suspension with the necessary concentration, it was poured in glass jar vessels 15 × 25 × 20 cm dimensions fitted with air bubblers. Ten snails having the same size and diameter (ca. 7 mm) were used in each experiment and maintained in the tested solution under laboratory conditions at ambient temperature for 24 h. Each experiment was repeated three times and the mean number of killed snails was taken for each concentration as shown in Table 1. A control group was taken by placing 10 snails in water containing few drops of Tween 20. These bioassays are in accordance with the W.H.O. guidelines [24].

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