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Synthesis and evaluation of molluscicidal and larvicidal activities of some novel enaminones derived from 4-hydroxyquinolinones: Part IX

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Abstract—A series of 10 3-(hetarylaminomethylene)quinolinediones, 12 3-(substituted aminopropenoyl)-4-hydroxyquinolinones, and 10 3-(substituted aminomethylene-5-oxo-pyrazolinyl)-4-hydroxyquinolinones were synthesized as novel enaminones derived from 3-(un)substituted 4-hydroxyquinolin-2(1*H*)-ones in 72–94% yields and assayed for their molluscicidal activities against *Biomphalaria alexandrina* and *Lymnaea natalensis* snails. Some of the tested enaminones presented high molluscicidal activities ($LC_{50} \leqslant 20$ ppm). The new compounds showed more potency against hatchability of *B. alexandrina* egg masses, the infection rate and prepatent period of the snails. In addition, these derivatives revealed potential larvicidal effects (100% mortality) on both miracidia and cercariae of *Schistosoma mansoni* at reduced exposure time. The selected active derivatives were examined against *Daphnia magna* and their nontoxic effect at all sublethal, lethal, and higher concentrations suggests that these compounds can play an important role as molluscicides and larvicides with environmental safe properties.

1. Introduction

Schistosomiasis is the second most imperative tropical parasitic disease of humans after malaria especially in the developing world with an estimation that at least 200 million people, in 74 countries, are currently infected and 600 million are at risk of infection. Annual mortality due to schistosomiasis was estimated at 15,000 deaths/year and the burden of disease at 1.702 million DALYs lost per year. About 20 million people suffer several consequences from the disease and 120 million are symptomatic.[1,2] Although the current strategy for morbidity control is largely based on chemotherapy,[2] control of the snail host using molluscicides to stop transmission cycle is still considered a vital role because the use of molluscicides in the prophylactic treatment leads to the rupture of evolutionary lifecycle of the worm via destructing its intermediate host.[3] The successful control program of the disease should be constructed as an integrated control scheme including chemotherapy, molluscicidal, ecological, and biological control methods.[4] Thus, it was reported that a problem of resistance of *Schistosoma mansoni* to praziquantel had been sought and further research is needed for exploring alternative drugs to treat praziquantel-resistant schistosomiasis.[5] On the other hand, the well-known environmental hazardous effects of the most used molluscicides, for example, copper sulfate and niclosamide, promoted a considerable and systematic search for new molluscicides which might provide effective control agents for snails and be harmless to the nontargeted beings in the environment.[6] Many quinoline alkaloids[7] and quinolinone derivatives[8] were reported to exhibit important molluscicidal potency. In addition, atanine, a quinolinone alkaloid, showed potential activity against larvae, adults of *Caenorhabditis elegans* and miracidia, and cercariae of *S. mansoni*.[9] As a part of our research work on synthesis of substituted quinolinones attached with biological properties, we describe the synthesis and investigation of the molluscicidal and larvicidal activity of new enaminones derived from 4-hydroxyquinolin-2(1*H*)-ones as potential drug candidates against schistosomiasis at transmission stages.

Keywords: Quinolinone; Enaminone; Molluscicide; Larvicide.
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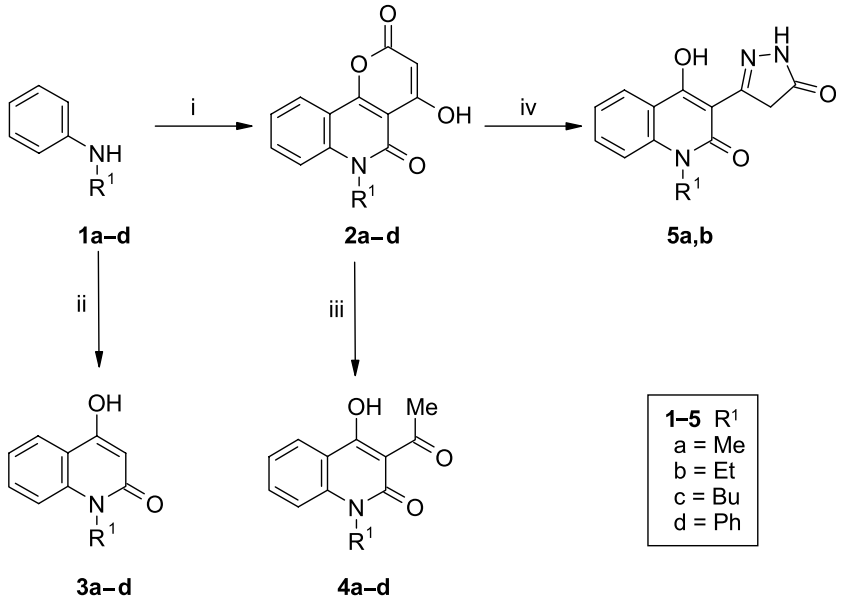
2. Results and discussion

2.1. Synthesis of the compounds

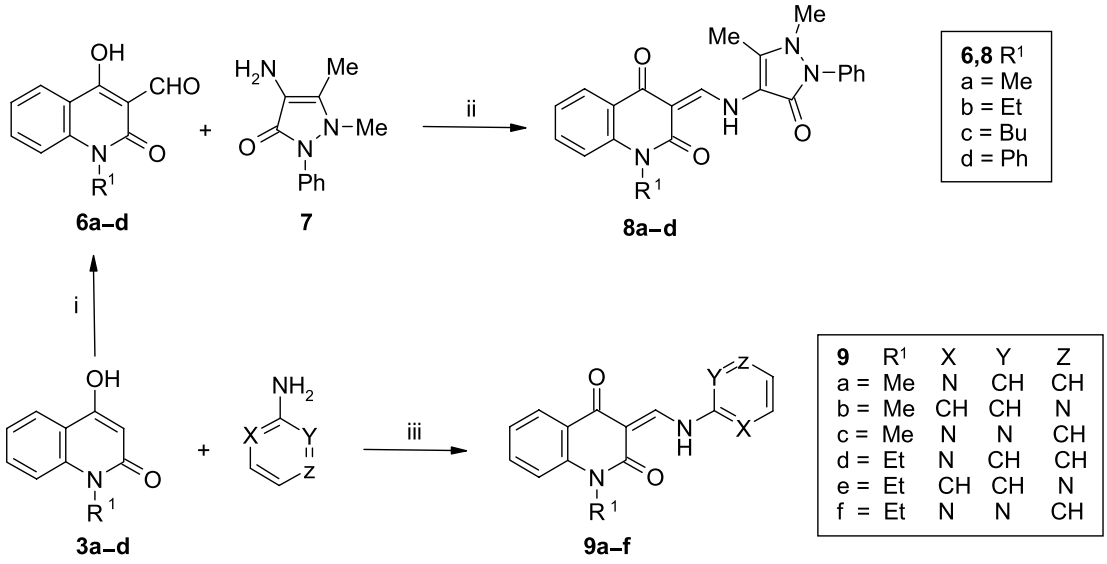
As illustrated in the Scheme 1, compounds **2a–d**[10,11] and **3a–d**[12] were prepared by condensation of the proper *N*-alkylanilines or diphenylamine with diethyl malonate. Alkaline hydrolysis of **2a–d** furnished the 3-acetylquinolinones **4a–d**,[11] while the hydrazinolysis of **2a,b** led to the formation of 3-(pyrazolinyl)quinolinones **5a,b**.[13]

Compounds **3a–d**, **4a–d**, and **5a,b** were utilized as synthetic precursors for three groups of enaminone derivatives. Thus, Riemer–Tiemann formylation of the 4-hydroxyquinolin-2(1*H*)-ones **3a–d** using chloroform and sodium hydroxide[14] afforded the corresponding aldehydes **6a–d** that on condensation with 4-aminoantipyrine (**7**) in the presence of glacial acetic acid gave 3-(pyrazolinylaminomethylene)quinolinediones **8a–d** in 81–94% yields. The synthesis of 3-(pyridyl or pyrimidyl-aminomethylene)quinolinediones **9a–f** was conveniently achieved in one pot by heating compound **3a** or **3b** with the adequate amounts of 2- or 3-aminopyridine or 2-aminopyrimidine and dimethylformamide dimethylacetal (DMF-DMA) (Scheme 2).

3-[3-(Dimethylamino)prop-2-enoyl]-4-hydroxyquinolin-2(1*H*)-one derivatives **10a–d** were prepared in fair yields



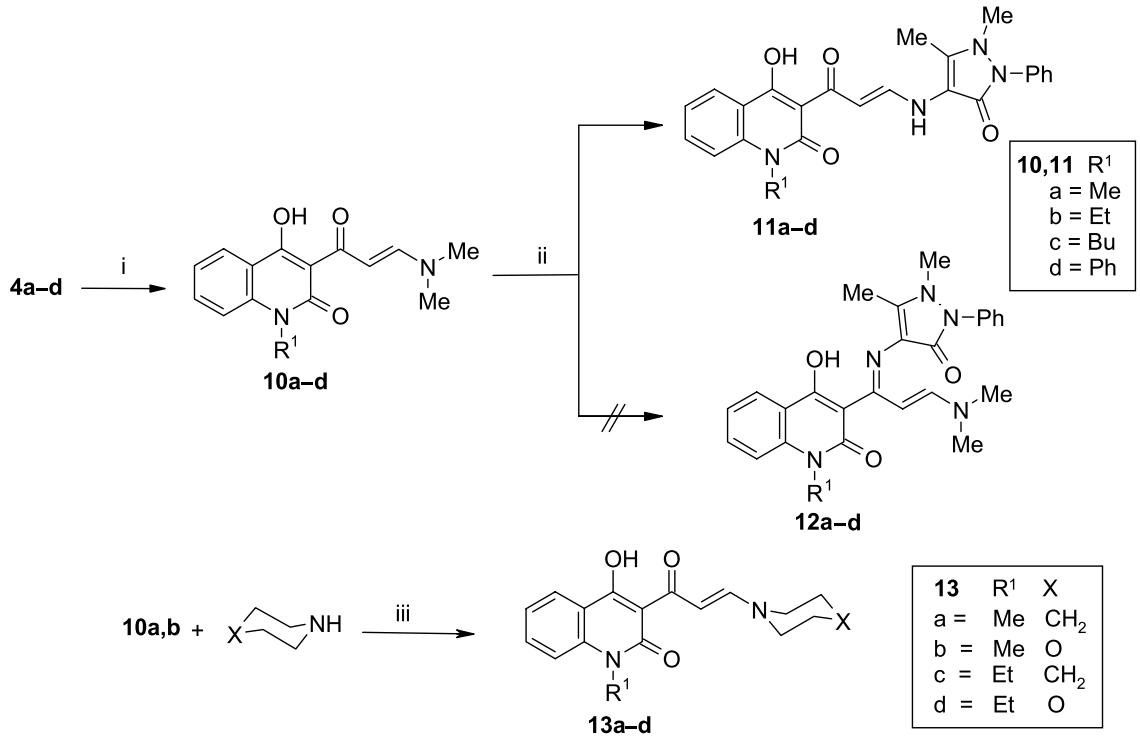
Scheme 1. Reagents and conditions: (i) diethyl malonate, 220 °C, 8 h; (ii) diethyl malonate, PPA, 170–200 °C, 2 h; (iii) NaOH (15 %), reflux, 2 h; (iv) $N_2H_4{\cdot}H_2O$, DMF, reflux, 1 h.



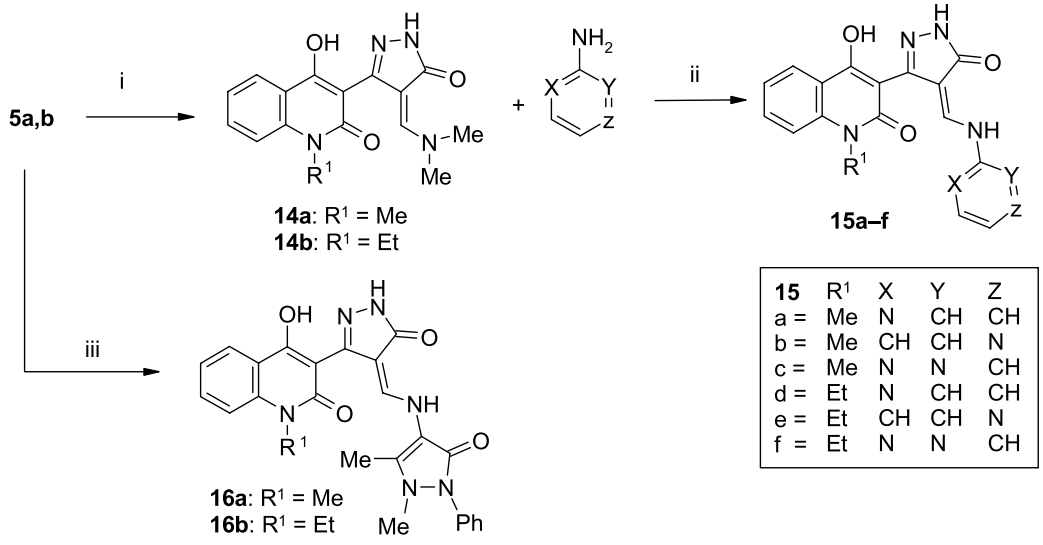
Scheme 2. Reagents and conditions: (i) $CHCl_3$, NaOH (15%), reflux, 6 h; (ii) AcOH, reflux, 2 h; (iii) DMF-DMA, toluene, 110 °C, 2 h.

via thermal condensation of their respective 1-substituted 3-acetylquinolinones **4a–d** with DMF-DMA. The structure of these propenoylquinolinones was assigned as the *E*-form, where the coupling constant of the olefinic protons is in the range 13–16 Hz. To obtain other enaminone derivatives bearing heterocycles of biological interest, the compounds **10a–d** were subjected to react with 4-aminoantipyrine (**7**) affording the corresponding 4-hydroxy-3-[3-(pyrazolinylamino)propenoyl]quinolinones **11a–d**. The probable product **12** for the later reaction was definitely excluded on the basis of ^{1}H NMR spectral data which evidently revealed that the product does not include the *N*,*N*-dimethylamino group, a result which was fortified by the found analytical data. Similarly, reaction of the compounds **10a,b** with piperidine and morpholine as alicyclic secondary amines smoothly proceeded leading to the corresponding 1-alkyl-3-[3-(piperidinyl or morpholinyl)propenoyl]quinolinones **13a–d** in good yields (Scheme 3).

In analogy to the above methodology, the pyrazolinones **5a,b** were subjected to condensation with DMF-DMA



Scheme 3. Reagents and conditions: (i) 4-aminoantipyrine (71), DMF-DMA, toluene, 110 °C, 2 h; (ii) AcOH, reflux, 2 h; (iii) reflux, 2 h.



Scheme 4. Reagents and conditions: (i) DMF-DMA, *p*-xylene, reflux, 2 h; (ii) AcOH, reflux, 1 h; (iii) 4-aminoantipyrine (7), $CH(OEt)_3$, $(CH_2OH)_2$, 110–190 °C, 1 h.

Table 1. Molluscicidal activity of the enaminone derivatives against *Biomphalaria alexandrina* and *Lymnaea natalensis* (10 snails per concentration) after 24 h exposure at ambient temperature 24 ± 1 °C

Compound	Snail	LC_{10} (ppm)	LC_{25} (ppm)	LC_{50} (ppm)	LC_{90} (ppm)	Slope[a]
8a	*B. alexandrina*	9.24	18.14	28.14	46.83	1.88
	L. natalensis	8.65	13.69	19.31	29.96	1.64
9a	*B. alexandrina*	7.90	13.69	20.13	32.36	1.74
	L. natalensis	2.01	8.10	14.90	27.96	2.54
9b	*B. alexandrina*	3.77	21.49	41.19	78.65	2.78
	L. natalensis	—	—	—	—	—
10a	*B. alexandrina*	14.84	30.31	47.51	89.18	2.00
	L. natalensis	12.91	30.31	40.41	59.88	1.72
10b	*B. alexandrina*	11.41	18.69	20.20	29.00	1.38
	L. natalensis	4.04	10.61	19.01	53.03	2.72
10c	*B. alexandrina*	2.66	6.11	15.88	34.40	2.96
	L. natalensis	4.80	8.30	15.80	61.10	2.99
14a	*B. alexandrina*	11.21	37.26	66.21	121.20	2.38
	L. natalensis	—	—	—	—	—

[a] Slope = $(LC_{84}/LC_{50} + LC_{50}/LC_{16})/2$.[24]

in boiling xylene to give 3-[4-(dimethylaminomethylene)pyrazolinyl]-4-hydroxyquinolinones **14a,b**. Herein again the dimethylamino group in this enaminone system acts as a good leaving group when these two compounds were treated with 2- or 3-aminopyridine or 2-aminopyrimidine in glacial acetic acid to afford the corresponding 4-(hetarylaminomethyene)pyrazolinones **15a–f** in 73–93% yields. A high yield and efficient synthesis of 4-(pyrazolinylaminomethyene)pyrazolinones **16a,b** was achieved via one pot reaction[13] of the pyrazolinones **5a,b** with 4-aminoantipyrine and triethyl orthoformate (Scheme 4).

2.2. Molluscicidal assays

Biomphalaria alexandrina is the historically implicated snail in the transmission of *S. mansoni* in Egypt.[15] In recent years, introduction of *Biomphalaria glabrata* and the recognized hybrids of the two species of intermediate host in Egyptian habitat has been reported.[16] For this reason, *B. alexandrina* is still a target for molluscicidal studies. In addition, many reports showed that *B. alexandrina* snails are more tolerant to the action of molluscicides than *Bulinus truncatus* snails which are also widespread in Egypt.[17] The examination of the new compounds against *B. alexandrina* would show their molluscicidal potency. Thus, Table 1 shows the evaluation of the toxic effect of some new enaminone derivatives on the adult *B. alexandrina* and *Lymnaea natalensis* snails. This table indicates the results of assays performed with LC_{10}, LC_{25}, LC_{50}, and LC_{90} (ppm) for some selected derivatives. The LC_{50} values in Table 1 indicated high molluscicidal activity of compounds **8a**, **9a,b**, and **10a–c** against *B. alexandrina* (LC_{50} 15.88–47.51 ppm). The rest of tested compounds estimated LC_{50} > 100 ppm, and hence they are considered inactive. Similar behavior for the screened compounds against *L. natalensis* snails (LC_{50} 14.90–40.41 ppm) was observed. The LC_{50} results revealed that the most active compounds against *B. alexandrina* snails are in the following sequence: **10c > 9a ⩾ 10b > 8a > 10a**. Against *L. natalensis* snails, the order of activity is **9a ⩾ 10c > 10b ⩾ 8a > 10a**. The structure–activity relationship in the group of compounds **10a–c** revealed

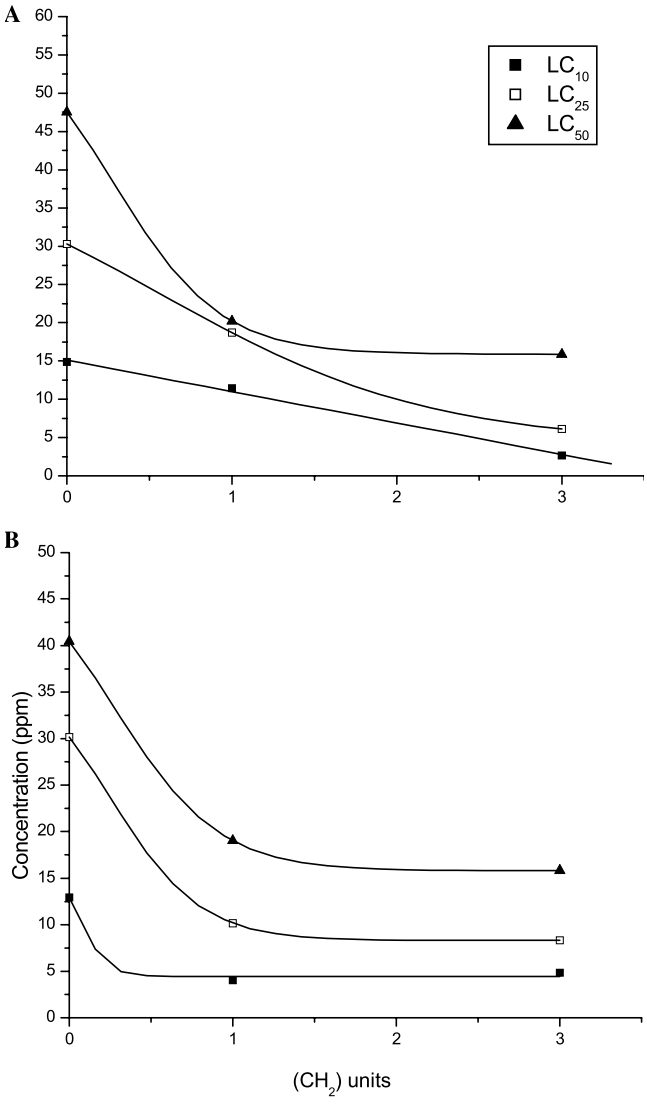


Figure 1. Effect of increment of (CH_2) units in *N*-alkyl group of compounds **10a–c** on LC_{10-50} values as function of activity against (A) *Biomphalaria alexandrina* and (B) *Lymnaea natalensis* snails.

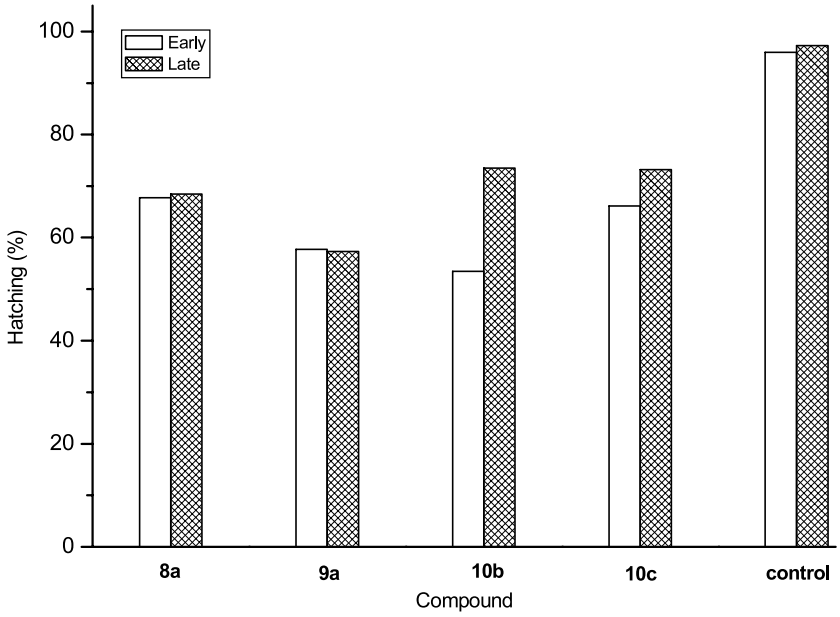


Figure 2. Effect of the tested enaminone derivatives (at LC_{25} values) on hatching % of *B. alexandrina* snails egg masses at the early and late stages.

that the activity of these derivatives increases within the increase of the lipophilicity of the molecule against either *B. alexandrina* or *L. natalensis* snails at sublethal and lethal concentrations (LC_{10}, LC_{25}, and LC_{50}). The relationship between LC_{10} values against *B. alexandrina* snails and the number of (CH_2) units, in the *N*-alkyl group in compounds **10a–c**, is linear and can be formulated as: $LC_{10} = 15-4n$, where n is the number of (CH_2) units. However, this equation is limited to $n = 0–3$, but the mode of lines in Figure 1 shows a fast change on going from *N*-methyl to *N*-ethyl derivatives and smaller differences with further alkyl chain elongation.

Figure 2 represents the hatchability of *B. alexandrina* snails' egg masses exposed to the sublethal concentration LC_{25} of compounds **8a**, **9a**, **10b**, and **10c**. The figure indicates that the tested compounds reduced the hatching percentage and their effect is extended to the aged eggs. Even if hatchability increases on late stage by ca. 7–20%, it is obvious that the values are still lesser than control value by ca. 24–40% (Fig. 2). Interestingly, it was found that LC_{50} concentrations of the cited four compounds caused a maximum effect on hatching percentage (0–5%) at both early and late stages after exposure for 24 h. These results showed that these compounds, in particular compound **9a**, can be considered for excellent control of generation of snails at lethal concentration.

The infection rate of *B. alexandrina* snails treated with *S. mansoni* miracidia was studied in both test and control aquaria. In test aquaria, the snails were exposed to the sublethal concentration (LC_{25}) of the tested compounds **8a**, **9a**, **10b**, and **10c**. It was found that compound **10b** is the most effective as it reduced the infection rate to 54.54%, a result that is about 40% less than control value (Table 2).

Table 2. Effect of the enaminone derivatives on the infection rate and prepatent period of *Biomphalaria alexandrina* snails, pre-exposed to LC_{25} concentrations

Compound	No. of shedding snails[a]	Infection rate (%)	Prepatent period (day)		
			Min	Max	Mean
8a	15	68.19	32	60	46 ± 19.8[b]
9a	18	81.82	32	46	39 ± 9.9[b]
10b	12	54.54	32	66	49 ± 24.0[c]
10c	14	63.64	40	46	43 ± 4.2[c]
Control	21	95.45	28	30	29 ± 1.4

[a] Number exposed per test = 22 snails.
[b] Normal distribution statistical significant $P < 0.01$.
[c] Normal distribution statistical significant $P < 0.001$.

Comparison of the prepatent period of *S. mansoni* in the *B. alexandrina* snails exposed to LC_{25} concentrations of compounds **8a**, **9a**, **10b**, and **10c** with the control value can indicate their strong effect. Table 2 shows that the exposure to the tested compounds extended the mean prepatent period to 39–49 days, while the control value is only 29 days. Normal distribution patterns were estimated and are statistically significant at $P < 0.01$ for compounds **8a** and **9a** and $P < 0.001$ for compounds **10b** and **10c** (Table 2).

2.3. Larvicidal assays

The larvicidal activity of compounds **8a**, **9a**, **10a**, **10b**, and **10c** was carried out against the free larval stages of *S. mansoni*: miracidia and cercariae. The miracidal activity is presented in Table 3, which indicated very high efficiency of the tested compounds on using their sublethal or lethal concentrations LC_{10}, LC_{25}, and LC_{50}. Compound **9a** caused 100% mortality at concentration of 7.9 ppm in 65 min, while compound **10c** showed the same activity at 6.11 ppm in 55 min. It is notable that 100% mortality took place on exposure to

Table 3. Time required for 100% mortality of *Schistosoma mansoni* miracidia and cercariae exposed to sub-lethal and lethal concentrations of the enaminone derivatives

Compound	Time of exposure (min)[a]					
	Miracidia			Cercariae		
	LC_{10}	LC_{25}	LC_{50}	LC_{10}	LC_{25}	LC_{50}
8a	160	60	45	640	300	195
9a	65	60	55	420	260	120
10a	125	100	65	720	360	240
10b	145	45	40	180	65	40
10c	140	55	55	185	125	25

[a] Control gives 100% mortality after 24 h.

the tested compounds at LC_{50} within an hour (Table 3). Cercaricidal activity is presented in Table 3, which revealed that 100% mortality occurred on exposure to LC_{50} concentrations of the tested compounds **8a**, **9a**, **10a**, **10b**, and **10c** within time range 25–240 min. It can be recognized from the results that compound **10c** caused 100% mortality of cercariae in only 25 min at concentration of 15.88 ppm. Time needed for 100% mortality using LC_{10} and LC_{25} concentrations revealed that lower concentrations would not give satisfactory results (Table 3).

2.4. Toxicity against *Daphnia magna*

Daphnia is a commonly used model organism in ecotoxicological studies. Acute toxicity test against *D. magna* is useful as an early warning test for monitoring environment hazardous chemical treatments of water.[18] The known molluscicides such as niclosamide and copper sulfate showed considerable toxic effect against *Daphnia* at their lethal concentrations.[18–21] Remarkably, the present tested molluscicides showed 0% mortality on *D. magna* test at all of their sublethal and lethal concentrations (LC_{10}, LC_{25}, LC_{50}, and LC_{90}) after 48 h exposure. Only compound **10b** revealed 50% mortality of *D. magna* at concentration of 100 ppm after 72 h. Moreover, examination of exposure *Daphnia* to high concentrations (300 ppm) of the tested compounds **8a**, **9a**, and **10c** for 48–72 h showed no significant toxicity toward this organism, while LC_{50} of copper sulfate caused 30% *Daphnia* mortality. The results point to the environmental safety of the use of these new synthetic molluscicides.

3. Conclusions

The present study deals with the synthesis of a novel family of potential molluscicides, in which their preparation is convenient and their yields are satisfactory. The synthesis of a series of enaminones derived from the readily available 4-hydroxy-, 3-acetyl-4-hydroxy-, and 4-hydroxy-3-(5-oxopyrazolinyl)quinolin-2(1*H*)-ones was described. The new compounds showed potent activities against *B. alexandrina* and *L. natalensis* snails. The structure–activity relationship revealed that molluscicidal activity of 1-alkyl-3-(dimethylaminopropenoyl)-4-hydroxyquinolinones is correlated with the lipophilicity of the molecule. The potent molluscicides showed strong effect on hatchability of *B. alexandrina* eggs at different stages. In addition, the infection rate and prepatent period of *B. alexandrina* snails were remarkably controlled on exposure to the tested enaminones. Larvicidal effect of the new compounds against *S. mansoni* miracidia and cercariae revealed their high efficacy. Examination of the toxicity of the candidate molluscicides against *D. magna* showed the advantages of these new compounds, which are environmentally safe, possess potent molluscicidal and larvicidal activities, and are easily prepared. Further experiments and studies on the molluscicidal and cercaricidal action of these new compounds are currently carried out along with their application in the field of chemotherapy of schistosomiasis.

4. Experimental

Melting points were uncorrected and were determined in open capillary tubes on a digital Gallen-kamp MFB-595 apparatus. Infrared spectra were recorded on a Perkin-Elmer 1650 FT-IR spectrophotometer, using samples in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Brucker AC200 (200 MHz) or Varian Gemini (200 MHz, operating at 50 MHz for ^{13}C), using TMS as internal standard and C*D*Cl$_3$ or DMSO-d_6 as solvents. Mass spectra were taken on a Shimadzu GCMS QP-1000EX instrument by direct inlet technique at beam energy 70 eV. Elemental microanalyses were performed on a Perkin-Elmer 2400 analyzer. Compounds **3a–d**,[12] **4a–d**,[11] **5a,b**,[13] and **6a–d**[14] were obtained according to the previously described procedures.

4.1. General procedure for the preparation of 3-[(pyrazolinylamino)methylene]quinoline-2,4-diones (8a–d)

A mixture of the appropriate aldehydes **6a–d** (10 mmol) and 4-aminoantipyrine (**7**) (12 mmol) in glacial acetic acid (30 mL) was heated under reflux for 2 h. Then, the reaction mixture was left to stand at room temperature overnight and the resulting crystalline material was collected by filtration, washed with cold ethanol, and recrystallized from the proper solvent.

4.1.1. 3-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)methylene]-1-methylquinoline-2,4(1*H*,3*H*)-dione (8a). Prepared from the aldehyde **6a** (2.03 g) and amine **7** (2.44 g) and crystallized from acetic acid. Yield 3.49 g (90%); mp 243–244 °C. IR (KBr): ν_{max} 3218, 3062, 2945, 1646 (C=O), 1605, 1580, and 1525 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.21 (s, 3H, 5-$CH_{3pyrazoline}$), 3.21 (s, 3H, N–$CH_{3pyrazoline}$), 3.80 (s, 3H, N–$CH_{3quinoline}$), 7.18–7.79 (m, 8H, H_{arom}), 8.18 (d, J = 7 Hz, 1H, 5-H), 8.45 (d, J = 12.9 Hz, 1H, C=C*H*–N), 11.25 (b, 1H, N–H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.7, 33.6, 35.8, 103.3, 112.7, 119.8, 120.9, 123.6, 124.6, 127.4, 128.1, 128.8, 129.2, 132.3, 139.8, 140.9, 145.2, 160.9, 164.8, 182.6; MS: *m*/*z* (I%) 388 (M^+, 29), 189 (100). Anal. Calcd for $C_{22}H_{20}N_4O_3$ (388.43): C, 68.03; H, 5.19; N, 14.42. Found: C, 67.94; H, 5.15; N, 14.43.

4.1.2. 3-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)methylene]-1-ethylquinoline-2,4(1*H*,-3*H*)-dione (8b). Prepared from the aldehyde **6b** (2.17 g) and amine **7** (2.44 g) and crystallized from ethanol. Yield 3.69 g (92%); mp 168–169 °C. IR (KBr): ν_{max} 3208, 3073, 2949, 2862, 1643 (C=O), 1621, 1603, 1574, and 1517 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, 3H, N–CH_2CH_3), 2.23 (s, 3H, 5-$CH_{3pyrazoline}$), 3.19 (s, 3H, N–$CH_{3pyrazoline}$), 3.52 (q, 2H, N–CH_2CH_3), 7.15–7.81 (m, 8H, H_{arom}), 8.17 (d, J = 6.8 Hz, 1H, 5-H), 8.43 (d, J = 12.8 Hz, 1H, C=C*H*–N), 11.65 (b, 1H, N–H); MS: *m*/*z* (I%) 402 (M^+, 32), 202 (100). Anal. Calcd for $C_{23}H_{22}N_4O_3$ (402.46): C, 68.64; H, 5.51; N, 13.92. Found: C, 68.56; H, 5.55; N, 13.84.

4.1.3. 1-Butyl-3-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-methylene]quinoline-2,4(1*H*,-3*H*)-dione (8c). Prepared from the aldehyde **6c** (2.45 g) and amine **7** (2.44 g) and crystallized from methanol. Yield 3.48 g (81%); mp 146–148 °C. IR (KBr): ν_{max} 3178, 3067, 2927, 2908, 2843, 1641 (C=O), 1622, 1602, 1571, and 1525 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.97 (t, 3H, N–$(CH_2)_3CH_3$), 1.30 (m, 4H, N–$CH_2(CH_2)_2CH_3$), 2.22 (s, 3H, 5-$CH_{3pyrazoline}$), 3.27 (s, 3H, N–$CH_{3pyrazoline}$), 3.82 (t, 2H, N– $CH_2(CH_2)_2$ CH_3), 7.12–7.68 (m, 8H, H_{arom}), 8.09 (d, J = 7 Hz, 1H, 5-H), 8.58 (d, J = 12.4 Hz, 1H, C=C*H*–N), 12.05 (b, 1H, N–H); MS: *m*/*z* (I%) 430 (M^+, 28), 186 (100). Anal. Calcd for $C_{25}H_{26}N_4O_3$ (430.51): C, 69.75; H, 6.09; N, 13.01. Found: C, 69.73; H, 5.96; N, 12.95.

4.1.4. 3-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)methylene]-1-phenylquinoline-2,4(1*H*,-3*H*)-dione (8d). Prepared from the aldehyde **6d** (2.65 g) and amine **7** (2.44 g) and crystallized from DMF. Yield 3.80 g (84%); mp 269–270 °C. IR (KBr): ν_{max} 3208, 3073, 2949, 2862, 1643 (C=O), 1621, 1603, 1574, and 1517 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.22 (s, 3H, 5-$CH_{3pyrazoline}$), 3.24 (s, 3H, N–$CH_{3pyrazoline}$), 7.12–7.83 (m, 13H, H_{arom}), 8.09 (d, J = 6.8 Hz, 1H, 5-H), 8.55 (d, J = 12.7 Hz, 1H, C=C*H*–N), 11.46 (b, 1H, N–H); MS: *m*/*z* (I%) 450 (M^+, 26), 77 (100). Anal. Calcd for $C_{27}H_{22}N_4O_3$ (450.50): C, 71.99; H, 4.92; N, 12.44. Found: C, 71.85; H, 4.78; N, 12.32.

4.2. General procedure for the preparation of 1-alkyl-3-[(pyridyl or pyrimidyl-amino)methylene]quinoline-2,4-diones (9a–f)

To a solution of the appropriate hydroxyquinolinones **3a–d** (10 mmol) in boiling toluene (50 mL) containing DMF-DMA (10 mmol), 2- or 3-aminopyridines or 2-pyrimidine (10 mmol) dissolved in hot toluene (25 mL) was added dropwise. After complete addition, the reaction mixture was heated at 110 °C for 2 h and then the excess solvent was evaporated in vacuum. The residual material was triturated with diethyl ether (25 mL), filtered off, and crystallized from the proper solvent.

4.2.1. 1-Methyl-3-[(2-pyridylamino)methylene]quinoline-2,4(1*H*,3*H*)-dione (9a). Prepared from the compound **3a** (1.75 g), 2-aminopyridine (0.94 g), and DMF-DMA (1.4 mL) and crystallized from DMF. Yield 2.32 g (83%); mp 274–275 °C. IR (KBr): ν_{max} 3240, 3171, 3067, 2946, 2884, 1660 (C=O), 1632 (C=O), 1618, 1602, 1563, and 1505 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.76 (s, 3H, N–CH_3), 6.69–7.63 (m, 6H, H_{arom}), 8.12 (d, J = 8 Hz, 1H, 2-$H_{pyridine}$), 8.18 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$), 8.49 (d, J = 12.6 Hz, 1H, C=C*H*–N), 11.51 (b, 1H, N–H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 34.5, 108.3, 112.7, 116.6, 120.8, 125.2, 127.6, 129.8, 134.1, 137.8, 147.1, 155.4, 162.8, 163.6, 187.5; MS: *m*/*z* (I%) 279 (M^+, 36), 186 (100). Anal. Calcd for $C_{16}H_{13}N_3O_2$ (279.30): C, 68.81; H, 4.69; N, 15.04. Found: C, 68.62; H, 4.55; N, 14.84.

4.2.2. 1-Methyl-3-[(3-pyridylamino)methylene]quinoline-2,4(1*H*,3*H*)-dione (9b). Prepared from the compound **3a** (1.75 g), 3-aminopyridine (0.94 g), and DMF-DMA (1.4 mL) and crystallized from dioxane. Yield 2.32 g (83%); mp 266–268 °C. IR (KBr): ν_{max} 3225, 3168, 3045, 2949, 2831, and 1658 (C=O), 1631 (C=O), 1622, 1605, 1586, and 1504 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.69 (s, 3H, N–CH_3), 6.89–7.65 (m, 5H, H_{arom}), 7.94 (d, J = 8 Hz, 1H, 6-$H_{pyridine}$), 8.15 (s, 1H, 2-$H_{pyridine}$), 8.18 (d, J = 6.8 Hz, 1H, 5-$H_{quinolinone}$), 8.41 (d, J = 12.4 Hz, 1H, C=C*H*–N), 11.78 (b, 1H, N–H); MS: *m*/*z* (I%) 279 (M^+, 54), 186 (100). Anal. Calcd for $C_{16}H_{13}N_3O_2$ (279.30): C, 68.81; H, 4.69; N, 15.04. Found: C, 68.70; H, 4.62; N, 14.88.

4.2.3. 1-Methyl-3-[(2-pyrimidylamino)methylene]quinoline-2,4(1*H*,3*H*)-dione (9c). Prepared from the compound **3a** (1.75 g), 2-aminopyrimidine (0.95 g), and DMF-DMA (1.4 mL) and crystallized from NMP. Yield 2.41 g (86%); mp 287–288 °C. IR (KBr): ν_{max} 3246, 3170, 3047, 2945, 2862, 1649 (C=O), 1630 (C=O), 1621, 1600, 1582, and 1506 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.64 (s, 3H, N–CH_3), 7.12–7.69 (m, 4H, H_{arom}), 7.89–7.96 (m, 2H, H_{arom}), 8.18 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$), 8.61 (d, J = 12.4 Hz, 1H, C=C*H*–N), 12.18 (b, 1H, N–H). Anal. Calcd for $C_{15}H_{12}N_4O_2$ (280.29): C, 64.28; H, 4.32; N, 19.99. Found: C, 64.15; H, 4.30; N, 20.01.

4.2.4. 1-Ethyl-3-[(2-pyridylamino)methylene]quinoline-2,4(1*H*,3*H*)-dione (9d). Prepared from the compound **3b** (1.89 g), 2-aminopyridine (0.94 g), and DMF-DMA (1.4 mL) and crystallized from ethanol. Yield 2.37 g (81%); mp 160–162 °C. IR (KBr): ν_{max} 3172, 3046, 2980, 2822, 2600, 1644–1630 (C=O), 1610, and 1595 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, 3H, N–CH_2CH_3), 3.69 (q, 2H, N–CH_2CH_3), 6.82–7.75 (m, 6H, H_{arom}), 8.05 (d, J = 8 Hz, 1H, 2-$H_{pyridine}$), 8.12 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$), 8.48 (d, J = 12.5 Hz, 1H, C=C*H*–N), 12.24 (b, 1H, N–H); MS: *m*/*z* (I%) 293 (M^+, 26), 201 (100). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.33): C, 69.61; H, 5.51; N, 14.33. Found: C, 69.50; H, 5.43; N, 14.08.

4.2.5. 1-Ethyl-3-[(3-pyridylamino)methylene]quinoline-2,4(1*H*,3*H*)-dione (9e). Prepared from the compound **3b** (1.89 g), 3-aminopyridine (0.94 g), and DMF-DMA (1.4 mL) and crystallized from ethanol. Yield 2.49 g (85%); mp 152–153 °C. IR (KBr): ν_{max} 3187, 2981, 2843, 1651 (C=O), 1637 (C=O), 1612, 1600, and

1576 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, 3H, N–CH_2CH_3), 3.53 (q, 2H, N–CH_2CH_3), 6.97–7.81 (m, 5H, H_{arom}), 8.05–8.12 (m, 3H, H_{arom}), 8.40 (d, J = 12.7 Hz, 1H, C=C*H*–N), 12.14 (b, 1H, N–H). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.33): C, 69.61; H, 5.51; N, 14.33. Found: C, 69.46; H, 5.37; N, 14.22.

4.2.6. 1-Ethyl-3-[(2-pyrimidylamino)methylene]quinoline-2,4(1*H*,3*H*)-dione (9f). Prepared from the compound **3b** (1.89 g), 2-aminopyrimidine (0.95 g), and DMF-DMA (1.4 mL) and crystallized from ethanol. Yield 2.35 g (80%); mp 145–147 °C. IR (KBr): ν_{max} 3183, 3076, 2962, 2823, 1645 (C=O), 1623, 1601, 1572, and 1508 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, 3H, N–CH_2CH_3), 3.52 (q, 2H, N–CH_2CH_3), 7.14–7.68 (m, 4H, H_{arom}), 7.96–8.14 (m, 3H, H_{arom}), 8.43 (d, J = 12.6 Hz, 1H, C=C*H*–N), 12.31 (b, 1H, N–H). Anal. Calcd for $C_{16}H_{14}N_4O_2$ (294.34): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.08; H, 4.54; N, 18.72.

4.3. General procedure for the preparation of 3-[3-(dimethylamino)propenoyl]quinolinones (10a–d)

To a solution of the acetylquinolinones **4a–d** (10 mmol), in dry toluene (50 mL), DMF-DMA (10 mmol) was added and then the reaction mixture was heated under reflux for 2 h. The excess solvent was evaporated in vacuum and the residual material was triturated with petroleum ether (60–80 °C; 25 mL), filtered off, and crystallized from the proper solvent.

4.3.1. 3-[2*E*-3-(Dimethylamino)prop-2-enoyl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (10a). Prepared from the acetylquinolinone **4a** (2.17 g) and DMF-DMA (1.4 mL) and crystallized from methanol. Yield 2.39 g (88%); mp 178–179 °C. IR (KBr): ν_{max} 3075, 2921, 2860, 1660 (C=O), 1649 (C=O), 1620, 1600, 1567, and 1504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.02 (s, 3H, $N(CH_3)_2$), 3.30 (s, 3H, $N(CH_3)_2$), 3.51 (s, 3H, N–CH_3), 7.05 (d, J = 15.7 Hz, 1H, COC*H*=CH–N), 7.21–7.66 (m, 3H, H_{arom}), 8.08 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$), 8.18 (d, J = 15.6 Hz, 1H, COCH=C*H*–N); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.21, 38.82, 39.01, 93.05, 115.44, 118.21, 122.35, 125.33, 128.82, 134.74, 141.32, 157.45, 161.05, 177.08, 187.39; MS: *m*/*z* (I%) 272 (M^+, 36), 228 (100). Anal. Calcd for $C_{15}H_{16}N_2O_3$ (272.31): C, 66.16; H, 5.92; N, 10.29. Found: C, 65.94; H, 5.76; N, 10.20.

4.3.2. 3-[2*E*-3-(Dimethylamino)prop-2-enoyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (10b). Prepared from the acetylquinolinone **4b** (2.31 g) and DMF-DMA (1.4 mL) and crystallized from ethanol. Yield 2.63 g (92 %); mp 148–149 °C. IR (KBr): ν_{max} 3124, 3038, 2974, 2928, 1643 (C=O), 1606, 1525, and 1493 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, 3H, N–CH_2CH_3), 3.09 (s, 3H, $N(CH_3)_2$), 3.25 (s, 3H, $N(CH_3)_2$), 4.27 (q, 2H, N–CH_2CH_3), 7.12 (d, J = 12.8 Hz, 1H, COC*H*=CH–N), 7.18–7.36 (m, 2H, H_{arom}), 7.60 (t, 1H, 7-$H_{quinolinone}$), 8.08 (d, J = 12.8 Hz, 1H, COCH=C*H*–N), 8.25 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$); MS: *m*/*z* (I%) 286 (M^+, 38), 242 (100). Anal. Calcd for $C_{16}H_{18}N_2O_3$ (286.33): C, 67.12; H, 6.34; N, 9.78. Found: C, 66.85; H, 6.21; N, 9.81.

4.3.3. 1-Butyl-3-[2*E*-3-(dimethylamino)prop-2-enoyl]-4-hydroxyquinolin-2(1*H*)-one (10c). Prepared from the acetylquinolinone **4c** (2.59 g) and DMF-DMA (1.4 mL) and crystallized from benzene. Yield 2.54 g (81%); mp 126–127 °C. IR (KBr): ν_{max} 3131, 3080, 2956, 2924, 2860, 1642 (C=O), 1622, 1526, and 1498 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, 3H, N-$(CH_2)_3CH_3$), 1.31 (m, 4H, N–$CH_2(CH_2)_2CH_3$), 3.02 (s, 3H, $N(CH_3)_2$), 3.21 (s, 3H, $N(CH_3)_2$), 3.87 (t, 2H, N- $CH_2(CH_2)_2CH_3$), 7.08 (d, J = 13.5 Hz, 1H, COC*H*=CH–N), 7.21–7.32 (m, 2H, H_{arom}), 7.59 (t, 1H, 7-$H_{quinolinone}$), 8.09 (d, J = 13.5 Hz, 1H, COCH=C*H*–N), 8.22 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$); MS: *m*/*z* (I%) 314 (M^+, 28), 270 (100). Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.39): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.68; H, 6.94; N, 8.56.

4.3.4. 3-[2*E*-3-(Dimethylamino)prop-2-enoyl]-4-hydroxy-1-phenylquinolin-2(1*H*)-one (10d). Prepared from the acetylquinolinone **4d** (2.79 g) and DMF-DMA (1.4 mL) and crystallized from DMF. Yield 3.13 g (94 %); mp 244–245 °C. IR (KBr): ν_{max} 3173, 3056, 2928, 2805, 1645 (C=O), 1603, 1525, and 1492 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.05 (s, 3H, $N(CH_3)_2$), 3.19 (s, 3H, $N(CH_3)_2$), 6.62 (d, J = 14.2 Hz, 1H, COC*H*=CH–N), 7.12–7.78 (m, 8H, H_{arom}), 8.09 (d, J = 14.1 Hz, 1H, COCH=C*H*–N), 8.18 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$). Anal. Calcd for $C_{20}H_{18}N_2O_3$ (334.38): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.52; H, 5.25; N, 8.33.

4.4. General procedure for the preparation of 3-[3-(pyrazolinylamino)propenoyl]-quinolinones (11a–d)

A mixture of the appropriate enaminones **10a–d** (5 mmol) and amine **7** (5 mmol), in glacial acetic acid (20 mL), was heated on a water bath under reflux for 1 h. The reaction mixture was left to cool and poured onto crushed ice to give solid deposits. The product was filtered off and crystallized from the proper solvent.

4.4.1. 3-{[2*E*-3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino]prop-2-enoyl}-4-hydroxy-1-methylquinolin-2(1*H*)-one (11a). Prepared from the enaminone **10a** (1.36 g) and amine **7** (1.02 g) and crystallized from DMF. Yield 1.87 g (87%); mp 234–235 °C. IR (KBr): ν_{max} 3211, 3056, 2921, 2883, 1662 (C=O), 1645 (C=O), 1618, 1601, and 1575 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.23 (s, 3H, 5-$CH_{3pyrazoline}$), 3.15 (s, 3H, N–$CH_{3pyrazoline}$), 3.71 (s, 3H, N–$CH_{3quinolinone}$), 6.68 (d, J = 12.8 Hz, 1H, COC*H*=CH–N), 7.12–7.66 (m, 8H, H_{arom}), 8.21 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$), 8.65 (d, J = 13 Hz, 1H, COCH=C*H*–N), 11.33 (b, 1H, N–H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 12.8, 34.6, 35.8, 102.7, 109.2, 110.3, 119.6, 120.4, 124.2, 124.6, 126.0, 127.2, 128.2, 128.8, 129.3, 138.8, 139.1, 140.6, 161.7, 162.5, 173.7, 187.4; MS: *m*/*z* (I%) 430 (M^+, 32), 199 (100). Anal. Calcd for $C_{24}H_{22}N_4O_4$ (430.47): C, 66.97; H, 5.15; N, 13.02. Found: C, 66.83; H, 5.26; N, 12.88.

4.4.2. 3-{[2*E*-3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino]prop-2-enoyl}-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (11b). Prepared from the enaminone **10b** (1.43 g) and amine **7** (1.02 g) and crystallized from

dioxane. Yield 1.69 g (76%); mp 191–192 °C. IR (KBr): ν_{max} 3226, 3174, 3063, 2980, 2675, 1660 (C=O), 1639 (C=O), 1617, 1599, and 1572 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.37 (t, 3H, N–CH_2CH_3), 2.18 (s, 3H, 5-$CH_{3pyrazoline}$), 3.26 (s, 3H, N–$CH_{3pyrazoline}$), 4.09 (q, 2H, N–CH_2CH_3), 6.64 (d, J = 12.5 Hz, 1H, COCH=CH–N), 7.11–7.63 (m, 8H, H_{arom}), 8.23 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$), 8.49 (d, J = 12.5 Hz, 1H, COCH=CH–N), 11.28 (b, 1H, N–H). Anal. Calcd for $C_{25}H_{24}N_4O_4$ (444.49): C, 67.56; H, 5.44; N, 12.60. Found: C, 67.37; H, 5.29; N, 12.41.

4.4.3. 1-Butyl-3-{[2*E*-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino]prop-2-enoyl}-4-hydroxyquinolin-2(1*H*)-one (11c). Prepared from the enaminone **10c** (1.57 g) and amine **7** (1.02 g) and crystallized from ethanol. Yield 1.70 g (72%); mp 149–150 °C. IR (KBr): ν_{max} 3182, 3071, 2992, 2945, 2886, 2676, 1658 (C=O), 1641 (C=O), 1622, 1601, 1576, and 1555 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H, N–$(CH_2)_3CH_3$), 1.31 (m, 4H, N–$CH_2(CH_2)_2CH_3$), 2.20 (s, 3H, 5-$CH_{3pyrazoline}$), 3.28 (s, 3H, N–$CH_{3pyrazoline}$), 3.81 (t, 2H, N–$CH_2(CH_2)_2CH_3$), 6.87 (d, J = 13.4 Hz, 1H, COCH=CH–N), 7.16–7.78 (m, 8H, H_{arom}), 8.09 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$), 8.46 (d, J = 13.3 Hz, 1H, COCH=CH–N), 11.92 (b, 1H, N–H). Anal. Calcd for $C_{27}H_{28}N_4O_4$ (472.55): C, 68.63; H, 5.97; N, 11.86. Found: C, 68.62; H, 5.92; N, 11.68.

4.4.4. 3-{[2*E*-3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H* -pyrazol-4-yl)amino]prop-2-enoyl}-4-hydroxy-1-phenylquinolin-2(1*H*)-one (11d). Prepared from the enaminone **10d** (1.67 g) and amine **7** (1.02 g) and crystallized from DMF. Yield 2 g (81%); mp 288–289 °C. IR (KBr): ν_{max} 3064, 2985, 2672, 1662 (C=O), 1645 (C=O), 1620, 1606, 1570, and 1556 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): 2.22 (s, 3H, 5-$CH_{3pyrazoline}$), 3.38 (s, 3H, N–$CH_{3pyrazoline}$), 6.57 (d, J = 14.2 Hz, 1H, COCH=CH–N), 6.98–7.82 (m, 13H, H_{arom}), 8.12 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$), 8.38 (d, J = 14.1 Hz, 1H, COCH=CH–N), 12.08 (b, 1H, N–H). Anal. Calcd for $C_{29}H_{24}N_4O_4$ (492.54): C, 70.72; H, 4.91; N, 11.38. Found: C, 70.51; H, 5.03; N, 11.20.

4.5. General procedure for the preparation of 3-[3-(1-piperidyl or 4-morpholinyl)-propenoyl]quinolinones (13a–d)

Equimolar amounts (5 mmol) of the enaminones **10a** or **10b** and piperidine or morpholine, in dioxane (25 mL), were heated under reflux for 1 h. The reaction mixture was left to cool and then poured onto crushed ice to give yellow precipitates. The product was collected by filtration off and crystallized from the proper solvent.

4.5.1. 4-Hydroxy-1-methyl-3-[2*E*-3-(1-piperidyl)prop-2-enoyl]quinolin-2(1*H*)-one (13a). Prepared from the enaminone **10a** (1.36 g) and piperidine (0.5 mL) and crystallized from ethanol. Yield 1.18 g (76%); mp 214–215 °C. IR (KBr): ν_{max} 3130, 2941, 2917, 2865, 1650 (C=O), 1626 (C=O), 1603, 1545, and 1499 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.71–1.80 (m, 6H, $(CH_2)_{3piperidine}$), 3.52 (m, 4H, $N(CH_2)_{2piperidine}$), 3.64 (s, 3H, N–$CH_{3quinolinone}$), 7.21–7.32 (m, 3H, 6-$H_{quinolinome}$ + 8-$H_{quinolinone}$ + COCH=CH–N), 7.64 (t, 1H, 7-$H_{quinolinone}$), 8.14 (d, J = 16 Hz, 1H, COCH=CH–N), 8.28 (d, J = 8 Hz, 1H, 5-$H_{quinolinone}$); MS: m/z (I%) 312 (M^+, 32), 69 (100). Anal. Calcd for $C_{18}H_{20}N_2O_3$ (312.37): C, 69.21; H, 6.45; N, 8.97. Found: C, 69.08; H, 6.41; N, 8.78.

4.5.2. 4-Hydroxy-1-methyl-3-[2*E*-3-(4-morpholinyl)prop-2-enoyl]quinolin-2(1*H*)-one (13b). Prepared from the enaminone **10a** (1.36 g) and morpholine (0.5 mL) and crystallized from ethanol. Yield 1.16 g (74%); mp 231–232 °C. IR (KBr): ν_{max} 3076, 2944, 2926, 2845, 1646 (C=O), 1606, 1541, and 1487 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.55 (m, 4H, $N(CH_2)_{2morpholine}$), 3.68 (s, 3H, N–$CH_{3quinolinone}$), 4.26 (m, 4H, $O(CH_2)_{2\ morpholine}$), 7.14–7.34 (m, 3H, 6-$H_{quinolinome}$ + 8-$H_{quinolinone}$ + COCH=CH–N), 7.66 (t, 1H, 7-$H_{quinolinone}$), 8.18 (d, J = 16 Hz, 1H, COCH=CH–N), 8.28 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$). Anal. Calcd for $C_{17}H_{18}N_2O_4$ (314.34): C, 64.96; H, 5.77; N, 8.91. Found: C, 64.80; H, 5.56; N, 8.83.

4.5.3. 1-Ethyl-4-hydroxy-3-[2*E*-3-(1-piperidyl)prop-2-enoyl]quinolin-2(1*H*)-one (13c). Prepared from the enaminone **10b** (1.43 g) and piperidine (0.5 mL) and crystallized from ethanol. Yield 1.22 g (75%); mp 168–169 °C. IR (KBr): ν_{max} 3086, 2952, 2883, 1651 (C=O), 1638 (C=O), 1602, 1544, and 1505 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, 3H, N–CH_2CH_3), 1.69–1.80 (m, 6H, $(CH_2)_{3piperidine}$), 3.55 (m, 4H, $N(CH_2)_{2piperidine}$), 3.82 (q, 2H, N–CH_2CH_3), 7.18–7.36 (m, 3H, 6-$H_{quinolinome}$ + 8-$H_{quinolinone}$ + COCH=CH–N), 7.64 (t, 1H, 7-$H_{quinolinone}$), 8.13 (d, J = 14.6 Hz, 1H, COCH=CH–N), 8.24 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$). Anal. Calcd for $C_{19}H_{22}N_2O_3$ (326.40): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.73; H, 6.54; N, 8.48.

4.5.4. 1-Ethyl-4-hydroxy-3-[2*E*-3-(4-morpholinyl)prop-2-enoyl]quinolin-2(1*H*)-one (13d). Prepared from the enaminone **10b** (1.43 g) and morpholine (0.5 mL) and crystallized from dioxane. Yield 1.18 g (72%); mp 177–178 °C. IR (KBr): ν_{max} 3072, 2981, 2934, 2844, 1652–1640 (C=O), 1607, 1556, and 1501 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (t, 3H, N–CH_2CH_3), 3.52 (m, 4H, $N(CH_2)_{2morpholine}$), 4.03 (q, 2H, N–CH_2CH_3), 4.25 (m, 4H, $O(CH_2)_{2morpholine}$), 7.22–7.37 (m, 3H, 6-$H_{quinolinome}$ + 8-$H_{quinolinone}$ + COCH=CH–N), 7.61 (t, 1H, 7-$H_{quinolinone}$), 8.19 (d, J = 16 Hz, 1H, COCH=CH–N), 8.26 (d, J = 7 Hz, 1H, 5-$H_{quinolinone}$). Anal. Calcd for $C_{18}H_{20}N_2O_4$ (328.37): C, 65.84; H, 6.14; N, 8.53. Found: C, 65.64; H, 6.03; N, 8.39.

4.6. General procedure for the preparation of 3-[4-(dimethylaminomethylene)pyrazolyl]-quinolinones (14a,b)

A mixture of the pyrazolinones **5a** or **5b** (10 mmol) and DMF-DMA (15 mmol), in *p*-xylene (50 mL), was heated under reflux for 2 h. The reaction mixture was left to cool in an ice bath for a night. The crystalline product so formed was collected by filtration and washed with petroleum ether (40–60 °C; 50 mL). The products were pure enough and used for subsequent reactions without further purification.

4.6.1. 3-{4-[(Dimethylamino)methylene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}-4-hydroxy-1-methylquinolin-2(1*H*)-one (14a). Prepared from the pyrazolinone **5a** (2.57 g) and DMF-DMA (2.1 mL). Yield 2.52 g (81%); mp 297–300 °C. IR (KBr): ν_{max} 3225 (N–H), 3174, 2945, 1662 (C=O), 1642 (C=O), 1620, 1552, and 1476 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.05 (s, 3H, $N(CH_3)_2$), 3.28 (s, 3H, $N(CH_3)_2$), 3.64 (s, 3H, N–CH_3), 7.23–7.65 (m, 3H, 6-H + 8-H + 7-H), 8.09 (d, J = 7 Hz, 1H, 5-H), 8.26 (s, 1H, C=C*H*–N), 11.52 (b, 1H, N–H), 12.61 (b, 1H, O–H); MS: *m*/*z* (I%) 312 (M^+, 25), 267 (100). Anal. Calcd for $C_{16}H_{16}N_4O_3$ (312.33): C, 61.53; H, 5.16; N, 17.94. Found: C, 61.36; H, 4.92; N, 18.08.

4.6.2. 3-{4-[(Dimethylamino)methylene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (14b). Prepared from the pyrazolinone **5b** (2.71 g) and DMF-DMA (2.1 mL). Yield 2.41 g (74%); mp 264–265 °C. IR (KBr): ν_{max} 3245 (N–H), 3178, 2972, 2861, 1654 (C=O), 1644 (C=O), 1618, 1573, and 1503 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.40 (t, 3H, N–CH_2CH_3), 3.03 (s, 3H, $N(CH_3)_2$), 3.22 (s, 3H, $N(CH_3)_2$), 3.86 (q, 2H, N–CH_2CH_3), 7.28–7.62 (m, 3H, 6-H + 8-H + 7-H), 8.13 (d, J = 7 Hz, 1H, 5-H), 8.25 (s, 1H, C=C*H*–N), 11.84 (b, 1H, N–H), 12.66 (b, 1H, O–H); MS: *m*/*z* (I %) 326 (M^+, 44), 281 (100). Anal. Calcd for $C_{17}H_{18}N_4O_3$ (326.36): C, 62.57; H, 5.56; N, 17.17. Found: C, 62.30; H, 5.51; N, 16.92.

4.7. General procedure for the preparation of 3-[4-(hetarylaminomethylene)pyrazolyl]-quinolinones (15a–f)

A mixture of compound **14a** or **14b** (5 mmol) and 2- or 3-aminopyridine or 2-aminopyrimidine (5 mmol), in glacial acetic acid (25 mL), was heated under reflux for 1 h. The reaction mixture was left to cool to room temperature and the precipitate so formed was collected by filtration and crystallized from the suitable solvent.

4.7.1. 4-Hydroxy-1-methyl-3-{5-oxo-4-[(2-pyridylamino)methylene]-4,5-dihydro-1*H*-pyrazol-3-yl} quinolin-2(1*H*)-one (15a). Prepared from compound **14a** (1.56 g) and 2-aminopyridine (0.48 g) and crystallized from ethanol. Yield 1.53 g (85%); mp 237–238 °C (lit., [13] yield 76%; mp 235–236 °C).

4.7.2. 4-Hydroxy-1-methyl-3-{5-oxo-4-[(3-pyridylamino)methylene]-4,5-dihydro- 1*H*-pyrazol-3-yl}quinolin-2(1*H*)-one (15b). Prepared from compound **14a** (1.56 g) and 3-aminopyridine (0.48 g) and crystallized from acetone. Yield 1.45 g (80%); mp 242–244 °C. IR (KBr): ν_{max} 3380 (N–H), 3135, 2992, 2883, 1666 (C=O), 1645 (C=O), 1619, 1611, 1586, and 1545 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 3.64 (s, 3H, N–CH_3), 6.98–8.09 (m, 8H, H_{arom}), 8.31 (d, J = 12.8 Hz, 1H, C=C*H*–N), 9.28 (b, 1H, N–H), 11.30 (b, 1H, N–H), 12.55 (b, 1H, O–H). Anal. Calcd for $C_{19}H_{15}N_5O_3$ (361.36): C, 63.15; H, 4.18; N, 19.38. Found: C, 63.05; H, 3.95; N, 19.21.

4.7.3. 4-Hydroxy-1-methyl-3-{5-oxo-4-[(2-pyrimidylamino)methylene]-4,5-dihydro-1*H*-pyrazol-3-yl}quinolin-2(1*H*)-one (15c). Prepared from compound **14a** (1.56 g) and 2-aminopyrimidine (0.49 g) and crystallized from DMF. Yield 1.42 g (78 %); mp 279–280 °C (lit.,[13] yield 68%; mp 279–281 °C).

4.7.4. 1-Ethyl-4-hydroxy-3-{5-oxo-4-[(2-pyridylamino)methylene]-4,5-dihydro-1*H*-pyrazol-3-yl} quinolin-2(1*H*)-one (15d). Prepared from compound **14b** (1.63 g) and 2-aminopyridine (0.48 g) and crystallized from ethanol. Yield 1.40 g (75%); mp 226–228 °C. IR (KBr): ν_{max} 3320 (N–H), 3180, 2989, 2846, 1663 (C=O), 1648 (C=O), 1618, 1607, and 1566 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.38 (t, 3H, N–CH_2CH_3), 3.84 (q, 2H, N–CH_2CH_3), 6.94–8.05 (m, 8H, H_{arom}), 8.35 (d, J = 12.2 Hz, 1H, C=C*H*–N), 9.45 (b, 1H, N–H), 11.86 (b, 1H, N–H), 12.68 (b, 1H, O–H). Anal. Calcd for $C_{20}H_{17}N_5O_3$ (375.39): C, 63.99; H, 4.56; N, 18.66. Found: C, 63.81; H, 4.52; N, 18.40.

4.7.5. 1-Ethyl-4-hydroxy-3-{5-oxo-4-[(3-pyridylamino)methylene]-4,5-dihydro-1*H*-pyrazol-3-yl}quinolin-2(1*H*)-one (15e). Prepared from compound **14b** (1.63 g) and 3-aminopyridine (0.48 g) and crystallized from acetone. Yield 1.74 g (93 %); mp 220–221 °C. IR (KBr): ν_{max} 3335 (N–H), 3176, 2978, 2864, 1658 (C=O), 1641 (C=O), 1621, 1608, and 1562 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.42 (t, 3H, N–CH_2CH_3), 3.87 (q, 2H, N–CH_2CH_3), 6.88–8.08 (m, 8H, H_{arom}), 8.41 (d, J = 12.4 Hz, 1H, C=C*H*–N), 9.28 (b, 1H, N–H), 11.60 (b, 1H, N–H), 12.45 (b, 1H, O–H). Anal. Calcd for $C_{20}H_{17}N_5O_3$ (375.39): C, 63.99; H, 4.56; N, 18.66. Found: C, 63.78; H, 4.43; N, 18.47.

4.7.6. 1-Ethyl-4-hydroxy-3-{5-oxo-4-[(2-pyrimidylamino)methylene]-4,5-dihydro-1*H*-pyrazol-3-yl}quinolin-2(1*H*)-one (15f). Prepared from compound **14b** (1.63 g) and 2-aminopyrimidine (0.49 g) and crystallized from DMF. Yield 1.38 g (73%); mp 256–257 °C. IR (KBr): ν_{max} 3324 (N–H), 3208, 2943, 2852, 1661 (C=O), 1638 (C=O), 1616, 1605, and 1556 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.41 (t, 3H, N–CH_2CH_3), 3.86 (q, 2H, N–CH_2CH_3), 7.12–8.08 (m, 7H, H_{arom}), 8.40 (d, J = 12.6 Hz, 1H, C=C*H*–N), 9.84 (b, 1H, N–H), 12.08 (b, 1H, N–H), 13.21 (b, 1H, O–H). Anal. Calcd for $C_{19}H_{16}N_6O_3$ (376.38): C, 60.63; H, 4.28; N, 22.23. Found: C, 60.45; H, 4.31; N, 22.05.

4.8. General procedure for the preparation of 3-[4-(pyrazolylaminomethylene)pyrazolyl]-quinolinones (16a,b)

A mixture of equimolar amounts (5 mmol) of the pyrazolinone **5a** or **5b**, triethyl orthoformate, and amine **7**, in ethylene glycol (20 mL), was heated under short air condenser at 110 °C for 30 min. Then, the reaction temperature was raised gradually to 190 °C during 1 h. The reaction mixture was left to cool to room temperature and triturated with cold methanol (20 mL). The solid deposits so obtained was collected by filtration and crystallized from the suitable solvent.

4.8.1. 3-{4-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-methylene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}-4-hydroxy-1-methylquinolin-2(1*H*)-one (16a). Prepared from compound **5a** (1.29 g), triethyl orthoformate (0.9 mL), and amine **7** (1.04 g) and crystallized from

dioxane. Yield 2.16 g (92%); mp 198–199 °C (lit.,[13] yield 84%; mp 195–197 °C).

4.8.2. 3-{4-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylamino)-methylene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (16b). Prepared from compound **5b** (1.36 g), triethyl orthoformate (0.9 mL), and amine **7** (1.04 g) and crystallized from ethanol. Yield 2.15 g (89%); mp 186–187 °C. IR (KBr): ν_{max} 3331 (N–H), 3212, 3145, 2956, 2847, 1663 (C=O), 1636 (C=O), 1618, 1608, 1572, 1550, and 1444 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 1.37 (t, 3H, N–CH_2CH_3), 2.21 (s, 3H, 5-$CH_{3pyrazolone}$), 3.30 (s, 3H, N–$CH_{3pyrazolone}$), 3.71 (q, 2H, N–CH_2CH_3), 7.06–7.78 (m, 8H, H_{arom}), 8.08 (d, J = 7H, 1H, 5-$H_{quinolinone}$), 8.52 (d, J = 12.3 Hz, 1H, C=C*H*–N), 9.65 (b, 1H, N–H), 10.25 (b, 1H, N–H), 12.88 (b, 1H, O–H). Anal. Calcd for $C_{26}H_{24}N_6O_4$ (484.52): C, 64.45; H, 4.99; N, 17.35. Found: C, 64.17; H, 4.95; N, 17.22.

4.9. Molluscicidal and larvicidal bioassays

4.9.1. Snails source and conditions. Adult laboratory bred *B. alexandrina* and *S. mansoni* miracidia and cercariae were obtained from Schistosoma Biological Supply Center (SBSC) at Theodor Bilharz Research Institute (TBRI) to ensure infection-free snails with high susceptibility for infection experiments. Healthy *B. alexandrina* (10–12 mm shell diameter) and *L. natalensis* (10–13 mm shell height) snails were collected from local irrigation canals and ponds at Giza and Kalubia and acclimatized to laboratory conditions for 3 weeks. Groups of 10 experimental snails were then transferred to well-aerated glass aquaria containing 2 L of dechlorinated water and kept at 24 ± 1 °C. The snails were fed on boiled or oven-dried lettuce leaves. Each aquarium was provided with a polyethylene sheet for ova-position, and the eggs were counted using a binuclear stereomicroscope. From each early and late embryonic stage, 100 eggs were used to study the effect of the molluscicides on egg development and hatchability.

4.9.2. Molluscicidal activity. Molluscicidal effect of the new compounds was evaluated according to WHO procedure[22] with slight modification[23] by inclusion of an inert solvent to help in the dissolution of samples. The compounds were dissolved first in a small amount of DMF and added to dechlorinated water to obtain 0.1% solution. The bioassay involved immersion of adult snails in the mixed aqueous solution of the investigated compounds at final concentration ranging from 5 to 100 ppm for 24 h, at room temperature and under normal diurnal lighting. Then, the aquaria were decanted and the snails were rinsed twice with dechlorinated water and offered lettuce leaves as food. The test snails were then left in water for another 24 h as a recovery period and examined to assess mortality and computed to estimate the LC_{10}, LC_{25}, LC_{50}, and LC_{90} values.[24] Snails were considered dead if they remained motionless and did not respond to the presence of food. In the control experiments, snails were exposed to 0.1% DMF without addition of the test molluscicides at the same experimental conditions. Hatchability experiments were carried out with the LC_{25} concentrations of the tested compounds and control group of eggs were maintained in dechlorinated water. Infection rate and prepatent period experiments were carried out using four groups each of 30 snails (4–6 mm shell diameter) maintained at the LC_{25} concentrations of each compound for 24 h. From the surviving snails, four groups of 22 snails per aquarium were exposed to *S. mansoni* miracidia with a dose of 10 miracidia/snail for 24 h at room temperature and ceiling illumination. A control group of 22 snails was exposed to miracidia in the absence of tested molluscicides.

4.9.3. Larvicidal activity. Miracidal and cercaricidal effect of the tested five compounds was examined at LC_{10}, LC_{25}, and LC_{50} concentrations. Twenty-five milliliters of dechlorinated water containing 100 freshly hatched miracidia or freshly sheded cercariae was mixed with 25 mL of double concentrations of the candidate molluscicide solutions. Fifty milliliters of dechlorinated water containing 100 freshly hatched miracidia or freshly sheded cercariae was used as a control. The mortality was microscopically checked at intervals of 5 min and the times required for 100% mortality of both *S. mansoni* miracidia and cercariae were recorded.

4.9.4. Toxicity test against *Daphnia*. The tests were conducted in *D. magna* following the European Guideline.[18] The Daphnia-bioassay-used daphnids were bred in culture medium imitating natural fresh water. Test plates with *D. magna* neonates were incubated for 24–48 h at 24 ± 1 °C in dark. Acute toxicity was assessed by noting the effects of the tested compounds on the mobility of *D. magna*. The neonates were considered immobile if, after 48 h of incubation with the toxicant, they remained settled at the bottom of the test container and did not resume swimming with 15 s observation period. For each test, 20 healthy neonates were exposed to 50 mL of LC_{10}, LC_{25}, LC_{50}, and LC_{90} concentrations of the tested compounds. Triplicate and control experiments were carried out for each concentration and the average mortality (immobilization) value was calculated.

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