Full Paper

Synthesis and Molluscicidal Activity of New Chromene and Pyrano[2,3-*c*]pyrazole Derivatives

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The chromene derivative **4** reacts with acetic anhydride, phenylisothiocyanate and ethyl orthoformate to afford the *N*-acetyl derivative **6**, the chromenopyrimidine **8** and the formimidate **9**, respectively. 2-(1*H*-Indol-3-ylmethylene)-malononitrile **10b** reacts with 1,3-cyclohexanedione and dimedone **11a**, **b** to afford the 4(3-indolyl)-chromene derivatives **12a**, **b** respectively, and with the pyrazolone derivatives **13a – d** to afford the arylidene exchange derivatives **14a – c** and the pyranopyrazole derivative **15**, respectively. The arylidene derivatives **10a**, **b** react also with indane-1,3-dione **16** to afford the arylidene exchange derivatives **18a**, **b**. The molluscicidal activity of the synthesized compounds towards *Biomphalaria alexandrina* snails, the intermediate host of *Schistosoma mansoni*, was investigated and most of them showed weak to moderate activity.

Keywords: Arylidene exchange / Chromenes / Molluscicidal activity / Pyrano[2,3-*c*]pyrazoles

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Introduction

Schistosomiasis is one of the most wide-spread endemic diseases in Egypt as well as in most of the tropical countries, and represents one of the serious problems due to its destructive health consequences. Great national and international efforts are made to combat this disease through hygienic awareness, chemotherapeutic treatment of infected persons, or through cutting the life cycle of the parasite through killing of the water snail *Biomphalaria alexandrina,* the intermediate hosts of the infective phase of *Schistosoma mansoni*, named cercaria. Although chemotherapy proved to be successful, the inavoidable contact with polluted water, however, leads to repeated infection. Therefore, snail control through molluscicides, is considered essential in *Schistsomal* control.

Naturally occuring compounds containing the fused pyran (or pyranone) ring were found to exhibit molluscicidal activity. For example Bergapten **1** [1, 2]; ricchiocarpin A **2**, and ricchiocarpin B **3** [3], the chromene derivative **4** [4] and the pyranopyrazole **5** [5] (Fig. 1); all have shown a considerable molluscicidal activity. The furan and the pyran rings as well as the methyl groups are common features in these compounds.

Is is known that the mollusc's soft tissues are rich in sterols contents which are highly lipophilic, and it seems that the molluscicides action is to chelate with some metals essential for vital processes in the organism [6]. Therefore, the more lipophilicity the compound has, the more its ability to merge and chelate with these metals. In the present work, we tried to introduce groups to increase the lipophilicity and / or the chelating ability of compounds **4** and **5**.

Based on the above discussion it was decided to modify compounds **4** by exploring its enaminonitrile moiety in order to obtain some new derivatives, while preserving the features to which the activity is attributed, the two geminal methyl groups on the cyclohexanone and the 3-furanyl moiety in the 4-position of the pyran [4]. Furthermore, it is well known that the indole system is contained in a variety of synthetic pharmaceuticals as well as naturally occuring alkaloids [7]. Therefore, we thought that substituting the 3-furanyl by a 3-indolyl ring system

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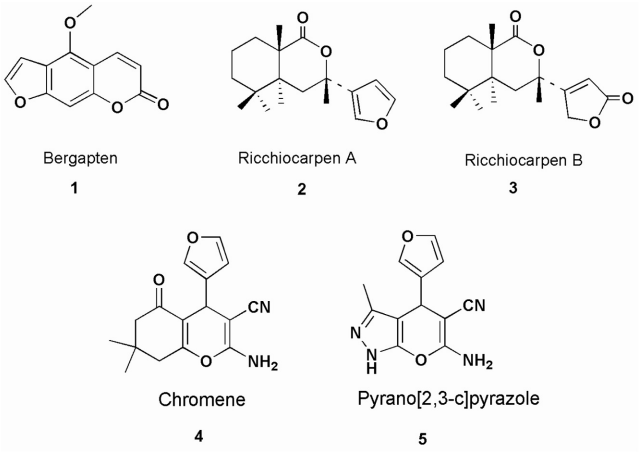


Figure 1. Chemical structures of compounds **1–5**.

might enhance the molluscicidal activity of the chromene **4** as well as the pyranopyrazole **5** by virtue of the extra NH of the indole which affords more chance for chelation.

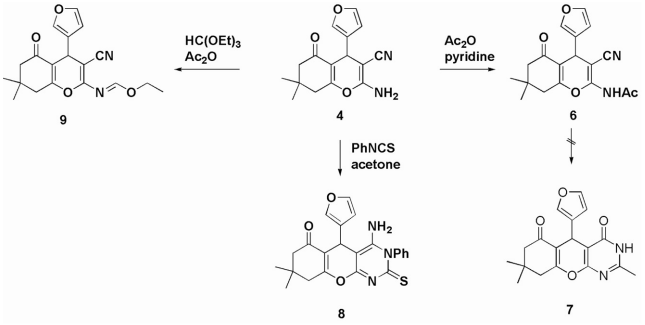
Results and discussion

Chemistry

Compound **4**, prepared as previously reported [4], smoothly underwent *N*-acetylation upon reflux with acetic anhydride in pyridine. It was expected to obtain the cyclized chromenopyrimidine derivative **7**, however, spectral data showed that our product is the *N*-acetyl derivative **6** (Scheme 1).

Compound **4** reacted with phenylisothiocyanate in refluxing acetone to afford the chromenopyrimidine thione derivative **8** apparently via a thiourea intermediate. Treatment of compound **4** with triethyl orthoformate in refluxing acetic anhydride afforded the formimidate **9**. The structures of compounds **6**, **8**, and **9** were all confirmed by spectral and analytical data (see section 3, Experimental). Similar results have been reported with analogous chromenes [8] previously. Structure **9** was further confirmed by an X-ray crystallographic analysis (Fig. 2; also see Experimental). The X-ray picture shows the pyran ring fused to the cyclohexanone ring, and that both are in the chair conformation. This also affords a further evidence of all our chromene derivatives published earlier [4, 5].

On the other hand, (1*H*-indol-3-ylmethylene)-malononitrile **10b** (Scheme 2) was prepared by condensation of indole-3-carbaldehyde with malononitrile using sodium ethoxide as the catalyst. This improved method gave a higher yield (95%) than reported before (85%, [11]), and



Scheme 1. Synthesis of compounds **6**, **8**, and **9**.

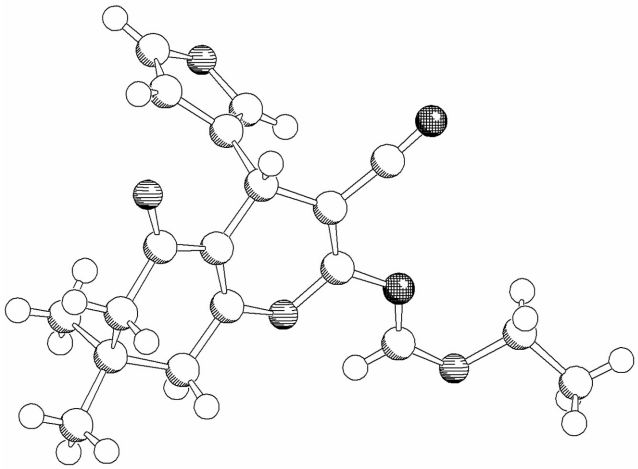
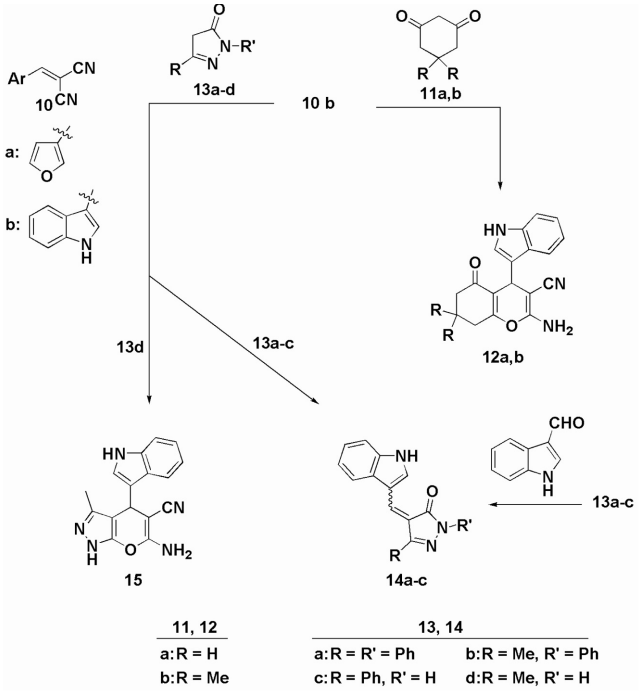


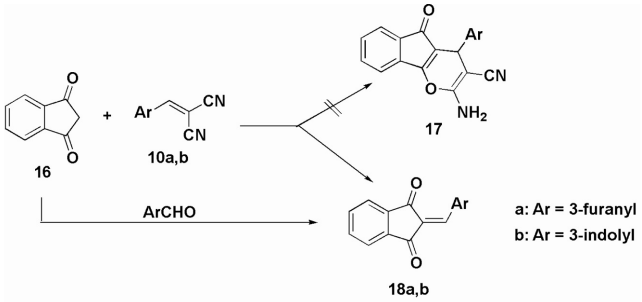
Figure 2. Crystal structure of formimidate **9** [9, 10].

the compound was obtained in analytically pure state without further purification (mp 225–226°C; reported: 219–220°C [12], 221–223°C [13], 228–230°C [14]). Compound **10b** reacted with cyclohexa-1,3-dione **11a** and with dimedone **11b** (Scheme 2) to afford the chromene derivatives **12a** and **12b**, respectively, similar to the behavior of **10a** towards the same diketones [4].

Compound **10b** interacted with the pyrazolone derivatives **13a–d** in two different ways depending on the substituents of the pyrazolone nucleus. Thus, all pyrazolones bearing a phenyl substituent (1,3-diphenyl **13a**, 3-methyl-1-phenyl **13b**, or 3-phenyl **13c**) reacted with **10b** to afford the arylidene exchange products **14a–c**, respectively. The 3-methylpyrazolone **13d**, however, reacted with **10b** to give the expected pyranopyrazole **15**, similar to the behavior of **10a** towards the same substrate [5]. Analytical and spectral data are in complete agreement with the depicted structures (Scheme 2) (see section 3, Experimental). The reaction of **13a–d** with **10b** is assumed to take place via the intermediacy of an acyclic Michael adducts, which either eliminate malononitrile (in case of **13a–c**) to afford **14a–c**, or undergo cyclization (in case of **13d**)



Scheme 2. Synthesis of compounds **12**, **14**, and **15**.



Scheme 3. Synthesis of compounds **18**.

through addition of the hydroxyl group of the enol tautomer to one of the cyano groups to give **15**. It seems that the presence of a phenyl group in the pyrazolone compounds facilitates the elimination of malononitrile rather than enolization. A conclusive evidence of structures **14a – c** was obtained from the condensation reaction of the pyrazolones **13a**, **13b**, and **13c** with indole-3-carbaldehyde. The products obtained were found to be identical to **14a**, **14b**, and **14c**, respectively in all respects. It should be noted that compound **14b** was reported in the literature to be obtained also by an arylidene exchange reaction between 3-methyl-1-phenylpyrazol-5-one **13b** and ethyl indol-3-ylidene cyanoacetate [15].

As an extension of this work, 1,3-indanedione **16** (Scheme 3) was allowed to react with the dinitriles **10a**, **b** aiming at the formation of indeno[1,2-*b*]pyran derivatives **17**, similar to the behavior of the ß-diketones **11a** and **11b** towards **10a**, **b**. However, we only obtained the products of arylidene exchange **18a**, **b**, respectively. It seems that due to the presence of the benzene moiety again the elimination of malononitrile from the intermediate is facilitated rather than enolization followed by cyclization. For rigorous structural proof, compounds **18a**, **b** were also prepared through the reaction of **16** with furan-3-carbaldehyde and indole-3-carbaldehyde, respectively.

A comparative study of the ^{13}C-NMR spectra of all the chromene compounds **6**, **8**, **9**, **12b**, and the pyranopyrazole compound **15** showed the pyran C-4 signal almost at the same chemical shifts (~25 – 28 ppm) except for compound **6** which showed this carbon downfield (41.48 ppm). This down-field shift is apparently due to the presence of the acetyl group which causes deshielding as an electron withdrawing group. A similar effect was observed in a related system in which the C-1 signal should appear at ~26 ppm in the parent compound, while this signal is down-shifted to 37.3 ppm in the *o*-acetyl derivative [16].

Molluscicidal activity

The toxicity of compounds **6**, **8**, **9**, **12a, b**, **14a – c**, **15**, and **18a**, **b** toward *Biomphalaria alexandrina* snails was evaluated. The tenth-, quarter-, half-, and sub-lethal doses (LC_{10}, LC_{25}, LC_{50}, and LC_{90} in ppm/μM) for each compound were determined and is shown in Table 1.

Inspection of the results listed in Table 1 shows that most of the tested compounds have moderate to low effects on the snails relative to bayluscide as a reference, and generally show very weak activity below 3 ppm. The most effective of them are **9** and **12b** (LC_{90} = 6 and 7 ppm, respectively). Compounds **14a-c** and **18a**, **b** did not show any activity at all. These results confirm our previous observations [4]; that the presence of *gem*-dimethyl substituents in the cyclohexanone ring and the fused pyran ring are prerequisits for enhanced activity. The 3-indolyl moiety in **12b** accomplished more activity (LC_{50} = 4 ppm; Table 1) than 3-furyl moiety in **4** (LC_{50} = 5 ppm [4]) perhaps due to the fact that the NH of the indolyl moiety affords a better condition for chelation (*cf.* Introduction, section 1). However, the formimidate side chain apparently increases the lipophilicity of **9**, which made it slighty superior to **12b** (LC_{90} = 6 and 7 ppm, respectively). A comparison of the molluscicidal activity of the new compounds reported here with the international standard 2',5-dichloro-4-nitrosalicylanilide (bayluscide) (LC_{100} = 1 ppm) [17, 18] showed that our compounds are still inferior as molluscicidal agents. However, compounds **9** and **12b** look promising after further structural modification, which will be considered in a future study.

Table 1. Molluscicidal activity of the synthesized compounds expressed as LC_{10}, LC_{25}, LC_{50}, and LC_{90} in ppm (μM).

Compd. No	LC_{10} ppm (μM)	LC_{25} ppm (μM)	LC_{50} ppm (μM)	LC_{90} ppm (μM)
Control	–	–	–	–
Bayluscide	<2(<6.12)	<2 (<6.12)	<2(<6.12)	<2(<6.12)
6	7 (21.45)	9.5 (29.11)	>10 (>30.64)	>10 (>30.64)
8	4 (9.54)	6 (14.30)	8 (19.07)	>10 (23.84)
9	2 (5.88)	<3 (<8.81)	4 (11.75)	6 (17.63)
12a	4 (13.10)	<6 (<19.65)	7 (22.93)	>10 (>32.75)
12b	2 (6.00)	<3 (<9.00)	4 (12.00)	7 (21.00)
14a	–	–	–	–
14b	–	–	–	–
14c	–	–	–	–
15	3 (10.30)	>4 (>13.73)	6 (20.60)	10 (34.33)
18a	–	–	–	–
18b	–	–	–	–

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Experimental

Melting points were measured on a digital Electrothermal 9100 apparatus (Kleinfeld, Gehrden, Germany) and are uncorrected. FT-IR spectra (KBr) were obtained on a Nicolet 205 spectrophotometer (Nicolet, Madison, WI, USA). ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker AC 300 P (^{1}H: 300 MHz, ^{13}C: 75.5 MHz; Bruker, Rheinstetten, Germany) in DMSO-d_6 if not mentioned otherwise. Chemical shifts are expressed in δ values. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra were recorded with a Hewlett Packard Esquire-LC (LC/MS; Hewlett Packard, Palo Alto, CA, USA). Elemental analyses were carried out in the microanalytical laboratory of the Department of Chemistry, Technische Universität Dresden. Satisfactory elemental analysis results (± 0.35%) have been obtained for all compounds. X-ray data were collected using a Bruker Nonius 5622 diffractometer (Bruker) and were corrected by SADABS factors and emperical absorption. The structure was solved by direct methods and expanded using Fourier technique. SCHAKAL 99 program system was used in the graphic representation of the structure [9]. The nonhydrogen atoms are refined anisotropically and the hydrogen atoms were refined according to theoretical models. Molluscicidal activity tests were conducted in the Research Institute for Tropical Medicine, Cairo, Egypt. 3-Furfurylidene malononitrile derivative **10a** and the chromene derivative **4** were prepared according to the methods reported previously [4].

Chemistry

*N-(3-Cyano-4-furan-3-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-2-yl)-acetamide **6***

Compound **4** (2.84 g, 10 mmol) was refluxed in a mixture of acetic anhydride and pyridine (25 mL; 1 : 1) for 2 h, then left to cool overnight. The contents of the flask were then poured on ice cold water and acidified with conc. HCl. The solid precipitate thus obtained was collected by filtration and recrystallized from ethanol to afford compound **6** (2.45 g, 75%) as pale yellow crystals; mp 190–192°C (EtOH); $C_{18}H_{18}N_2O_4$ (M = 326.35); MS (LC/MS) *m/z* 327 [M+H$^+$]; IR 3151, 3111 (NH), 2206 (CN), 1694 (C=O), 1665 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.07 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.32 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.57 (s, 2H, CH_2), 5.41 (s, 1H, pyran 4-H), 6.26 (dd, *J* = 0.8 Hz, *J* = 1.7 Hz, 1H, furan-4H), 7.30–7.40 (m, 2H, furan-2H,5H), 11.79 (s, 1H, D_2O exchangeable, NH); ^{13}C-NMR ($CDCl_3$) δ 27.58 (q), 28.04 (q), 28.75 (q), 32.47 (s), 39.95 (t), 41.48 (d), 50.41 (t), 72.22 (s), 108.19 (d), 112.93 (s), 117.13 (s), 125.11 (s), 140.01 (d), 144.18 (d), 160.91 (s), 163.19 (s) 194.36 (s), 195.74 (s).

*10-Furan-3-yl-4-amino-7,7-dimethyl-3-phenyl-2-thioxo-1,2,3,4,6,7,8,10-octahydro-9-oxa-1,3-diazaanthracen-5-one **8***

To a solution of compound **4** (2.84 g, 10 mmol) in dry pyridine (20mL) was added phenylisothiocyanate (1.35 g, 10 mmol), and the reaction mixture was refluxed for 2 h, after which it was left to cool to room temperature. The reaction mixture was then poured on crushed ice and acidified with HCl until just neutral to pH paper. The formed paste soon solidified to give an apricot colored solid, which was filtered off and recrystallized from ethanol to afford compound **8** (2.90 g, 69%); mp 183°C (EtOH); $C_{23}H_{21}N_3O_3S$ (M = 419.50); MS (LC/MS) *m/z* 420 [M+H$^+$]; IR 3382-3206 (NH_2), 1681 (C=O) cm^{-1}; ^{1}H-NMR d 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.18 (d, *J* = 16.1 Hz, 1H), 2.28 (d, *J* = 16.1 Hz, 1H), 2.47 (br s, 2H, CH_2), 4.19 (s, 1H, pyran 4-H), 6.25 (d, *J* = 0.8 Hz, 1H, furan-4H), 7.00 (s, 2H, NH_2), 7.30–7.60 (m, 7H, furan + phenyl H); ^{13}C-NMR d 25.88 (d), 26.70 (q), 28.26 (q), 31.67 (s), 39.64 (t), 49.94 (t), 56.80 (s), 109.52 (d), 112.33 (s), 123.55 (d), 125.84 (d), 127.90 (d), 128.54 (s), 138.87 (d), 139.38 (s), 143.22 (d), 149.22 (s), 159.09 (s), 162.40 (s), 179.58 (s), 195.58 (s).

*Ethyl-N-(3-cyano-4-furan-3yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-2-yl)formimidate **9***

To a solution of compound **4** (2.84 g, 10 mmol) in acetic anhydride (20 mL) was added an excess of triethyl orthoformate (4.45 g, 30 mmol), and the mixture was heated for 6 h under efficient reflux and then left to cool to room temperature. The solvent was evaporated under vacuum to half of its original volume, then the flask was left at room temperature for 3 d, whereby colorless cubic crystals appeared. These were filtered off and washed thoroughly with cold ethanol to give **9** (2.65 g, 78%); mp 133–134°C (EtOH); $C_{19}H_{20}N_2O_4$ (M = 340.37); MS (LC/MS) *m/z* 341 [M+1]$^+$; IR 2208 (CN), 1664 (C=O), 1605 (N=C) cm^{-1}; ^{1}H-NMR δ 0.98 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 2.20 (d, *J* = 16.1 Hz, 1H), 2.30 (d, *J* = 16.1 Hz, 1H), 2.51 (br s, 2H, CH_2), 4.33 (q, *J* = 7.1 Hz, 2H, CH_2), 4.42 (s, 1H, pyran 4-H), 6.36 (s, 1H, furan-H), 7.50–7.60 (m, 2H, furan), 8.54 (s, 1H, N=CH); ^{13}C-NMR δ 13.87 (q), 26.96 (q), 27.59 (q), 28.23 (d), 31.91 (s), 39.98 (t), 50.06 (t), 64.14 (t), 81.17 (s), 109.85 (d), 111.16 (s), 117.40 (s), 126.94 (s), 139.92 (d), 143.65 (d), 156.84 (s), 162.00 (d), 162.95 (s), 195.76 (s). X-ray crystallographic data: light yellow crystals, $C_{19}H_{20}N_2O_4$ (M_r = 340.37 g/mol), triclinic, space group *P*-1(2), a = 8.041 (1) Å, b = 9.720 (1) Å, c = 12.999 (1) Å, α [°] = 73.52 (1), β [°] = 72.25 (1), γ [°] = 65.78 (1); *V* [Å^3] = 867.61 (16), Z = 2, $D_{calc.}$ = 1.303 g/cm^3, F (000) = 360 e, μ (M_g $K_α$) = 0.092 nm^{-1}; the final difference Fourier ρ = 0.30 (–0.27) e Å^{-3}.crystal dimensions = 0.33 nm · 0.23

nm · 0.20 nm. Max. resolution [sin θ/λ] = 0.7 Å^{-1}/99.1%. Data were collected using a Bruker Nonius area detector at T (°C) = 198 (2), with graphite monochromator with Mo Ka radiation (λ = 0.71073 Å) using the CCD data collection and SADABS absorption correction method; min. 91.5%; max 98.2%. Total independent reflections are 5044 were counted with observed reflections 3511. R_{int} = 0.0518. The final R and R_W^2 = 0.0450 and 0.1078, respectively.

*2-(1H-Indol-3-ylmethylene)-malononitrile **10b***

A mixture of indole-3-carbaldehyde (7.25 g, 50 mmol) and malononitrile (3.30 g, 50 mmol) in absolute ethanol (100 mL) was warmed until complete dissolution. To this solution were added five drops of a sodium ethoxide solution prepared by dissolving sodium metal (0.1 g) in dry ethanol (10 mL) while shaking. After a vigorous exothermic reaction and boiling of the contents of the flask, a canary yellow precipitate instantly formed. The mixture was left to cool down, triturated with cold ethanol, and the solid was filtered off and washed thoroughly with cold ethanol to afford **10b** (9.2 g, 95% yield); mp 225 – 226°C (EtOH); $C_{12}H_7N_3$ (M = 193.20); ^{1}H-NMR δ 7.20 – 7.35 (m, 2H), 7.58 (d, *J* = 7.3 Hz, 1H), 8.03 (d, *J* = 7.3 Hz, 1H), 8.50 (s, 1H, olefinic H), 8.65 (s, 1H, indole 2-H), 12.70 (br s, 1H, NH); ^{13}C-NMR δ 69.26 (s), 110.97 (s), 113.03 (d), 115.91 (s), 115.95 (s), 119.01 (d), 122.55 (d), 123.93 (d), 126.72 (s), 133.23 (d), 136.17 (s), 152.45 (d).

*2-Amino-4-(1H-indol-3-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile **12a***

To a solution of cyclohexa-1,3-dione **11a** (1.12 g, 10 mmol) in tetrahydrofuran (25 mL) was added 2-(1*H*-indol-3-ylmethylene)-malononitrile **10b** (1.93 g, 10 mmol) followed by a few drops of piperidine. The reaction mixture was stirred at room temperature for 2 h and then left to stand overnight. The white-pale to yellow precipitate formed was filtered off and recrystallized from ethanol to afford the chromene derivative **12a** (2.20 g, 72%) as pale yellow fine crystals; mp 188 – 189°C (EtOH); $C_{18}H_{15}N_3O_2$ (M = 305.33); IR 3460, 3385, 3324, 3214 (NH_2, NH), 2192.5 (CN), 1682.5 (C=O); ^{1}H-NMR δ 1.70 – 1.85 (m, 2H, CH_2), 2.16 – 2.22 (m, 2H, CH_2), 2.44 – 2.54 (m, 2H, CH_2), 4.40 (s, 1H, pyran-4H), 6.80 (s, 2H, NH_2), 6.85 – 7.40 (m, 5H, Ph + indole 2H), 10.8 (s, 1H, NH).

*2-Amino-4-(1H-indol-3-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile **12b***

To a mixture of dimedone **11b** (1.4 g, 10 mmol) and 2-(1*H*-indol-3-ylmethylene)-malononitrile **10b** (1.93 g, 10 mmol) in ethanol (25 mL) was added a catalytic amount of triethylamine (5 drops). The mixture was refluxed for 5 min, whereby a coagulated white precipitate appeared. Heating was stopped, and the flask was left to cool overnight. The solid was collected by filtration and recrystallized from dioxane to afford **12b** (2.60 g, 79% yield); mp 178 – 179°C (dioxane); $C_{20}H_{19}N_3O_2$ (M = 333.38); MS (LC/MS) *m/z* 351 [M+NH_4^+], 356 [M+Na^+]; IR 3405-3153 (NH_2, NH), 2186 (CN), 1683 (C=O); ^{1}H-NMR δ 0.86 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.06 (d, *J* = 16.1 Hz, 1H), 2.23 (d, *J* = 16.1 Hz, 1H), 2.46 – 2.56 (m, 2H, CH_2), 4.48 (s, 1H, pyran 4-H), 6.89 (s, 2H, NH_2), 6.93 – 7.35 (m, 5H, Ph + indole 2H), 10.86 (s, 1H, NH); ^{13}C-NMR 26.78 (q), 27.31 (d), 28.57 (q), 31.75 (s), 39.66 (d or t), 39.82 (d or t), 50.18 (t), 58.57 (s), 111.74 (d), 112.8 (s), 117.62 (s), 118.39 (d), 118.45 (d), 120.28 (s), 120.83 (d), 123.23 (d), 125.38 (s), 136.65 (s), 158.68 (s), 161.76 (s), 195.85 (s).

*Reaction of 10b with the pyrazolones **13a – d**; Preparation of **14a – c** and **15***

To a refluxing mixture of 2-(1*H*-indol-3-ylmethylene)-malononitrile **10b** (1.93 g, 10 mmol) and each of the pyrazolone derivatives **13a – d** (10 mmol) in ethanol (25 mL) was added piperidine (0.5 mL), whereby a homogeneous solution was obtained. Reflux was continued for about 15 min until colored precipitates appeared. The mixture was left to cool to room temperature, and the solids were filtered off and recrystallized from ethanol to afford the pure products.

*4-(1H-Indol-3-ylmethylene)-2,5-diphenyl-2,4-dihydropyrazol-3-one **14a***

Bright orange cotton like crystals, yield 3.40 g (93%); mp 283 – 284°C (EtOH/DMF); $C_{24}H_{17}N_3O$ (M = 363.41); MS (LC/MS) *m/z* 364 [M+H^+]; IR 3232 – 3136 (NH), 1655 (C=O) cm^{-1}; ^{1}H-NMR δ 7.20 – 8.15 (m, 15H, aromatic + olefinic H), 9.90 (br s, 1H, indole 2-H), 12.80 (br s, 1H, NH); ^{13}C-NMR 112.54 (s), 113.21 (d), 116.38 (s), 117.96 (d), 118.70 (d), 122.59 (d), 123.81 (d), 124.55 (d), 128.09 (s), 128.69 (d), 128.84 (d), 129.05 (d), 129.47 (d), 131.40 (s), 136.53 (s), 138.56 (d), 138.81 (s), 139.01 (d), 152.17 (s), 162.93 (s).

*4-(1H-Indol-3-ylmethylene)-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one **14b***

Reddish-orange crystals, yield 2.16 g (72%); mp 228 – 229°C (EtOH/DMF); $C_{19}H_{15}N_3O$ (M = 301.34); MS (LC/MS) *m/z* 302 [M+H^+]; IR 3245 – 3144 (NH), 1651 (C=O) cm^{-1}; ^{1}H-NMR δ 2.40 (s, 3H, CH_3), 7.10 – 8.20 (m, 10H, aromatic + olefinic H), 9.83 (s, 1H, indole 2-H), 12.70 (s, 1H, NH). ^{13}C-NMR 13.09 (q), 112.34 (s), 113.01 (d), 118.11 (d), 118.41 (s), 118.73 (d), 122.20 (d), 123.62 (d), 124.01 (d), 128.22 (d), 128.79 (d), 136.49 (s), 137.36 (d), 138.32 (d), 138.98 (s), 151.04 (s), 162.88 (s).

*4-(1H-Indol-3-ylmethylene)-5-phenyl-2,4-dihydropyrazol-3-one **14c***

Yellow fine needle crystals, yield 2.50g (87%); mp 220 – 222°C (MeOH); $C_{18}H_{13}N_3O$ (M = 287.32); MS (LC/MS) *m/z* 288 [M+H^+], 310 [M+Na^+]; IR 3268 – 3181 (NH), 1660 (C=O) cm^{-1}; ^{1}H-NMR δ 7.25 – 8.08 (m, 9H, aromatic H), 8.54 (s, 1H, olefinic H), 8.72 (s, 1H, pyrazole NH), 9.87 (s, 1H, indole 2H), 11.60 (s, 1H, indole NH).

*6-Amino-4-(1H-indol-3-yl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **15***

Pale yellow powder, yield 1.8 g (62%); mp 205 – 206°C (dioxane); $C_{16}H_{13}N_5O$ (M = 291.31); MS (LC/MS) *m/z* 292 [M+H^+]; IR 3371 – 3132 (NH_2, NH), 2178 (CN) cm^{-1}; ^{1}H-NMR δ 1.75 (s, 3H, CH_3), 4.85 (s, 1H, pyran 4-H), 6.75 (s, 2H, NH_2), 6.84 – 7.35 (m, 5H, Ph + indole 2-H), 10.85 (s, 1H, NH), 12.03 (s, 1H, NH); ^{13}C-NMR 9.68 (q), 28.24 (d), 57.80 (s), 97.63 (s), 111.77 (d), 116.94 (s), 118.34 (d), 118.62 (d), 120.97 (d), 121.24 (s), 123.01 (d), 125.41 (s), 135.72 (s), 137.00 (s), 154.98 (s), 160.67 (s).

*Reaction of arylidene malononitriles **10a, b** with 1,3-indanedione **16***

To a solution of 3-furfurylidenemalononitrile **10a** (1.44 g, 10 mmol) or 3-indolylidenemalononitrile **10b** (1.93 g, 10 mmol) in ethanol (25 mL) was added 1,3-indanedione **16** (1.46 g, 10 mmol). To the refluxing mixture were added a few drops of triethylamine, whereby a precipitate appeared, and the color

turned to dark violet. After cooling to room temperature, the product was filtered off, washed thoroughly with cold ethanol, and was then recrystallized to afford the arylidene exchange products **18a** and **18b**, respectively. Exactly the same products were obtained upon reacting 1,3-indanedione **16** with furan-3-carbaldehyde or indole-3-carbaldehyde, respectively. The identity of the products was deduced from the mp, ^{1}H-NMR, and elemental analyses.

2-Furan-3-ylmethyleneindan-1,3-dione ***18a***

Cream white crystals, yield 1.90 g (86%); mp 155–157°C (EtOH); $C_{14}H_8O_3$ (M = 225); MS (LC/MS) *m/z* 224.9 [M+H$^+$]; IR 1720, 1677 (C=O) cm^{-1}; ^{1}H-NMR δ 7.56–7.97 (m, 7H, aromatic + furan H), 8.85 (s, 1H, olefinic H); ^{13}C-NMR 112.24 (d), 121.71 (s), 122.80 (d), 122.84 (d), 127.00 (s), 134.35 (d), 135.56 (d), 135.70 (d), 139.59 (s), 141.60 (s), 145.19 (d), 153.59 (d), 188.88 (s), 189.30 (s).

2-(1H-Indol-3-ylmethylene)-indane-1,3-dione ***18b***

Bright red crystals, yield 2.50 g (93%); mp 299–301°C (EtOH); $C_{18}H_{11}NO_2$ (M = 273.29); MS (LC/MS) *m/z* 274 [M+H$^+$]; IR 3228, 3146 (NH), 1711, 1652 (C=O) cm^{-1}; ^{1}H-NMR δ 7.28–8.02 (m, 8H, arom. H.), 8.15 (s, 1H, olefinic H), 9.62 (d, *J* = 3.3 Hz, 1H, indole 2-H), 12.70 (br s, 1H, NH); ^{13}C-NMR 112.43 (s), 113.21 (d), 118.27 (d), 121.16 (s), 122.14 (d), 122.30 (d), 122.68 (d), 123.75 (d), 128.35 (s), 134.74 (d), 134.97 (d), 135.31 (d), 136.72 (s), 138.48 (d), 139.26 (s), 141,41 (s), 189.71 (s), 190.28 (s).

Molluscicidal activity tests

The molluscicidal activity tests were carried out by determination of the tenth-, quarter-, half-, and sub-lethal doses LC_{10}, LC_{25}, LC_{50}, and LC_{90} of each compound under investigation. *Biomphalaria alexandrina* snails (ca. 6 mm shell diameter) were collected from the field (water canals), maintained under laboratory conditions for a period of 10 d before the tests, and fed daily with lettuce leaves. Nine concentrations of each compound under investigation were prepared ranging from 2 ppm to 10 ppm. The required amount of the compound under investigation was mixed thoroughly with a few drops of Tween 20 and 2 mL of DMSO to render the compounds completely soluble, followed by addition of the appropriate volume of raw irrigation 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 having the same size and diameter (ca. 6 mm) were used in each experiment and maintained in the test solution under laboratory conditions at 25°C for 24 h, and then the snails were transferred into fresh water and left for further 24 h. Each experiment was repeated three times, and the results were recorded by counting the mean number of the killed snails for each concentration. A control group was taken by placing ten snails in water containing a few 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 [19], slightly modified by using two mixed solvents to dissolve the compounds.

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