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Novel bis(1-acyl-2-pyrazolines) of potential anti-inflammatory and molluscicidal properties

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Abstract—A variety of bis[3-aryl-4,5-dihydro-1*H*-pyrazol-1-carboxaldehydes] **4a**–**h** were obtained via reaction of bis[1-aryl-2-propen-1-ones] **3a**–**h** with hydrazine hydrate in refluxing formic acid. In addition, the corresponding bis[1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazoles] **4i**–**m** were formed through conducting the reaction of **3** with hydrazine hydrate in refluxing acetic acid. The starting bis(2-propen-1-ones) **3a**–**h** were prepared stereoselectively as *E*,*E*′-geometric isomer via condensation of bisbenzaldehydes **1a,b** with (un)substituted acetophenones **2** in ethanolic KOH solution. Anti-inflammatory as well as ulcerogenic activities of the prepared pyrazolines were evaluated in vivo and compared with that of a standard drug (indomethacin). Many of the tested compounds show remarkable anti-inflammatory properties with an ulcerogenic liability (especially **4f**, **g**, **j**, and **k**) lower than that of the standard used drug. Compound **4f** was established to be the best effectively prepared anti-inflammatory active pyrazoline derivative and safer than indomethacin with respect to its ulcerogenic liability. Molluscicidal activity of the prepared compounds against *Biomphalaria alexandrina* snails (the intermediate host of *Schistosoma mansoni*) was screened. Where, some of the prepared compounds show considerable activities.

1. Introduction

Chalconoids constitute an important class of naturally occurring compounds[1–3] exhibiting a wide spectrum of biological activities. The term chalconoid has been used to designate the whole family of compounds possessing a 1,3-diarylpropane skeleton, which can be functionalized in the propane chain by the presence of olefinic, keto and/or hydroxyl groups. The most common and widespread compounds of the chalconoid group are the chalcones, which possess a 1,3-diaryl-2-propen-1-one carbon framework.[1,2] Several potential properties of chalcones were exhibited as antimalarial,[4–7] and anti-tuberculosis,[8] activities. Moreover, many recent publications were reported dealing with the cytotoxic[9–12] as well as anti-HIV[13] properties of hydroxychalcone derivatives.

Chalcones, one class of the anthochlor pigments, usually give yellow to orange colours to the tissues in which they are located. Although these compounds are not responsible for pigmentation in the most yellow-coloured flowers, they are still attractive to insects and in such a way they contribute to the flowers' pollination.[14] The importance of these compounds is due not only to their colours but also to their chemical in addition to biological activities and the fact that they are good accessible starting materials used for construction of various heterocyclic derivatives.[1–3,15,16] One of these important heterocyclic systems which attracts progressive interest of many researchers is pyrazoline. The interest of scientists in such compounds has been stimulated by their biological, pharmacological and industrial importance. For example, 1-unsubstituted-3,5-diaryl-2-pyrazolines were reported to exhibit human acyl CoA cholesterol acyltransferase[17] as well as low-density lipoprotein oxidation inhibitors.[18] Moreover, 1,3,5-triaryl-2-pyrazolines were reported to possess antidepressant properties[19,20] in addition to monoamine oxidase inhibitory activities.[21,22]

Recent progressive interest was directed towards 1,3,5-triaryl-2-pyrazoline derivatives' nanocrystal

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investigation[23–28] due to their well-known fluorescence properties with high quantum yield useful as whitening or brightening agents for textile fibre, plastic and paper industries.[29–32] Many efforts have been also directed towards utilization of this behaviour for construction of organic electroluminescence devices with a multi-layer structure and as fluorescence probes in some elaborated chemosensors.[33–39]

In the present work, it is intended to synthesize a novel variety of bis(1-acyl-2-pyrazoline) containing compounds. This investigation is prompted mainly by the aforementioned biological and/or pharmacological activities of that ring system in addition to the recognized anti-inflammatory, analgesic as well as antipyretic properties of 1-acetyl-2-pyrazoline analogues.[40,41] Moreover, many bispyrazole derivatives are involved in a wide variety of medicinally and pharmacologically active materials.[42,43] Construction of new heterocyclic derivatives containing two biologically active moieties (1-formyl- or 1-acetyl-2-pyrazolines) could enhance the total observed biological activities and may be a hint for determination of highly pronouncing effective new materials. Ulcerogenic properties of the most anti-inflammatory active synthesized compounds will be also considered.

The molluscicidal activity of the newly prepared compounds against *Biomphalaria alexandrina* snails (the intermediate host of *Schistosoma mansoni*) will be also screened. Schistosomiasis is the most important endemic trematode disease in human in many tropical and subtropical regions. It is considered a national problem in many countries (including Egypt). Searching for an effective, easily available and low-cost molluscicidal active material could be a promising tool for controlling the disease from spreading widely.

2. Results and discussion

2.1. Chemistry

Reaction of 2,2′-[1,2-ethanediylbis(oxy)]bisbenzaldehyde (**1a**) with (un)substituted acetophenones **2** in 4% ethanolic KOH solution afforded the corresponding 3,3′-[1,2-ethanediylbis(oxy-2,1-phenylene)]bis[1-aryl-2-propen-1-ones] **3a**–**e**. The structure of **3** was established through spectroscopic (IR, ^{1}H NMR) and elemental analyses data. The IR spectra of **3a**–**e** reveal the presence of a strong band at $\nu = 1658$–$1643\ cm^{-1}$ region assignable for the α,β-unsaturated ketonic residue. ^{1}H NMR spectra of **3a**–**e** exhibit each of the olefinic protons as a doublet signal at $\delta = 7.79$–7.84, 7.89–7.97 regions with a mutual coupling constant value $J = 15.6$–15.9 Hz. These observed coupling constant values indicate the presence of *E*,*E*′-configurational form structure.

Single crystal X-ray diffraction of **3a** (Fig. 1) adds a sharp evidence for the presence of *E*,*E*′-configurational stereochemical structure. Where, the observed torsion angles 'H(6)–C(6)–C(7)–O(3) = −169.8(6), H(6)–C(6)–C(13)–H(13) = −178.(3), H(9)–C(9)–C(19)–O(4) = 177.(2), and H(9)–C(9)–C(15)–H(15) = 176.(3)' confirm this assumption.

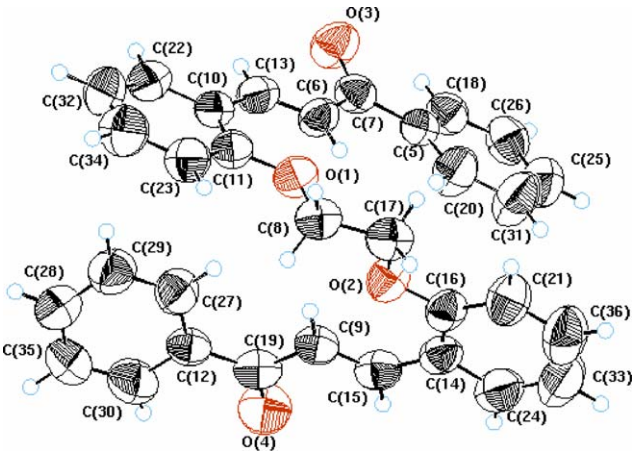


Figure 1. Single crystal X-ray diffraction of **3a**. Selected intramolecular bond lengths (Å) and bond angles (°) of **3a**. O(1)–C(8) = 1.439(3), O(1)–C(11) = 1.369(3), O(2)–C(16) = 1.359(3), O(2)–C(17) = 1.432(3), O(3)–C(7) = 1.231(2), O(4)–C(19) = 1.233(3), C(5)–C(7) = 1.484(3), C(5)–C(18) = 1.382(3), C(5)–C(20) = 1.385(3), C(6)–C(7) = 1.471(3), C(6)– C(13) = 1.319(3), C(8)–C(17) = 1.486(3), C(9)–C(15) = 1.326(3), C(9)–C(19) = 1.471(3), C(10)–C(11) = 1.412(3), C(10)–C(13) = 1.461(3), C(10)–C(22) = 1.396(3), C(11)–C(23) = 1.380(3), C(12)–C(19) = 1.490(3), C(12)–C(27) = 1.371(4), C(12)–C(30) = 1.386(4), C(14)–C(15) = 1.463(4), C(14)–C(16) = 1.399(3), C(14)–C(24) = 1.406(4), C(16)–C(21) = 1.385(3), C(18)–C(26) = 1.357(4), C(20)–C(31) = 1.379(3), C(21)–C(36) = 1.382(5), C(22)–C(32) = 1.376(4), C(23)–C(34) = 1.389(4), C(24)–C(33) = 1.395(4), C(25)–C(26) = 1.363(4), C(25)–C(31) = 1.363(4), C(27)–C(29) = 1.376(3), C(28)–C(29) = 1.360(4), C(28)–C(35) = 1.361(4), C(30)–C(35) = 1.366(4), C(32)–C(34) = 1.375(4), C(33)–C(36) = 1.349(4), C(6)–H(6) = 0.960(2), C(9)–H(9) = 1.00(2), C(13)–H(13) = 0.86(2), C(15)–H(15) = 0.94(2), C(8)–O(1)–C(11) = 119.4(2), C(16)–O(2)–C(17) = 118.9(2), C(7)–C(5)–C(18) = 119.6(2), C(7)–C(5)–C(20) = 123.5(2), C(18)–C(5)–C(20) = 116.9(2), C(7)–C(6)–C(13) = 122.3(2), O(3)–C(7)–C(5) = 119,2(2), O(3)–C(7)–C(6) = 121.0(2), C(5)–C(7)–C(6) = 119.8(2), O(1)–C(8)–C(17) = 107.2(2), C(15)–C(9)–C(19) = 121.7(3), C(11)–C(10)–C(13) = 125.2(2), C(11)–C(10)–C(22) = 116.9(2), C(13)–C(10)–C(22) = 117.9(2), O(1)–C(11)–C(10) = 115.3(2), O(1)–C(11)–C(23) = 123.2(3), C(10)–C(11)–C(23) = 121.4(3), C(19)–C(12)–C(27) = 123.2(3), C(19)–C(12)–C(30) = 119.5(3), C(27)–C(12)–C(30) = 117.3(3), C(6)–C(13)–C(10) = 131.2(2), C(15)–C(14)–C(16) = 125.1(3), C(15)–C(14)–C(24) = 116.6(3), C(16)–C(14)–C(24) = 118.3(3), C(9)–C(15)–C(14) = 128.8(3), O(2)–C(16)–C(14) = 116.8(2), O(2)–C(16)–C(21) = 123.6(3), C(14)–C(16)–C(21) = 119.5(3), O(2)–C(17)–C(8) = 107.9(2), C(5)–C(18)–C(26) = 122.1(3), O(4)–C(19)–C(9) = 121.4(3), O(4)–C(19)–C(12) = 119.2(3), C(9)–C(19)–C(12) = 119.4(3), C(5)–C(20)–C(31) = 121.3(2), C(16)–C(21)–C(36) = 120.3(3), C(10)–C(22)–C(32) = 122.2(3), C(11)–C(23)–C(34) = 119.2(3), C(14)–C(24)–C(33) = 121.3(3), C(26)–C(25)–C(31) = 120.3(3), C(18)–C(26)–C(25) = 119.9(3), C(12)–C(27)–C(29) = 121.7(3), C(29)–C(28)–C(35) = 119.8(3), C(27)–C(29)–C(28) = 119.7(3), C(12)–C(30)–C(35) = 121.0(3), C(20)–C(31)–C(25) = 119.5(3), C(22)–C(32)–C(34) = 119.4(3), C(24)–C(33)–C(36) = 118.6(3), C(23)–C(34)–C(32) = 120.9(3), C(28)–C(35)–C(30) = 120.5(3), C(21)–C(36)–C(33) = 122.0(3), C(7)–C(6)–H(6) = 119.4(3), C(13)–C(6)–H(6) = 118.3(3), C(15)–C(9)–H(9) = 118.3(11), C(19)–C(9)–H(9) = 119.8(11), C(6)–C(13)–H(13) = 114.5(14), C(10)–C(13)–H(13) = 114.3(14), C(9)–C(15)–H(15) = 116.7(14), C(14)–C(15)–H(15) = 114.4(13).

Similarly, reaction of 4,4′-[1,2-ethanediylbis(oxy)]bis-benzaldehyde (**1b**) with acetophenones **2** under the previously described reaction conditions gave the corresponding bis-2-propen-1-ones **3f–h** in good yield (Scheme 1). ^{1}H NMR spectra of **3f–h** confirm that, the isolated products are 2*E*,2′*E*-isomeric form structure depending on the mutual coupling constant values between the α,β-unsaturated olefinic protons 'J = 15.3–15.6 Hz'.

Reaction of **3a–h** with hydrazine hydrate in refluxing formic acid yielded exclusively, bis[3-aryl-4,5-dihydro-1*H*-pyrazole-1-carboxaldehydes] **4a–h**. The structure of **4a–h** was inferred from spectroscopic as well as elemental analyses data. The IR spectra exhibit the presence of only one carbonyl band at ν = 1680–1658 cm^{-1} assignable for the carbonyl formyl function. ^{1}H NMR spectra of **4a–h** reveal the presence of two unequivalent protons of a methylene group 'at δ = 3.03–3.23, 3.54–3.88' coupled with each other and in turn with the vicinal methine proton (*H*-5) 'at δ = 5.49–5.67.' It has also been noticed that, the upfield shifted proton of methylene residue coupled with the vicinal methine one (*H*-5) with a coupling constant value 'J = 4.8–5.4 Hz,' indicating the presence of *trans*-configuration. In other words, this mentioned proton is located *cis* to the aryl group attached to the pyrazole *C*-5. Also, the coupling constant value between the downfield shifted proton of methylene function and the vicinal methine proton (*H*-5) 'J = 11.7–12 Hz' supports this assumption.[44–46] Moreover, the formyl proton appear as a sharp singlet signal at δ = 8.80–8.96.

Similarly, reaction of **3** with hydrazine hydrate in refluxing acetic acid afforded the corresponding bis[1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazoles] **4i–m** (Scheme 1). IR spectra of **4i–m** exhibit the presence of a strong carbonyl band at ν = 1666–1658 cm^{-1} region. ^{1}H NMR spectra of **4i–m** reveal each of the methylene protons as a doublet signal at δ = 2.98–3.14 and 3.51–3.75 region beside the vicinal methine proton at δ = 5.49–5.76. Moreover, the methyl protons of acetyl group appear as a singlet signal at δ = 2.21–2.41 region.

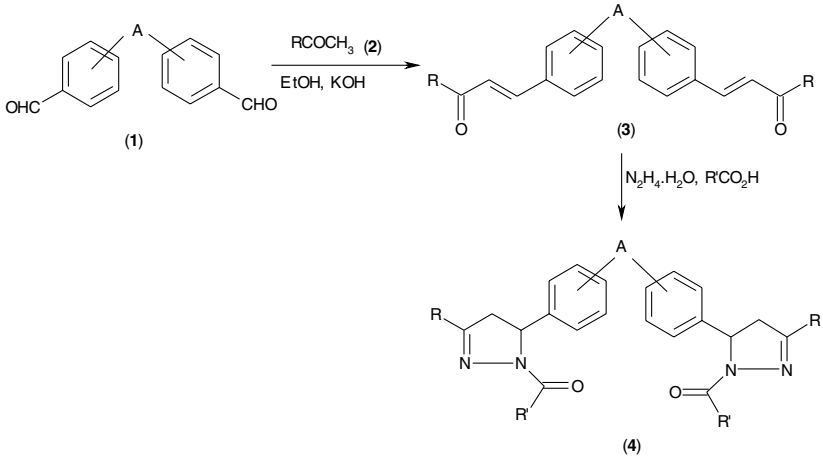
2.2. Anti-inflammatory activity

The anti-inflammatory activity of the prepared pyrazolines **4** was determined by the carrageenin-induced paw oedema standard method in rats.[40,41,47,48] From the obtained results (Table 1, Figs. 2 and 3), it has been noticed that all the tested pyrazoline derivatives show considerable anti-inflammatory activities. In addition,

Table 1. Anti-inflammatory activity of the tested compounds using carrageenin-induced paw oedema in rats

Compound	Oedema weight (g)	% inhibition of oedema
Control	0.74 ± 0.02	0.00
Indomethacin (reference standard)	0.20 ± 0.00*	72.97
4a	0.34 ± 0.04*	54.05
4c	0.43 ± 0.10*	42.57
4d	0.44 ± 0.05*	40.54
4e	0.42 ± 0.03*	43.24
4f	0.12 ± 0.02*	83.78
4g	0.24 ± 0.02*	67.57
4h	0.32 ± 0.08*	56.76
4i	0.34 ± 0.06*	54.05
4j	0.28 ± 0.03*	62.16
4k	0.28 ± 0.03*	62.16
4l	0.40 ± 0.03*	45.95
4m	0.46 ± 0.04*	37.84

All values are represented as means ± SE 'standard error'.
Statistical analysis was carried out by using one-way ANOVA (*F* test) followed by Dunnett's *t* test at $p < 0.05$.
* Significantly different from the control value at $p < 0.05$.



Scheme 1. **1a**, A = 2-O(CH$_2$)$_2$O-2′; **1b**, A = 4-O(CH$_2$)$_2$O-4′; **3a**, A = 2-O(CH$_2$)$_2$O-2′, R = Ph; **3b**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-ClC$_6$H$_4$; **3c**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-FC$_6$H$_4$; **3d**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-H$_3$CC$_6$H$_4$; **3e**, A = 2-O(CH$_2$)$_2$O-2′, R = 2-thienyl; **3f**, A = 4-O(CH$_2$)$_2$O-4′, R = Ph; **3g**, A = 4-O(CH$_2$)$_2$O-4′, R = 4-ClC$_6$H$_4$; **3h**, A = 4-O(CH$_2$)$_2$O-4′, R = 4-H$_3$CC$_6$H$_4$; **4a**, A = 2-O(CH$_2$)$_2$O-2′, R = Ph, R′ = H; **4b**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-ClC$_6$H$_4$, R′ = H; **4c**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-FC$_6$H$_4$, R′ = H; **4d**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-H$_3$CC$_6$H$_4$, R′ = H; **4e**, A = 2-O(CH$_2$)$_2$O-2′, R = 2-thienyl, R′ = H; **4f**, A = 4-O(CH$_2$)$_2$O-4′, R = Ph, R′ = H; **4g**, A = 4-O(CH$_2$)$_2$O-4′, R = 4-ClC$_6$H$_4$, R′ = H; **4h**, A = 4-O(CH$_2$)$_2$O-4′, R = 4-H$_3$CC$_6$H$_4$, R′ = H; **4i**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-ClC$_6$H$_4$, R′ = CH$_3$; **4j**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-FC$_6$H$_4$, R′ = CH$_3$; **4k**, A = 2-O(CH$_2$)$_2$O-2′, R = 4-H$_3$CC$_6$H$_4$, R′ = CH$_3$; **4l**, A = 2-O(CH$_2$)$_2$O-2′, R = 2-thienyl, R′ = CH$_3$; **4m**, A = 4-O(CH$_2$)$_2$O-4′, R = 4-H$_3$CC$_6$H$_4$, R′ = CH$_3$.

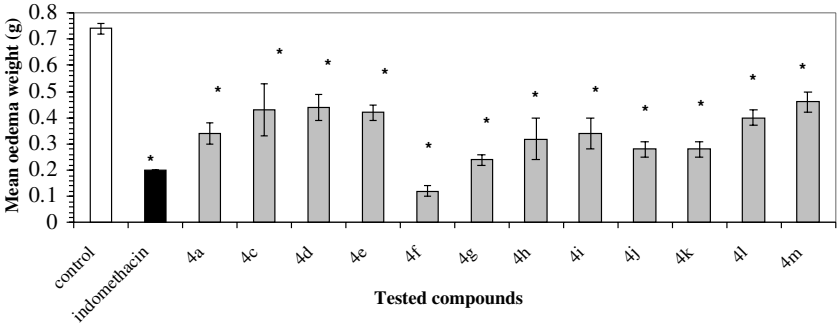


Figure 2. Mean oedema weight (g) of the tested compounds.

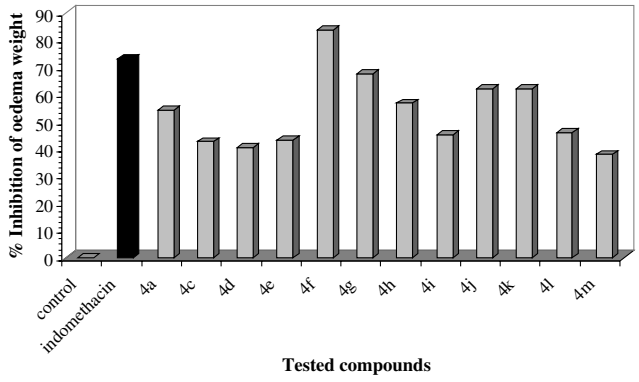


Figure 3. % inhibition of oedema of the tested compounds.

it has been found that, the 1-acetyl-2-pyrazoline analogues '**4j**–**l**' reveal slightly enhanced anti-inflammatory properties than those of the corresponding 1-formyl derivatives '**4c**–**e**.' Moreover, it has been also observed that, the bis(2-pyrazoline-1-carboxaldehyde) analogues linked by *para*-phenylene moiety '**4f**, **h**' exhibit better activities than those linked by the *ortho*-phenylene residue '**4a**, **d**.'

Generally, it has been observed that, several newly prepared compounds (such as **4g**, **j** and **k**) reveal remarkable anti-inflammatory properties (67.57–62.16% inhibition of oedema) comparable to those of indomethacin which used as a reference standard (72.97% inhibition of oedema). Moreover, **4f** exhibits better anti-inflammatory activity (83.78% inhibition of oedema) than that of the used reference standard (indomethacin) itself.

2.3. Ulcerogenic liability

The ulcerogenic liability of the most observed anti-inflammatory actively prepared compounds (**4f**, **g**, **j** and **k**) was determined in albino rats following the previously reported standard method.[49,50] From the obtained data (Table 2, Fig. 4), it has been noticed that all the tested prepared pyrazoline derivatives possess less ulcerogenic potentialities comparable with that of indomethacin (used as a reference standard). Considering oral administration of the tested compounds and the reference drug, compound **4f** (the most effectively prepared anti-inflammatory agent) was found to be safer than indomethacin with respect to ulcerogenic liability (ulcer indexes of **4f** and indomethacin are 5, 21.75, respectively).

Table 2. Ulcerogenic liability of the most observed anti-inflammatory actively prepared compounds

Compound	Number of animals with ulcer	% incidence divided by 10	Average of ulcer number	Average severity	Ulcer index
Control	0	0	0	0	0
Indomethacin	5/5	10	8.25	3.5	21.75
4f	2/5	4	0.6	0.4	5
4g	5/5	10	2.6	1.8	14.4
4j	4/5	8	2.25	1.25	11.5
4k	5/5	10	5.8	2.6	18.4

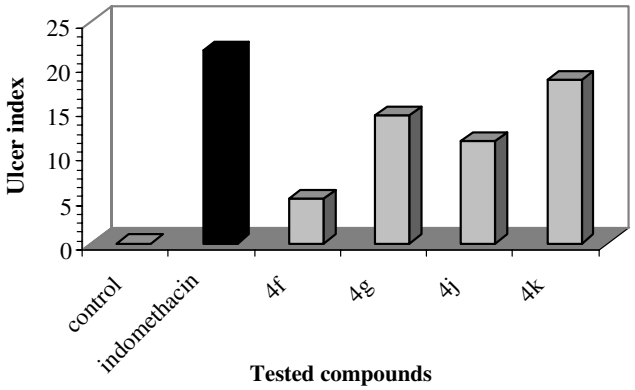


Figure 4. Ulcer index of the tested compounds.

2.4. Molluscicidal activity

Schistosomiasis (also called Bilharziasis) is the most important trematode disease in human. It is an endemic disease in many tropical and subtropical regions. The intermediate host of *Schistosoma mansoni*, which affects the intestinal system, is *Biomphalaria alexandrina* snails. The toxicities of the prepared products towards these snails were carried out using the previously reported standard procedure.[51–54] From the molluscicidal activity screening data (Table 3), it is obvious that most of the prepared chalcone as well as pyrazoline derivatives show moderate properties. It has also been noticed that, the bispyrazolines **4** exhibit better molluscicidal properties than those of their starting bispropenones **3**. Moreover, the substituents attached to the phenyl group have been

Table 3. Molluscicidal activity of the prepared compounds

Compound	% of snails killed at a concentration of		
	20 ppm	10 ppm	5 ppm
3a	20	10	0
3b	30	20	0
3c	10	0	0
3d	0	0	0
3e	10	0	0
3f	20	10	0
3g	0	0	0
3h	0	0	0
4a	30	20	10
4b	20	10	10
4c	50	30	30
4d	10	0	0
4e	20	0	0
4f	40	30	20
4g	30	10	0
4h	0	0	0
4i	30	10	0
4j	50	30	20
4k	10	0	0
4l	20	10	10
4m	30	20	10
Baylucide (reference standard)[a]	100	100	100
Control	0	0	0

[a] Baylucide '2-aminoethanol salt of 2′,5-dichloro-4′-nitrosalicylanilide'.

found to be of great importance, enhancing the observed biological activity. The best results obtained of compounds **4**, where the phenyl residue is either unsubstituted (**4a**, **f**) or substituted with a halogen moiety (chloro 'as in case of **4b**, **g**, **i**' or fluoro 'as in case of **4c**, **j**' substitutions).

3. Experimental

Melting points are uncorrected and recorded on an Electrothermal digital 9100 melting point apparatus. IR spectra were recorded (KBr) on a Mattson Genesis II FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian MERCURY 300 (300 MHz) spectrometer. The starting compounds **1a**, **b**[55,56] were prepared according to the previously reported procedures.

3.1. Preparation of bis-2-propen-1-ones 3 (general procedure)

A mixture of the appropriate **1a**, **b** (5 mmol) and the corresponding acetophenone **2** (10 mmol) in ethanolic KOH solution (25 ml, 4%) was stirred at room temperature (25–30 °C) for the suitable time. The solid separated was collected, washed with water and crystallized from a suitable solvent affording the corresponding **3a**–**h** (for physical and spectroscopic data of compounds **3a**–**h**, cf. Tables 4 and 5).

3.2. Reaction of 3a–h with hydrazine hydrate (general procedure)

A solution of **3a**–**h** (2.5 mmol) and hydrazine hydrate (10 mmol, 80%) in the corresponding aliphatic carboxylic acid (25 ml) 'in case of **4e**–**h**, **l**, **m**, 5 ml of *N*,*N*-dimethylformamide was added to the reaction mixture to assist solubility of the reactant' and was boiled under reflux for the appropriate time. The solid separated upon pouring the reaction mixture into ice-cold water (200 ml) was collected, washed with water and crystallized from a suitable solvent affording **4a**–**m** (for physical and spectroscopic data of compounds **4a**–**m**, cf. Tables 4 and 5).

3.3. Single crystal X-ray crystallographic data of 3a[57]

The crystallographic data were collected at $T = 298$ K on a Kappa CCD Enraf Nonius FR 590 diffractometer using a graphite monochromator with Mo-K_α radiation ($\lambda = 0.71073$ Å). The crystal structure was determined by SIR92[58] and refined by maXus[59] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{32}H_{26}O_4$, $M_r = 474.556$, monoclinic, crystallizes in space group $P21/c$, Cell lengths 'a = 11.8232(5), b = 13.0964(6) and c = 17.4029(11) Å,' cell angles 'α = 90.00, β = 109.363(2), γ = 90.00°,' $V = 2542.3(2)$ Å^3, $Z = 4$, $D_c = 1.240$ mg/m^3, θ values 2.910–22.986°, absorption coefficient μ(Mo-K_α) = 0.08 mm^{-1} and $F(000) = 1000$. The unique reflections measured 4232 of which 1442 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 379 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2 + 0.10000F_o^2]$. The final agreement factors were $R = 0.040$ and $wR = 0.072$ with a goodness-of-fit of 1.549.

3.4. Anti-inflammatory activity

Adult albino rats of either sex (pregnant female animals were excluded) weighing 160–190 g were divided into 14 groups of five animals each. Indomethacin (reference standard) and the tested compounds (100 mg/kg) were suspended in saline solution by the aid of few drops of Tween 80 (to improve wettability of particles) and given intraperitoneally 1h before induction of inflammation. The control group was given saline solution containing few drops of Tween 80.

Carrageenin paw oedema was induced according to a modified method of Winter et al.[47] by subcutaneous injection of 0.05 ml of 1% carrageenin sodium gel into the subplantar region of the right hind paw of rats. All rats were sacrificed by cervical dislocation 3 h after the injection of carrageenin. The hind feet were cut off at the tibio-talar joint and weighed. The weight of oedema was determined from the difference between the injected and non-injected foot. Data were collected, checked and revised. Quantitative variables from normal distribution were expressed as means ± SE 'standard error'. The significant difference between groups was tested by using one-way ANOVA (F test) followed by Dunnett's t test at $p < 0.05$.[60] The anti-inflammatory activity was expressed as a percentage inhibition of oedema weight in treated animals in comparison with the control group[40,41,48] (Table 1, Figs. 2 and 3)

$$\%\text{Inhibition of oedema} = \frac{W_c - W_t}{W_c} \times 100,$$

Table 4. Physical data of the prepared compounds

Compound	Mp (°C) (solvent)	Yield (%), reaction time (h), (colour)	Mol. formula (Mol. wt.)	Analysis (%) Calcd/Found		
				C	H	N
3a	146–147	84, 48	$C_{32}H_{26}O_4$	80.99	5.52	—
	(benzene)	(pale yellow)	(474.53)	81.20	5.61	—
3b	156–157	81, 48	$C_{32}H_{24}Cl_2O_4$	70.72	4.45	—
	(benzene)	(almost colourless)	(543.42)	70.87	4.68	—
3c	186–187	86, 48	$C_{32}H_{24}F_2O_4$	75.28	4.74	—
	(benzene)	(almost colourless)	(510.51)	75.22	4.70	—
3d	185–187	88, 48	$C_{34}H_{30}O_4$	81.25	6.02	—
	(acetic acid)	(yellow)	(502.58)	81.39	6.28	—
3e	203–205[a]	74, 48	$C_{28}H_{22}O_4S_2$	69.11	4.56	—
		(colourless)	(486.58)	69.42	4.78	—
3f	188–190	88, 24	$C_{32}H_{26}O_4$	80.99	5.52	—
	(benzene)	(colourless)	(474.53)	80.83	5.39	—
3g	228–230 [a]	85, 72	$C_{32}H_{24}Cl_2O_4$	70.72	4.45	—
		(almost colourless)	(543.42)	70.59	4.41	—
3h	237–239	84, 24	$C_{34}H_{30}O_4$	81.25	6.02	—
	(1,4-dioxane)	(colourless)	(502.58)	80.97	5.70	—
4a	242–244	72, 9	$C_{34}H_{30}N_4O_4$	73.10	5.41	10.03
	(benzene)	(colourless)	(558.61)	73.21	5.53	10.19
4b	243–244	57, 9	$C_{34}H_{28}Cl_2N_4O_4$	65.07	4.50	8.93
	(benzene)	(colourless)	(627.50)	65.32	4.69	9.19
4c	169–171	60, 9	$C_{34}H_{28}F_2N_4O_4$	68.68	4.75	9.42
	(methanol)	(pale yellow)	(594.59)	68.77	4.86	9.48
4d	225–227[b]	82, 9	$C_{36}H_{34}N_4O_4$	73.70	5.84	9.55
		(pale yellow)	(586.66)	73.49	5.69	9.47
4e	245–247[c]	56, 9	$C_{30}H_{26}N_4O_4S_2$	63.14	4.59	9.82
		(very pale yellow)	(570.66)	63.09	4.50	9.94
4f	214–216	57, 9	$C_{34}H_{30}N_4O_4$	73.10	5.41	10.03
	(benzene)	(colourless)	(558.61)	72.93	5.23	9.88
4g	214–216[a]	81,9	$C_{34}H_{28}Cl_2N_4O_4$	65.07	4.50	8.93
		(colourless)	(627.50)	65.29	4.63	8.85
4h	206–207	75, 9	$C_{36}H_{34}N_4O_4$	73.70	5.84	9.55
	(benzene)	(colourless)	(586.66)	73.66	5.79	9.66
4i	179–181	64, 6	$C_{36}H_{32}Cl_2N_4O_4$	65.95	4.92	8.55
	(benzene)	(colourless)	(655.56)	65.71	4.74	8.33
4j	193–195	58, 6	$C_{36}H_{32}F_2N_4O_4$	69.44	5.18	9.00
	(benzene)	(colourless)	(622.65)	69.50	5.27	9.16
4k	205–207[b]	67, 6	$C_{38}H_{38}N_4O_4$	74.24	6.23	9.11
		(colourless)	(614.71)	74.50	6.42	9.24
4l	231–233[c]	60, 6	$C_{32}H_{30}N_4O_4S_2$	64.19	5.05	9.36
		(pale yellow)	(598.71)	64.32	5.27	9.52
4m	152–154[b]	59, 6	$C_{38}H_{38}N_4O_4$	74.24	6.23	9.11
		(very pale yellow)	(614.71)	74.33	6.29	8.96

[a] *N*,*N*-Dimethylformamide.
[b] Chloroform–ethanol mixture as 1:3 v/v.
[c] *N*,*N*-Dimethylformamide (50%).

where W_c and W_t are the weights of oedema for the control and drug-treated animal groups, respectively.

3.5. Ulcerogenic liability

The ulcerogenic liability was determined in albino rats following the previously reported standard method.[49,50] Rats of either sex weighing 120–140 g were divided into six groups of five animals each. Pregnant female rats were excluded. The animals were fasted 18 h before drug administration. Indomethacin (reference standard) and the tested compounds (100 mg/kg) were suspended in saline solution by the aid of few drops of Tween 80 and were administered orally for three successive days to fasted rats. The control group animals were given saline with few drops of Tween 80. One hour following the last dose, the animals were sacrificed by cervical dislocation and the stomach was removed, opened along the greater curvature and rinsed with saline. The gastric mucosa was examined with a magnifying lens (10×) for the presence of lesions and erosions. The ulcer index was calculated (Table 2, Fig. 4) and the degree of ulcerogenic effect was expressed in terms of

1. Average number of ulcers per stomach.
2. Average severity of ulcers.
3. Percentage incidence of ulcer divided by 10.

The ulcer index is the value that resulted from the sum of the above three values.

Table 5. Spectroscopic data of the prepared compounds

Compound	MIR (ν_{max}/cm^{-1})	^{1}H NMR (solvent), δ
3a	1657 (C=O), 1601, 1568 (C=C)	($CDCl_3$) 4.60 (s, 4H, $2OCH_2$), 7.05–7.62 (m, 14H, arom H), 7.82 (d, 2H, 2PhCOC*H*, *J* = 15.9 Hz), 7.84 (dd, 4H, arom H, *J* = 1.2, 8.7 Hz), 7.97 (d, 2H, 2 ArC*H*=CH, *J* = 15.9 Hz)
3b	1658 (C=O), 1599, 1572 (C=C)	($CDCl_3$) 4.59 (s, 4H, $2OCH_2$), 7.01–7.74 (m, 16H, arom H), 7.79 (d, 2H, 2 ArCOC*H*, *J* = 15.6 Hz), 7.89 (d, 2H, 2 ArC*H*=CH, *J* = 15.9 Hz)
3c	1658 (C=O), 1601, 1570 (C=C)	($CDCl_3$) 4.59 (s, 4H, $2OCH_2$), 6.69–7.85 (m, 16H, arom H), 7.84 (d, 2H, 2 ArCOC*H*, *J* = 15.6 Hz), 7.91 (d, 2H, 2 ArC*H*=CH, *J* = 15.9 Hz)
3d	1655 (C=O), 1606, 1593 (C=C)	($CDCl_3$) 2.30 (s, 6H, $2CH_3$), 4.56 (s, 4H, $2OCH_2$), 6.91–7.76 (m, 16H, arom H), 7.81 (d, 2H, 2 ArCOC*H*, *J* = 15.9 Hz), 7.95 (d, 2H, 2 ArC*H*=CH, *J* = 15.9 Hz)
3e	1643 (C=O), 1593, 1572 (C=C)	(DMSO-d_6) 4.61 (s, 4H, $2OCH_2$), 6.80–7.86 (m, 14H, arom H), 7.83 (d, 2H, 2ArCOC*H*, *J* = 15.6 Hz), 7.90 (d, 2H, 2 ArC*H*=CH, *J* = 15.9 Hz)
3f	1653 (C=O), 1599, 1570 (C=C)	($CDCl_3$) 4.42 (s, 4H, $2OCH_2$), 7.00–7.59 (m, 10H, arom H), 7.59 (d, 2H, 2PhCOC*H*, *J* = 15.3 Hz), 7.63 (d, 4H, arom H, *J* = 8.7 Hz), 7.81 (d, 2H, 2 ArC*H*=CH, *J* = 15.6 Hz), 8.03 (dd, 4H, arom H, *J* = 1.5, 9.6 Hz)
3g	1655 (C=O), 1593, 1574 (C=C)	(DMSO-d_6) 4.43 (s, 4H, $2OCH_2$), 7.09 (d, 4H, *para*-sub. arom H, *J* = 8.7 Hz), 7.63 (dd, 4H, *para*-sub. arom H, *J* = 1.8, 8.7 Hz), 7.73 (d, 2H, 2ArCOC*H*, *J* = 15.3 Hz), 7.82 (d, 2H, 2ArC*H*=CH, *J* = 15.6 Hz), 7.88 (d, 4H, *para*-sub. arom H, *J* = 9 Hz), 8.16 (dd, 4H, *para*-sub. arom H, *J* = 1.8, 8.7 Hz)
3h	1651 (C=O), 1604, 1587 (C=C)	(DMSO-d_6) 2.40 (s, 6H, $2CH_3$), 4.42 (s, 4H, $2OCH_2$), 7.08 (d, 4H, *para*-sub. arom H, *J* = 8.7 Hz), 7.37 (d, 4H, *para*-sub. arom H, *J* = 8.1 Hz), 7.69 (d, 2H, 2ArCOC*H*, *J* = 15.6 Hz), 7.79 (d, 2H, 2ArC*H*=CH, *J* = 15.3 Hz), 7.85 (d, 4H, *para*-sub. arom H, *J* = 8.7 Hz), 8.04 (d, 4H, *para*-sub. arom H, *J* = 8.1 Hz)
4a	1668 (C=O), 1599, 1493 (C=N, C=C)	(DMSO-d_6) 3.08 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.1, 18 Hz), 3.75 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 11.7, 18 Hz), 4.24 (s, 4H, $2OCH_2$), 5.57 (dd, 2H, 2pyr. *H*-5, *J* = 5.1, 11.7 Hz), 6.84–7.69 (m, 18 H, arom H), 8.86 (s, 2H, 2C*H*O)
4b	1674 (C=O), 1597, 1493 (C=N, C=C)	($CDCl_3$) 3.10 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.4, 17.7 Hz), 3.58 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 17.7 Hz), 4.20 (s, 4H, $2OCH_2$), 5.65 (dd, 2H, 2pyr. *H*-5, *J* = 5.4, 12 Hz), 6.67–7.58 (m, 16 H, arom H), 8.93 (s, 2H, 2C*H*O)
4c	1678 (C=O), 1604, 1514 (C=N, C=C)	($CDCl_3$) 3.08 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.4, 17.7 Hz), 3.63 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 17.7 Hz), 4.25 (s, 4H, $2OCH_2$), 5.67 (dd, 2H, 2pyr. *H*-5, *J* = 6, 12 Hz), 6.70–7.68 (m, 16 H, arom H), 8.92 (s, 2H, 2C*H*O)
4d	1676 (C=O), 1599, 1493 (C=N, C=C)	($CDCl_3$) 2.27 (s, 6H, $2CH_3$), 3.03 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.4, 17.7 Hz), 3.54 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 11.7, 17.7 Hz), 4.09–4.17 (m, 4H, $2OCH_2$), 5.56 (dd, 2H, 2pyr. *H*-5, *J* = 5.4, 11.7 Hz), 6.60–7.50 (m, 16 H, arom H), 8.86 (s, 2H, 2C*H*O)
4e	1680 (C=O), 1599, 1491 (C=N, C=C)	(DMSO-d_6) 3.11 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.4, 17.7 Hz), 3.76 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 18 Hz), 4.27 (s, 4H, $2OCH_2$), 5.58 (dd, 2H, 2pyr. *H*-5, *J* = 5.4, 12 Hz), 6.88–7.71 (m, 14 H, arom H), 8.80 (s, 2H, 2C*H*O)
4f	1670 (C=O), 1610, 1510 (C=N, C=C)	($CDCl_3$) 3.23 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 4.8, 18 Hz), 3.80 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 11.7, 17.7 Hz), 4.28 (s, 4H, $2OCH_2$), 5.51 (dd, 2H, 2pyr. *H*-5, *J* = 4.5, 11.7 Hz), 6.88–7.77 (m, 18 H, arom H), 8.96 (s, 2H, 2C*H*O)
4g	1672 (C=O), 1603, 1512 (C=N, C=C)	(DMSO-d_6) 3.18 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.1, 18 Hz), 3.88 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 18 Hz), 4.26 (s, 4H, $2OCH_2$), 5.49 (dd, 2H, 2pyr. *H*-5, *J* = 5.1, 12 Hz), 6.93 (d, 4H, *para*-sub. arom H, *J* = 8.7 Hz), 7.15 (d, 4H, *para*-sub. arom H, *J* = 8.7 Hz), 7.53 (dd, 4H, *para*-sub. arom H, *J* = 2.1, 6.6 Hz), 7.79 (dd, 4H, *para*-sub. arom H, *J* = 2.1, 6.6 Hz), 8.86 (s, 2H, 2C*H*O)
4h	1658 (C=O), 1610, 1512 (C=N, C=C)	($CDCl_3$) 2.42 (s, 6H, $2CH_3$), 3.20 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 4.8, 17.7 Hz), 3.78 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 11.7, 17.7 Hz), 4.28 (s, 4H, $2OCH_2$), 5.49 (dd, 2H, 2pyr. *H*-5, *J* = 4.8, 11.7 Hz), 6.89–7.66 (m, 16 H, arom H), 8.94 (s, 2H, 2C*H*O)
4i	1662 (C=O), 1597, 1493 (C=N, C=C)	($CDCl_3$) 2.36 (s, 6H, $2CH_3$), 2.98 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.1, 17.7 Hz), 3.51 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 17.7 Hz), 4.17–4.28 (m, 4H, $2OCH_2$), 5.72 (dd, 2H, 2pyr. *H*-5, *J* = 5.1, 12 Hz), 6.68–7.58 (m, 16 H, arom H)
4j	1662 (C=O), 1606, 1493 (C=N, C=C)	($CDCl_3$) 2.38 (s, 6H, $2CH_3$), 2.99 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 5.1, 17.7 Hz), 3.54 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 17.7 Hz), 4.20–4.33 (m, 4H, $2OCH_2$), 5.76 (dd, 2H, 2pyr. *H*-5, *J* = 5.1, 12.3 Hz), 6.74–7.67 (m, 16 H, arom H)
4k	1664 (C=O), 1601, 1493 (C=N, C=C)	($CDCl_3$) 2.35 (s, 6H, $2ArCH_3$), 2.40 (s, 6H, $2COCH_3$), 3.00 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 4.5, 17.4 Hz), 3.55 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 17.4 Hz), 4.18–4.31 (m, 4H, $2OCH_2$), 5.74 (dd, 2H, 2pyr. *H*-5, *J* = 4.5, 11.4 Hz), 6.71-7.61 (m, 16 H, arom H)
4l	1666 (C=O), 1601, 1496 (C=N, C=C)	(DMSO-d_6) 2.21 (s, 6H, $2CH_3$), 3.01 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 4.8, 17.7 Hz), 3.75 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 12, 17.7 Hz), 4.30–4.35 (m, 4H, $2OCH_2$), 5.65 (dd, 2H, 2pyr. *H*-5, *J* = 4.8, 12 Hz), 6.88–7.71 (m, 14 H, arom H)
4m	1658 (C=O), 1610, 1512 (C=N, C=C)	($CDCl_3$) 2.41 (s, 12H, $2ArCH_3$ + $2COCH_3$), 3.14 (dd, 2H, 2pyr. *H*-4_{trans}, *J* = 4.5, 17.4 Hz), 3.71 (dd, 2H, 2pyr. *H*-4_{cis}, *J* = 11.7, 17.7 Hz), 4.27 (s, 4H, $2OCH_2$), 5.49 (dd, 2H, 2pyr. *H*-5, *J* = 4.5, 11.7 Hz), 6.86–7.66 (m, 16 H, arom H)

3.6. Molluscicidal activity

The toxicity of the prepared compounds (chalcone and pyrazoline derivatives) towards *Biomphalaria alexandrina* snails (the intermediate host of *Schistosoma mansoni*) was carried out according to the standard reported method.[51–54] The snails were collected from irrigation canals that were not treated with molluscicides. Each of the tested compounds (0.1 g) was dissolved in acetone (10 ml) and the appropriate volume of that solution was added to one litre of water to get the required concentration. Ten snails were used in each experiment. Control experiments were carried out using the same volume of acetone added in one litre of water. Exposure and recovery periods are 24 h each. The observed molluscicidal activity screening data are reported in Table 3.

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