Some Newly Substituted Chromene and Pyrano[2,3-c]pyrazole Derivatives

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Síntesis y actividad antimolusco de algunos derivados con nuevos substituyentes de cromeno y de pirano[2,3-c]pirazol

Síntesi i activitat antimol·lusc d'alguns derivats amb nous substituents de cromè i de pirano[2,3-c]pirazole

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RESUMEN

Los derivados de arilideno 3a-f reaccionan con 1,3-ciclohexanodiona y dimedona 4a,b para rendir los derivados de cromeno 4-(2- o 3-piridil) o 4-pironil substituidos 6a-l. Los derivados de arilideno 3a-c reaccionan con los derivados de pirazolona 7a,b para dar los derivados de pirano[2,3-*c*]pirazol 9a-f. Se investiga la actividad antimolusco de los compuestos sintetizados frente al caracol *Biomphalaria alexandrina*, el huésped intermediario de *Schistosoma mansoni*, observándose que la mayoría de ellos muestran actividad baja a moderada.

Palabras clave: **4-Piridilcromenos. 4-piridilpirano[2,3-*c*]pirazoles. 4-pironilcromenos. 4-pironilpirano[2,3-*c*]pirazoles. Actividad antimolusco.**

SUMMARY

The arylidene derivatives 3a-f react with 1,3-cyclohexanedione and dimedone 4a,b to afford the 4-(2- or 3-pyridyl) or 4-pipronyl-chromene derivatives 6a-l. The arylidene derivatives 3a-c react with the pyrazolone derivatives 7a,b to afford the pyrano[2,3-*c*]pyrazole derivatives 9a-f. 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.

Key words: **4-Pyridylchromenes. 4-Pyridylpyrano[2,3-*c*]pyrazoles. 4-Pipronylchromenes. 4-Pipronylpyrano[2,3-*c*]pyrazoles. Molluscicidal activity.**

RESUM

Els derivats d'arilidè 3a-f reaccionen amb 1,3-ciclohexandiona i dimedona 4a,b per rendir els derivats de cromè 4-(2- o 3-piridil) o 4-pipronil substituïts 6a-l. Els derivats d'arilidè 3a-c reaccionen amb els derivats de pirazolona 7a,b per donar els derivats de pirano[2,3-*c*]pirazole 9a-f. S'investiga l'activitat antimol·lusc dels compostos sintetitzats front el cargol *Biomphalaria alexandrina*, l'hoste intermediari de *Schistosoma mansoni*, observant-se que la majoria d'ells mostren activitat baixa a moderada.

Mots clau: **4-Piridilcromens. 4-piridilpirano[2,3-*c*]pirazoles. 4-pipronilcromens. 4-pipronilpirano[2,3-*c*]pirazoles. Activitat antimol·lusc.**

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INTRODUCTION

Schistosomiasis is one of the most widespread endemic diseases in Egypt and other tropical countries, and represents one of the serious problems due to its destructive health concequencies. Great national and international efforts are made to combat this disease. Praziquantel proved to be a successful chemotherapeutic agent to infected persons, however the nonavoidable contact, specially of illiterant people, with polluted water leads to repeated infection. Therefore 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, 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]; all have shown a considerable molluscicidal activity. In our previous works we could prepare the chromene derivatives **4** and the pyranopyrazoles **5**[4-6] (Fig. 1) as synthetic substitutes to ricchiocarpin A: **2**, and these compounds show also a considerable molluscicidal activity but not the extent that enables their field use.

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. Therefore, the more lipophilicity of the compound, the more its ability to merge in the tissues and chelate with these metals. In the present work we tried to introduce new substituents in position 4 of compounds **4** and **5** to increase their lipophilicity and / or the chelating ability[7].

It has been found that the pyridine and pipronal moieties are contained in a variety of synthetic bioactive compounds[8, 9]. Therefore we thought that replacing the Ar in compounds **4** and **5** (in figure 1) by a pyridyl or pipronyl groups, and also the cyano group by an ester group, might enhance their molluscicidal activity.

RESULTS AND DISCUSSION

a. Chemistry

The arylidene derivatives **3a-f** were prepared by condensation of pyridine-2-aldehyde **1a**, pyridine-3-aldehyde **1b** or pipronal **1c** with each of malononitrile **2a** and ethyl cyanoacetate **2b** using piperidine as the catalyst following the same reported method[4] (*cf*. experimental).

Compounds **3a-f** react with cyclohexan-1,3-dione and dimedone **4a,b** respectively in refluxing ethanol catalyzed by piperidine to afford the chromene derivatives **6a-l** presumably via the acyclic intermediates **5a-l**, which undergo cyclization through addition of the enol OH to the cyano group. It was expected that the cyclization of the intermediates **5d-f** and **5j-l** would occur via elimination of ethanol, however the IR spectra of compounds **6d-f** and **6j-l** did not reveal any cyano absorption bands in the range 2190-2230 cm^{-1}, and instead ester carbonyl absorption bands were found at ~ 1710 cm^{-1}. The ^1H NMR spectra of these compounds showed also the characteristic triplet (CH_3) and quartet (CH_2) of the ester group at δ~ 1.3 and 3.9 ppm respectively (*cf*. experimental).

Compounds **3a-c** reacted with the pyrazolone derivatives **7a,b** to give the expected pyranopyrazole derivatives **9a-f**. The formation of compounds **9** is assumed to proceed via the addition of the active methylene of the pyrazolones **7** to the activated double bond of **3** to afford the intermediates **8**, which semultaneously undergo cyclization via addition of the enol OH to one of the cyano groups. Analytical and spectral data are in complete agreement with the depicted structures **9a-f** (Scheme 2) (*cf*. Experimental).

b. Molluscicidal Activity

The toxicity of compounds **6a-l** and **9a-f** toward *Biomphalaria alexandrina* snails was evaluated. The half and sublethal doses (LC_{50} and LC_{90} in ppm/μM) for each compound was determined and the results are 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 5 ppm. The most effective of them are **6g**, **6h** in the chromene series (LC_{50} = 4 and 5 ppm, respectively) and **9a** and **9b** in the pyrazole series (LC_{50} = 6 and 7 ppm, respectively). The other compounds show very weak activity. 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 2-pyridyl moiety in **6g** accomplished more activity (LC_{50} = 4 ppm; Table 1) than 3-pyridyl moiety in **6h** (LC_{50} = 5 ppm) perhaps

TABLE I

Molluscicidal activity of compounds 6a-l and 9a-f.

Compd No	LC_{50} ppm (μM)	LC90 ppm (μM)
Bayluscide	<1(<3.06)	1 (3.06)
6a	5 (18.7)	9 (33.6)
6b	6 (22.5)	10 (37.4)
6c	15 (48.3)	>15 (>48.3)
6d	14 (44.5)	>15 (>47.7)
6e	13 (41.3)	>15 (>47.7)
6f	>15 (>42)	>15 (>42.0)
6g	4 (13.5)	8 (27.1)
6h	5 (16.9)	10 (33.8)
6i	13 (38.4)	>15 (>44.3)
6j	13 (38.0)	>15 (>43.8)
6k	13 (38.0)	>15 (>43.8)
6l	>15 (>38.9)	>15 (>38.9)
9a	6 (23.7)	9 (35.5)
9b	7 (27.6)	9 (35.5)
9c	11 (37.1)	>15 (>50.6)
9d	13 (41.2)	>15 (>47.6)
9e	13 (41.2)	>15 (>47.6)
9f	>15 (>41.8)	>15 (>41.8)
Blanc	–	–

due to the fact that the N of the 2-pyridyl moiety affords a better condition for chelation than in the 3-pyridyl (*cf*. introduction section). The same observation can be seen in the pyrano[2,3-*c*]pyrazole derivatives **9a** and **9b** (LC_{50} = 6 and 7 ppm, respectively). The pipronyl miety did not add much to the activity and the presence of the ester group increased the solubilty of the compounds but did not increase their activities. 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)[10, 11] showed that our compounds are still inferior as molluscicidal agents. However, compounds **6g** and **6h** look promising after further structural modification, which will be considered in a future study.

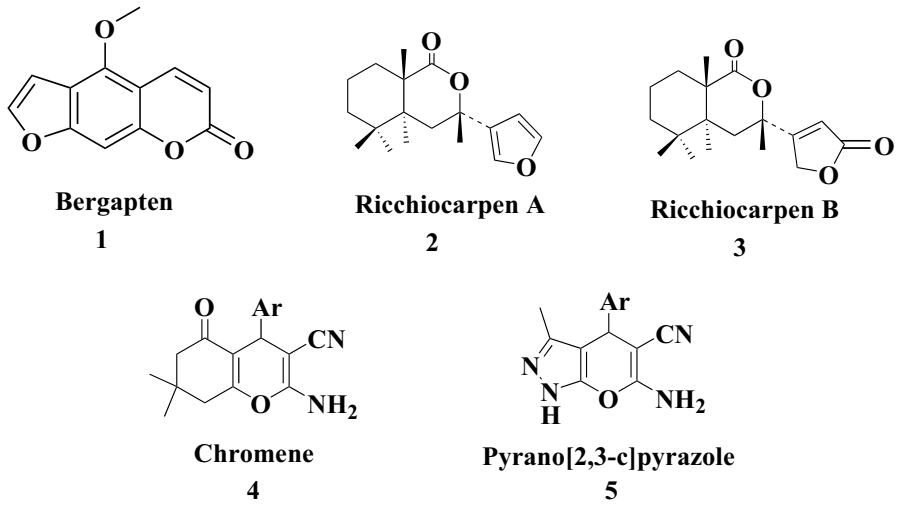
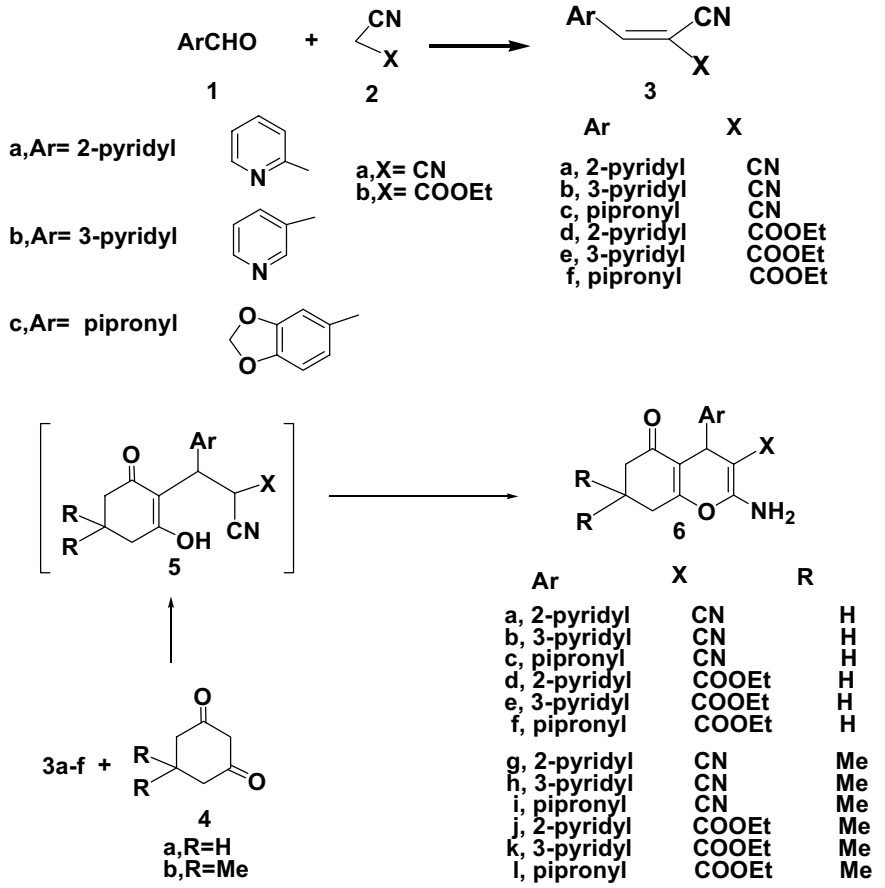
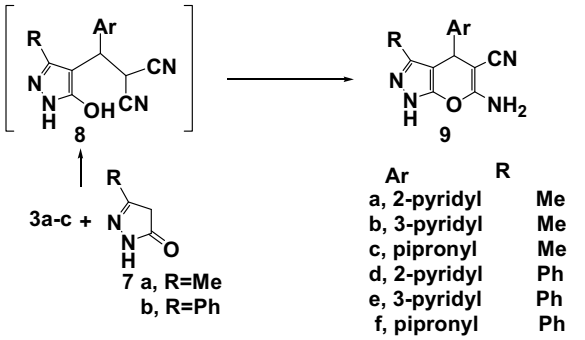


Figure 1.



Scheme 1.



Scheme 2.

EXPERIMENTAL SECTION

a. Chemistry

Melting points were measured on an Electro-thermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Micro analytical Center at Cairo University.

Preparation of the arylidene derivatives (3a-f):

These compounds were prepared from the condensations of each of the aromatic aldehydes **1a-c** with each of the malonic acid derivatives **2a,b** according to literature procedures[4, 6].

Reaction of the arylidenes 3a-f with the diketones 4a,b – Preparation of (6a-l):

To a refluxing mixture of the arylidenemalononitriles **3a-f** (10 mmol) and each of the the diketones **4a,b** (10 mmol) in ethanol (25 mL) was added piperidine (0.5 mL), whereby a homogeneous solution was obtained. The reflux was continued in each case for about 2 hrs (tlc control), then left to cool to room temperature. The reaction mixture was then poured on ice-cold water and neutralized by few drops of conc. HCl. The solid precipitates that appeared were filtered off and recrystallized from ethanol to afford the pure products.

2-Amino-5-oxo-4-pyridin-2-yl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6a):

Yellow crystals, Yield 46%, mp 232 ºC (EtOH); $C_{15}H_{13}N_3O_2$ (M = 267.28); IR 3355, 3305 (NH_2), 2193 (CN), 1663 (C = O) cm^{-1}; ^{1}H NMR δ 1.85-1.90 (m, 2H, CH_2), 2.16-2.32 (m, 2H, CH_2), 2.44-2.54 (m, 2H, CH_2), 4.29 (s, 1H, pyran-4H), 7.35-8.40 (m, 6H, Pyrid. H + NH_2). *Anal*. Calcd. C, 67.40; H, 4.90; N, 15.72; Found C, 67.55; H, 5.15; N, 15.92.

2-Amino-5-oxo-4-pyridin-3-yl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6b):

Yellow crystals, Yield 53%, mp 242 ºC (EtOH); $C_{15}H_{13}N_3O_2$ (M = 267.28); IR 3462, 3303 (NH_2), 2191 (CN), 1665 (C = O) cm^{-1}; ^{1}H NMR δ 1.85-1.94 (m, 2H, CH_2), 2.26-2.35 (m, 2H, CH_2), 2.46-2.58 (m, 2H, CH_2), 4.24 (s, 1H, pyran-4H), 7.29-8.40 (m, 6H, Pyrid. H + NH_2). *Anal*. Calcd. C, 67.40; H, 4.90; N, 15.72; Found C, 67.60; H, 5.08; N, 16.0.

2-Amino-4-benzo[1,3]dioxol-5-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6c):

Yellow crystals, Yield 66%, mp 218 ºC (EtOH); $C_{17}H_{14}N_2O_4$ (M = 310.30); IR 3359, 3310 (NH_2), 2196 (CN), 1665 (C = O) cm^{-1}; ^{1}H NMR δ 1.80-1.95 (m, 2H, CH_2), 2.15-2.35 (m, 2H, CH_2), 2.45- 2.65 (m, 2H, CH_2), 4.25 (s, 1H, pyran-4H), 5.75 (s, 2H, CH_2), 7.08-8.48 (m, 5H, phenyl H + NH_2). *Anal*. Calcd. C, 65.80; H, 4.55; N, 9.03; Found C, 65.85; H, 4.50; N, 9.27.

Ethyl 2-amino-5-oxo-4-pyridin-2-yl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (6d):

White crystals, Yield 78%, mp 203 ºC (EtOH); $C_{17}H_{18}N_2O_4$ (M = 314.34); IR 3454, 3262 (NH_2), 1708 (CO), 1666 (CO) cm^{-1}; ^{1}H NMR δ 1.34 (t, 3H, CH_3), 1.79-1.86 (m, 2H, CH_2), 2.15-2.30 (m, 2H, CH_2), 2.30- 2.50 (m, 2H, CH_2), 3.95 (q, 2H, CH_2), 4.33 (s, 1H, pyran 4-H), 7.20-8.40 (m, 6H, pyridine H + NH_2). *Anal*. Calcd. C, 64.96; H, 5.77; N, 8.91; Found C, 65.20; H, 5.85; N, 9.20.

Ethyl 2-amino-5-oxo-4-pyridin-3-yl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (6e):

White crystals, Yield 81%, mp 206 ºC (EtOH); $C_{17}H_{18}N_2O_4$ (M = 314.34); IR 3345, 3260 (NH_2), 1695 (CO), 1667 (CO) cm^{-1}; ^{1}H NMR δ 1.32 (t, 3H, CH_3), 1.85-1.95 (m, 2H, CH_2), 2.25-2.30 (m, 2H, CH_2), 2.32- 2.50 (m, 2H, CH_2), 3.85 (q, 2H, CH_2), 4.34 (s, 1H, pyran 4-H), 7.28-8.40 (m, 6H, pyridine H + NH_2). *Anal*. Calcd. C, 64.96; H, 5.77; N, 8.91; Found C, 64.85; H, 5.70; N, 8.65.

Ethyl 2-Amino-4-benzo[1,3]dioxol-5-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbo-xylate (6f):

Yellow crystals, Yield 76%, mp 169 ºC (EtOH); $C_{19}H_{19}NO_6$ (M = 357.36); IR 3350, 3260 (NH_2), 1710 and 1669 (2CO) cm^{-1}; ^{1}H NMR δ 1.85-1.92 (m, 2H, CH_2), 1.35 (t, 3H, CH_3), 2.25-2.35 (m, 2H, CH_2), 2.42-2.54 (m, 2H, CH_2), 3.85 (q, 2H, CH_2), 4.30 (s, 1H, pyran 4-H), 5.72 (s, 2H, CH_2), 7.10-8.20 (m, 5H, phenyl H + NH_2). *Anal*. Calcd. C, 63.86; H, 5.36; N, 3.92; Found C, 63.65; H, 5.40; N, 4.05.

2-Amino-7,7-dimethyl-5-oxo-4-pyridin-2-yl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6g):

Pale yellow crystals, Yield 70%; mp 206 °C (EtOH); $C_{17}H_{17}N_3O_2$ (M = 295.34); IR 3340, 3314 (NH_2), 2190 (CN), 1665 (CO) cm^{-1}; ^{1}H NMR δ 1.07 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.10 (s, 2H, CH_2), 2.40 (s, 2H, CH_2), 4.50 (s, 1H, pyran 4-H), 6.90-7.40 (m, 6H, pyridine H + NH_2). *Anal*. Calcd. C, 69.14; H, 5.80; N, 14.23; Found C, 69.20; H, 5.72; N, 14.30.

2-Amino-7,7-dimethyl-5-oxo-4-pyridin-3-yl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6h):

White crystals, Yield 98%, mp 199 ºC (EtOH); $C_{17}H_{17}N_3O_2$ (M = 295.34); IR 3345, 3315 (NH_2), 2188 (CN), 1667 (CO) cm^{-1}; ^{1}H NMR δ 1.05 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.0 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 4.43 (s, 1H, pyran 4-H), 7.15-8.10 (m, 6H, pyridine H + NH_2). *Anal*. Calcd. C, 69.14; H, 5.80; N, 14.23; Found C, 69.25; H, 5.90; N, 14.35.

2-Amino-4-benzo[1,3]dioxol-5-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydr-4H-chromene-3-carbonitrile (6i):

White crystals, Yield 60%, mp 220 ºC (EtOH); $C_{19}H_{18}N_2O_4$ (M = 338.36); MS (LC/MS) *m/z* 338 [M+]; IR 3356, 3190 (NH2), 2195 (CN), 1669 (CO) cm^{-1}; ^{1}H NMR δ 1.03 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.12 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 4.12 (s, 1H, pyran 4-H), 5.95 (s, 2H, CH_2), 6.55-7.25 (m, 5H, phenyl H + NH_2). *Anal*. Calcd. C, 67.44; H, 5.36; N, 8.28; Found C, 67.48; H, 5.45; N, 8.47.

Ethyl 2-amino-7,7-dimethyl-5-oxo-4-pyridin-2-yl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (6j):

White crystals, Yield 48%, mp 175 ºC (EtOH); $C_{19}H_{22}N_2O_4$ (M = 342.39); MS (LC/MS) *m/z* 342 [M^+]; IR 3355, 3252 (NH_2), 1705 (CO), 1668 (CO) cm^{-1}; ^1H NMR δ 1.05 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.18 (t, 3H, CH_3), 2.22 (s, 2H, CH_2), 2.57 (s, 2H, CH_2), 3.85 (q, 2H, CH_2), 4.53 (s, 1H, pyran 4-H), 7.20-8.35 (m, 6H, pyridine H + NH2). *Anal*. Calcd. C, 66.65; H, 6.48; N, 8.18; Found C, 66.60; H, 6.52; N, 8.36.

Ethyl 2-amino-7,7-dimethyl-5-oxo-4-pyridin-3-yl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (6k):

White crystals, Yield 54%, mp 179 ºC (EtOH); $C_{19}H_{22}N_2O_4$ (M = 342.39); IR 3350, 3250 (NH_2), 1715 (CO), 1670 (CO) cm^{-1}; ^1H NMR δ 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.34 (t, 3H, CH_3), 2.34 (s, 2H, CH_2), 2.45 (s, 2H, CH_2), 3.92 (q, 2H, CH_2), 4.40 (s, 1H, pyran 4-H), 7.00-8.10 (m, 6H, pyridine H + NH_2). *Anal*. Calcd. C, 66.65; H, 6.48; N, 8.18; Found C, 66.72; H, 6.70; N, 8.42.

Ethyl 2-Amino-4-benzo[1,3]dioxol-5-yl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chro-mene-3-carboxylate (6l):

White crystals, Yield 83%, mp 133 ºC (EtOH); $C_{21}H_{23}NO_6$ (M = 385.41); MS (LC/MS) *m/z* 385 [M^+]; IR 3340, 3190 (NH_2), 1716 (CO), 1669 (CO) cm^{-1}; ^1H NMR δ 1.03 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.29 (t, 3H, CH_3), 1.94 (s, 2H, CH_2), 2.44 (s, 2H, CH_2), 3.94 (q, 2H, CH_2), 4.52 (s, 1H, pyran 4-H), 5.90 (s, 2H, CH_2), 6.84-8.15 (m, 5H, phenyl H + NH_2). *Anal*. Calcd. C, 65.44; H, 6.02; N, 3.63; Found C, 65.50; H, 6.22; N, 3.85.

Reaction of 3a-c with the pyrazolones 6a,b – Preparation of (9a-f):

To a mixture of the arylidenemalononitriles **3a-c** (10 mmol) and each of the pyrazolone derivatives **7a,b** (10 mmol) in ethanol (25 mL) was added piperidine (0.5 mL). The reaction mixture was refluxed for about 2-3 hrs in each case (tlc control). The solvent was evaporated in vaccu to one third its volume and left to cool overnight whereby colored solid precipitates appeared. These solids were filtered off and recrystallized from ethanol to afford the pure products.

6-Amino-3-methyl-4-pyridin-2-yl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (9a):

Pale brown powder, Yield 55%, mp 230 °C (EtOH); $C_{13}H_{11}N_5O$ (M = 253.26); MS (LC/MS) *m/z* (%) 253 (90) [M^+]; IR 3411, 3318, 3173 (NH & NH_2), 2192 (CN) cm^{-1}; ^1H NMR δ 1.85 (s, 3H, CH_3), 5.05 (s, 1H, pyran 4-H), 6.98-8.50 (m, 6H, pyrid. H + NH_2), 12.90 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. C, 61.65; H, 4.38; N, 27.65; Found C, 61.55; H, 4.45; N, 27.95.

6-Amino-3-methyl-4-pyridin-3-yl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (9b):

Reddish brown powder, Yield 76% (1.8 g); mp 241 °C (EtOH); $C_{13}H_{11}N_5O$ (M = 253.26); IR 3415, 3320, 3175 (NH & NH_2), 2190 (CN) cm^{-1}; ^1H NMR δ 1.79 (s, 3H, CH_3), 4.68 (s, 1H, pyran 4-H), 6.94-8.46 (m, 6H, pyrid. H + NH_2), 12.75 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. C, 61.65; H, 4.38; N, 27.65; Found C, 61.72; H, 4.50; N, 27.83.

6-Amino-4-benzo[1,3]dioxol-5-yl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbo- nitrile (9c):

Yellowish white powder, Yield 52%; mp 231 °C (EtOH); $C_{15}H_{12}N_4O_3$ (M = 296.28); IR 3415, 3320, 3175 (NH & NH_2), 2190 (CN) cm^{-1}; ^1H NMR δ 1.83 (s, 3H, CH_3), 4.62 (s, 1H, pyran 4-H), 5.90 (s, 2H, CH_2), 6.97-8.48 (m, 5H, phenyl H + NH_2), 12.75 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. C, 60.81; H, 4.08; N, 18.91; Found C, 60.90; H, 4.28; N, 19.15.

6-Amino-3-phenyl-4-pyridin-2-yl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (9d):

Pale brown powder, Yield 48%; mp 239 °C (EtOH); $C_{18}H_{13}N_5O$ (M=315.33); IR 3483, 3169, 3107 (NH & NH_2), 2201 (CN) cm^{-1}; 1H NMR δ 5.50 (s, 1H, pyran 4-H), 6.80-7.53 (m, 11H, arom. H + NH_2), 12.95 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. C, 68.56; H, 4.16; N, 22.21; Found C, 68.60; H, 4.25; N, 22.35.

6-Amino-3-phenyl-4-pyridin-3-yl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (9e):

Deep brown powder, Yield 90%; mp 240 °C (EtOH); $C_{18}H_{13}N_5O$ (M = 315.33); IR 3485, 3171, 3110 (NH & NH_2), 2186 (CN) cm^{-1}; ^1H NMR δ 4.52 (s, 1H, pyran 4-H), 6.50-7.57 (m, 11H, arom. H + NH_2), 12.85 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. C, 68.56; H, 4.16; N, 22.21; Found C, 68.65; H, 4.27; N, 22.40.

6-Amino-4-benzo[1,3]dioxol-5-yl-3-Phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbo-nitrile (9f):

Yellowish brown powder, Yield 62%; mp 229 °C (EtOH); $C_{20}H_{14}N_4O_3$ (M = 358.35); IR 3412, 3325, 3178 (NH & NH_2), 2189 (CN) cm^{-1}; ^1H NMR δ 4.90 (s, 1H, pyran 4-H), 5.90 (s, 2H, CH_2), 6.57-7.54 (m, 10H, phenyl H + NH_2), 12.95 (s, 1H, D_2O exchangeable, NH). *Anal*. Calcd. C, 67.03; H, 3.94; N, 15.63; Found C, 67.30; H, 4.17; N, 15.75.

b. Molluscicidal activity tests

The molluscicidal activity tests were carried out by determination of the half, and sublethal doses LC_{50} and LC_{90} of each compound under investigation. *Biomphalaria alexandrina* snails were collected from the field (water canals), maintained under laboratory conditions for a period of 7 days before the test, and fed daily by lettuce leaves. Eight concentrations of each compound under investigation were prepared ranging from 1 ppm to 15 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 water (taken directly from the water canals) to get a homogeneous solution 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 shell diameter) 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[12], slightly modified by using two mixed solvents to dissolve the compounds.

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