Synthesis and Molluscicidal Activity of New Derivatives of 1-(Hydroxy/substituted Phenyl)-3-arylpropenones

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Several 1-(hydroxy/substituted phenyl)propenones were tested as molluscicidal agents among which the 1-(2-hydroxy/substituted phenyl)-3-(2-furyl)propenones **1a-c** show the most promising results. In an attempt to improve their activity, new dihydropyrazolo[1,5-*c*][1,3]benzoxazines, their thio and their dehydrogenated derivatives were prepared. The pyrazolo[1,5-*c*][1,3]benzoxazines **4a,b** were hydrolyzed affording the 3-(2-furyl)-5-(2-hydroxy/substituted phenyl) pyrazoles **8a,b**. The hydroxyimino derivatives **10a-c** were synthesized together with their corresponding isoxazole derivatives **11a-c**. - Molluscicidal assay indicated that the oximes **10b,c**, the isoxazole **11b**, the pyrazole **8b**, and its *N*-carbamoyl derivative **9b** are most effective. They have in common the conjugated system shown in Fig. 1 which is presumably the active core.

Synthese und molluscicide Wirkung neuer 1-(substituierter Hydroxyphenyl)-3-arylpropenone

Einige 1-(substituierte Hydroxyphenyl)-3-arylpropenone wurden auf molluscicide Wirkung geprüft. Die 1-(substituierten 2-Hydroxyphenyl)-3-(2-furyl)-propenone **1a-c** zeigten die besten Ergebnisse. Um ihre Wirkung zu verstärken, wurden neue Dihydropyrazolo[1,5-*c*][1,3]benzoxazine, ihre Thio- und Dehydro-Derivate hergestellt. Die Pyrazolo[1,5-*c*][1,3]benzoxazine **4a,b** wurden zu den 3-(2-Furyl)-5-(substituierten 2-hydroxyphenyl)-pyrazolen **8a,b** hydrolysiert. Die Hydroxyimino-Derivate **10a-c** wurden zusammen mit den Isoxazolen **11a-c** hergestellt. - Die Prüfung auf molluscicide Wirkung zeigte, daß die Oxime **10b,c**, das Isoxazol **11b**, das Pyrazol **8b** und sein *N*-Carbamoyl-Derivat **9b** am stärksten wirken. Alle beinhalten das in Abb. 1 dargestellte konjugierte System, das möglicherweise die aktive Gruppe darstellt.

Salicylanilides represent an important class of molluscicides[1,2]. Meanwhile, some pyrazoles[3] and chalcones[4] are reported to possess molluscicidal activity. Therefore, we have reported the synthesis and the molluscicidal activity of some 5-heteroaryl salicylanilides[5]. Here we describe a series of 1-(hydroxy/substituted phenyl)-3-arylprop-2-en-1-ones **1**.

According to our molluscicidal assay, the 3-(2-furyl)propenones **1a-c** were the most effective members and thus they were chosen as starting materials for constructing more efficient compounds either through the preparation of substituted heteroaryl derivatives which have shown such activity[3] or by the incorporation of known active moieties like salicylanilide[1].

On heating the propenones **1a,b** with 24% hydrazine hydrate, the corresponding pyrazolines **2a,b** were obtained in good yield. Compounds **2a,b** were cyclized with commercially available phosgene solution (12% in toluene) in the presence of two moles of NaH affording the dihydropyrazolo[1,5-*c*][1,3]benzoxazines **3a,b**.

The ^{1}H-NMR spectrum of **3a** showed no D_2O exchangeable protons, present in **2a** but the characteristic three signals of the pyrazoline moiety, each integrating for one proton, at 3.5 ppm (dd, $J_{gem.}$ = 15 Hz, $J_{vic.}$ = 12 Hz), 4.0 ppm (dd, $J_{gem.}$ = 15 Hz, $J_{vic.}$ = 10 Hz) and 5.5 ppm (dd, J = 12 Hz, J = 10 Hz) assigned to the axial methylene-H, equatorial methylene-H and the methine one. The IR spectra of **3** showed an intense CO absorption at 1750-1790 cm^{-1} but no NH and OH absorptions.

The chemical behaviour of **3** towards tetrachloro-*o*-benzoquinone yielding **4**[6] and P_2S_5 leading to **6** supports the given structure.

The IR-spectra of the thiated derivatives **6** showed the C=S absorption near 1340 cm^{-1}, their ^{1}H-NMR-spectra showed the characteristic three signals of the pyrazoline moiety as in **3**.

The dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-thione derivatives **6** could be dehydrogenated using tetrachloro-*o*-benzoquinone to give the pyrazolo[1,5-*c*][1,3]benzoxazin-5-thiones **7a,b**. **7a,b** were also obtained by thiation of **4a,b** with P_2S_5.

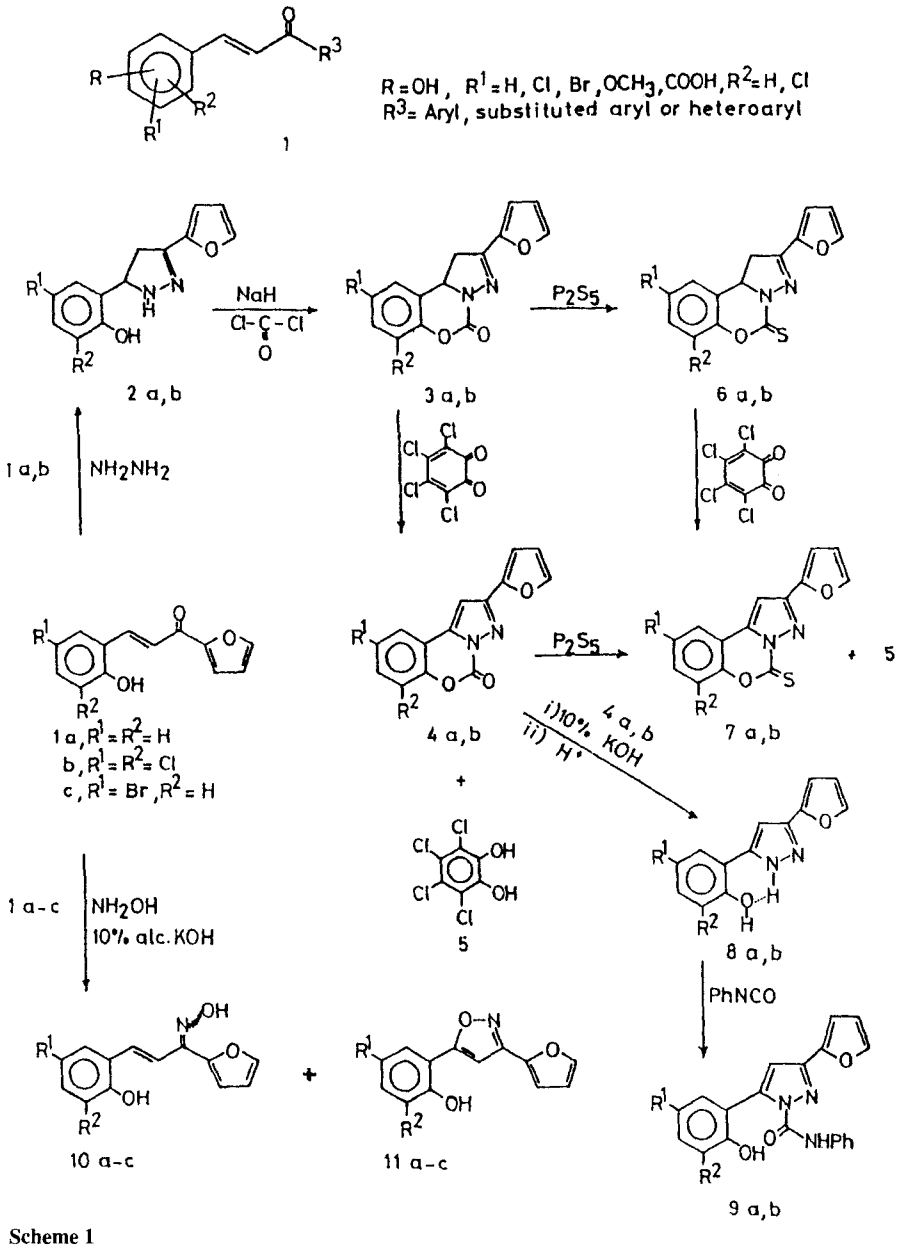
The IR-spectra of **4a,b** showed a C=O-band at ~ 1735 cm^{-1} while that of **7a,b** showed C=S absorbance at ~ 1335 cm^{-1}. The ^{1}H-NMR spectra of **4** and **7** showed the expected pyrazole H in the aromatic region instead of the three characteristic signals of the pyrazoline in **3** or **6**.

The pyrazolo[1,5-*c*][1,3]benzoxazine-5-ones **4a,b** could be hydrolized by KOH to the 3-(2-furyl)-5-(2-hydroxy/substituted phenyl)pyrazoles **8a,b**.

Their IR-spectra - exemplified by that of **8b** - showed OH and NH absorptions at 3400 and 3300 cm^{-1}, respectively, similar to those in the pyrazolines **2a,b** these groups appeared in the ^{1}H-NMR spectra as D_2O exchangeable signals at 10.3 and 11.2 ppm. The UV spectra of **8a,b** include the maximum at 255 nm exhibited by pyrazoles[7].

Structure **8** is assumed to be formed by hydrolysis and decarboxylation. - When **8a,b** were reacted with phenyl isocyanate they afforded the *N*-carbamoyl derivatives **9a,b** in satisfactory yield. Their IR spectra - exemplified by that of **9a** - show a *N*-carbamoyl absorption at 1650 cm^{-1} (*O*-carbamoyl absorption would be observed at 1710 cm^{-1} [3]). Their ^{1}H-NMR-spectra show D_2O exchangeable signals at 10.3 and 11.1 ppm (OH- and NH group, respectively).

Oximes are known for their biological importance[8] and hence the propenone **1a** was treated with $H_2NOH \cdot HCl$ in aqueous-methanolic KOH solution, affording two products which could be separated. The product with mp. 179°C,



Scheme 1

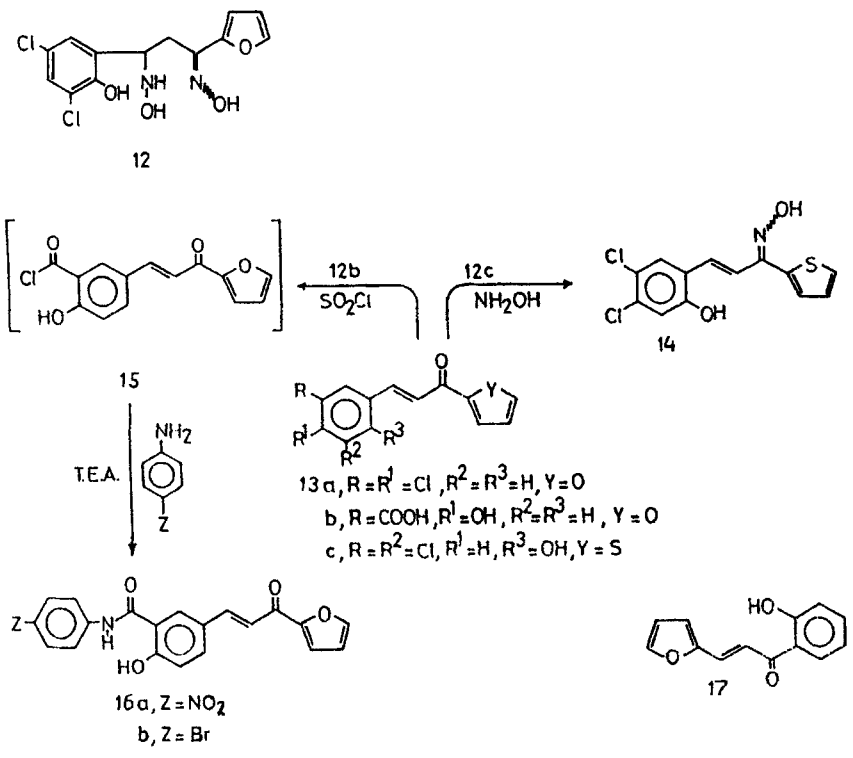
$C_{13}H_{11}NO_3$ ($M^{+\cdot}$ at m/z = 229), was identified as the hydroxyimino derivative **10a** while the structure of the second component with mp. 165°C, $C_{13}H_9NO_3$ ($M^{+\cdot}$ at m/z = 227), was elucidated as the isoxazole **11a**.

Similarly the propenones **1b,c** were treated with $H_2NOH \cdot HCl$ under identical conditions. The products show the spectral features of **10a** and **11a** and accordingly structures **10b,c** and **11b,c** were given to them. A 3. component could be isolated from the reaction of **1b** besides **10b** and **11b**. It has $M^{+\cdot}$ compatible with $C_{13}H_{12}N_2O_4Cl_2$ (m/z = 330) and shows a ^{1}H-NMR spectrum having aliphatic protons at 3.0 ppm integrating to 2 H and 5.5 ppm integrating to 1 H. These data as well as the IR-spectrum and microanalyses could be interpreted for the hydroxyaminopropane structure **12**. In accordance the mass spectrum of **12** showed the characteristic fragments at m/z 206 (^{35}Cl; 55%) and 125 (100) attributed to the β- and *McLafferty* cleavage, respectively, as reported for analogous compounds[9].

The formation of the hydroxyaminopropane **12** in alkaline medium is in accordance with previous reports[9,10] and it is assumed that its cyclization and concomitant dehydrogenation lead to the isoxazole **11**[11].

The hydroxyimino derivative **10b** could be obtained as the sole product when the reaction of **1b** with $H_2NOH \cdot HCl$ was carried out in ethanol at room temp. in the absence of base[10] (Experimental Part).

The IR-spectra of the oximino derivatives **10** show two OH-bands at 3500 and 3360 cm^{-1}. In their ^{1}H-NMR spectra there are two D_2O exchangeable signals at 10.1 and 12.6 ppm to be seen, while the ^{1}H-NMR-spectra of the isoxazole derivatives **11** showed only one D_2O exchangeable signal at 9.7 ppm assigned to the phenolic OH which appeared at ~ 3500 cm^{-1} in the IR-spectra.



Scheme 2

In an attempt to study the role played by the presence and position of the hydroxyl group and the furan moiety, the propenones **13a-c**, **17** and the oxime derivative **14** were prepared. The latter could be obtained solely from the reaction of **13** with $H_2NOH \cdot HCl$ in ethanol in absence of base as done with the propenone **1b**. Furthermore, the biologically active salicylanilide moiety was incorporated by the reaction of 1-(3-salicylyl)-3-(2-furyl)propenone **13b** with $SOCl_2$ and 4-substituted anilines yielding the 5-(2-furoylethenyl)salicylanilides **16a,b**.

Molluscicidal Activity

The toxicity of the products to *Biomphalaria alexandria* snails, the intermediate host of *Schistosoma mansoni* in Egypt was evaluated. The best results were obtained with the hydroxyimino compounds **10a-c** especially the 3,5-dichloro derivative **10b** which gave an 80% kill of the snails at 1 ppm/L (Table 2). The isoxazoles **11a-c** were also promising. It seems that the activity of these compounds is related to the conjugated system (see Fig. 1) present in the parent compounds **1a-c**, their oximes and the corresponding isoxazoles.

In accordance with this view, the pyrazolines **2a,b** are less active than the dehydrogenated derivatives **8a,b**; a parallel result was observed upon comparing the molluscicidal activity of the pyrazolobenzoxazoles **3a,b** with that of the dehydrogenated compounds **4a,b**. The introduction of the known active carbamoyl moiety to the pyrazoles **8a,b** slightly enhanced the activity.

The role of the hydroxyl group in the mentioned conjugation was checked by changing its position as in **13b** or its removal as in **14a**: both compounds are less active than those with the *o*-hydroxy group even when the salicylanilide moiety was incorporated (cf. **16a,b**).

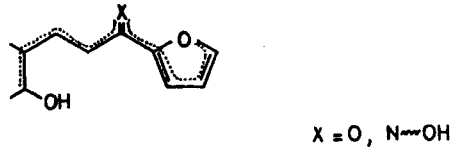


Fig. 1

As regarding the influence of the furan moiety, it was found that its replacement, by the thiophene analogue or changing its position with that of the phenyl moiety, as in **13c** and **17**, both lead to negative results.

So, we conclude that the conjugation illustrated in Fig. 1 in this special arrangement is probably the active core in this class of compounds.

Experimental Part

Mps.: uncorrected.- IR spectra: (KBr), Pye-Unicam SP-1000.- ^{1}H-NMR-spectra: Varian EM 390 (90 MHz) and GEMINI-200 spectrometers, TMS as int. reference.- Mass spectra: 70 eV, Varian MAT 311 A.- Elemental analyses: Central Service Laboratory, National Research Centre.

Propenones **1a-c**, **13a-c**, **17** and pyrazolines **2a,b** were prepared according to reported methods[6,12,13].

2-(2-Furyl)-7,9-disubstituted-1,10b-dihydropyrazolo[1,5-c][1,3]benzoxazine-5-ones **3a,b**

To an ice cooled solution of **2a** or **2b** (0.01 mol) in toluene (40 ml) and (0.02 mol) of NaH an equimol. amount of commercially available phosgene (12% of toluene, 8.4 ml) was added dropwise, while stirring for 1 h. After further 3 h the mixture was washed with water, dried (Na_2SO_4) and concentrated. The precipitated solid was crystallized from the appropriate solvent.

2-(2-Furyl)-7,9-disubstituted-1,10b-dihydropyrazolo[1,5-c][1,3]benzoxazine-5-thione **6a,b** *and 2-(2-Furyl)-7,9-disubstituted pyrazolo[1,5-c][1,3]benzoxazine-5-thione* **7a,b**

P_2S_5 (0.01 mol) and each of **3a**, **3b**, **4a**, and **4b** (0.01 mol) were refluxed in dry toluene (50 ml) for 6 h. The mixture was filtered while hot, the filtrate concentrated and the solid formed was crystallized from the appropriate solvent to afford **6a,b** and **7a,b**, respectively. (Table 1).

2-(2-Furyl)-7,9-disubstituted pyrazolo[1,5-c][1,3]benzoxazine-5-one **4a,b** *and 2-(2-Furyl)-7,9-disubstituted pyrazolo[1,5-c][1,3]benzoxazine-5-thione* **7a,b**

A solution of tetrachloro-*o*-benzoquinone (0.01 mol) in dry toluene (25 ml) was added dropwise to a boiling solution of each of **3a**, **3b**, **6a**, and **6b** (0.01 mol) in dry toluene (50 ml) while stirring for 1 h. After further 1 h the mixture was concentrated; the separated solid was crystallized from the proper solvent to give **4a,b** and **7a,b**, respectively.

The mother liquor was extracted with 10% NaOH, acidified with dil. HCl and the precipitate obtained was shown to be the *o*-tetrachlorocatechol **5** (mp. and mixed mp. of its diacetate derivative 184°C[15]).

3-(2-Furyl)-5-(3,5-disubstituted-2-hydroxyphenyl)-pyrazole **8a,b**

To a solution of each of **4a**, **4b** (0.01 mol) in dioxane (20 ml), 10% aqueous KOH (20 ml) was added, while stirring at 70°C for 6 h. The solution was then acidified with dil. HCl and the separated solid was crystallized from the proper solvent (Table 1).

3-(2-Furyl)-5-(3,5-disubstituted-2-hydroxyphenyl)-1-phenylcarbamoylpyrazole **9a,b**

A mixture of **8a** or **8b**, respectively, (0.01 mol), phenyl isocyanate (0.01 mol) in dry toluene (30 ml), and of triethylamine (1 ml) was heated under reflux for 6 h, then concentrated, cooled and the separated solid was crystallized from the proper solvent (Table 1).

3-(2-Furyl)-1-(3,5-disubstituted-2-hydroxyphenyl)-2-hydroxyiminoprop-2-ene **10a-c**, *3-(2-furyl)-5-(3,5-disubstituted-2-hydroxyphenyl)isoxazole* **11a-c** *and 3-(2-furyl)-1-(3,5-dichloro-2-hydroxyphenyl)-3-hydroxyamino-2-hydroxyiminopropane* **12**

To a solution of each of the propenones **1a-c** (0.01 mol) in methanol (20 ml), 10% aqueous KOH (10 ml) and $H_2NOH \cdot HCl$ (0.01 mol) were added. The mixture was heated under reflux for 1 h, then methanol was evaporated and the aqueous layer was decanted. The oily residue was triturated with methanol. The solid product, so formed, was crystallized to give **11a-c**. - The aqueous layer was kept for 8 h at 5°C, a solid product precipitated which was crystallized to afford the oximes **10a-c** (Table 1). In case of **1b**, a mixture of **10b** and **12** was obtained which was separated by column chromatography (silica gel) using ether:petrolether 40-60°C (1:1 v/v) as eluent: the first fraction gave **10b**, the second yielded compound **12**.

3-(2-Furyl)-1-(5-salicylic acid prop-2-ene (**13b**)[12]

Analytical data: Table 1.- IR: 3220-2920 (2 OH); 1680 (CO); 1650 (CO).- ^{1}H-NMR: δ (ppm) = 6.9 (d; J = 12 Hz, 1H, olef. H), 7.05 (d; J = 9 Hz, 1H, salicylate 3-H), 7.2-7.3 (m, 2H, furan 3-H, 4-H), 7.8 (m, 2H, furan 5-H, olef. H), 8.1 (dd; J_1 = 9 Hz, J_2 = 4 Hz, 1H, salicylate 4-H), 8.25 (d; J = 4 Hz, 1H, salicylate 6-H), 12.9 (brs, 2H, 2 OH).

3-(2-Heteroaryl)-1-(3,5-disubstituted-2-hydroxyphenyl)-2-hydroxyimino-prop-2-ene **10b** *and* **14**

Each of **1b** and **12c** (0.01 mol) was stirred in ethanol (30 ml) with $NH_2OH \cdot HCl$ (0.01 mol) at 25°C for 3 weeks. The mixture was then refrigerated for 8 h and the precipitate formed was crystallized from the proper solvent (Table 1).

Table 1: Physical data of compounds **3-16**

Compound No.	m.p./ Solvent	Yield %/ colour	Mol. F./ Mol.Wt	Analysis % Calc. / Found C	H	N	S	Cl
3a	152-54	75	$C_{14}H_{10}N_2O_3$	66.1	3.96	11.0	-	-
	EtOH	pale brown	254.2	66.0	3.74	10.8	-	-
3b	175	70	$C_{14}H_8N_2O_3Cl_2$	52.0	2.49	8.7	-	21.9
	EtOH	pale brown	323.1	51.8	2.31	8.4	-	21.7
4a	185	70	$C_{14}H_8N_2O_3$	66.7	3.19	11.1	-	-
	toluene	pale brown	252.2	66.6	3.00	10.8	-	-
4b	195	80	$C_{14}H_6N_2O_3Cl_2$	52.4	1.88	8.7	-	22.1
	toluene	pale brown	321.1	52.2	1.73	8.5	-	21.8
6a	165	65	$C_{14}H_{10}N_2O_2S$	62.2	3.72	10.4	11.7	-
	toluene	yellow	270.3	62.1	3.49	10.1	11.6	-
6b	180-82	60	$C_{14}H_8N_2O_2SCl_2$	49.6	2.37	8.3	9.5	20.9
	toluene	yellow	339.2	49.3	2.21	8.0	9.2	20.6
7a	168-70	62	$C_{14}H_8N_2O_2S$	62.7	3.00	10.4	12.0	-
	toluene	colourless	268.3	62.4	2.87	10.2	11.6	-
7b	173	60	$C_{14}H_6N_2O_2SCl_2$	49.9	1.79	8.3	9.5	21.0
	toluene	colourless	337.2	49.7	1.53	8.0	9.2	20.8
8a	133-134	50	$C_{13}H_{10}N_2O_2$	69.0	4.45	12.4	-	-
	MeOH	colourless	226.2	68.9	4.27	12.1	-	-

Table 1: continued

8b	185	55	$C_{13}H_8N_2O_2Cl_2$	52.9	2.73	9.5	-	24.0
	dioxane	colourless	295.1	52.7	2.49	9.2	-	23.8
9a	220	45	$C_{20}H_{15}N_3O_3$	69.6	4.37	12.2	-	-
	dioxane	colourless	345.3	69.4	4.20	11.9	-	-
9b	231	45	$C_{20}H_{13}N_3O_3Cl_2$	58.0	3.16	10.1	-	17.1
	dioxane	colourless	414.2	57.8	3.03	9.9	-	16.9
10a	179	40	$C_{13}H_{11}NO_3$	68.1	4.83	6.1	-	-
	MeOH	colourless	229.2	68.0	4.61	5.9	-	-
10b	172	35	$C_{13}H_9NO_3Cl_2$	52.4	3.04	4.7	-	23.8
	MeOH	colourless	298.1	52.2	2.91	4.4	-	23.4
10c	116-118°C	40	$C_{13}H_{10}BrNO_3$	50.7	3.27	4.5	-	-	25.9
	MeOH	colourless	308.1	50.5	3.03	4.3	-	-	21.6
11a	165	30	$C_{13}H_9NO_3$	68.7	3.99	6.2	-	-	-
	MeOH	pale yellow	227.2	68.5	3.70	5.8	-	-	-
11b	185	35	$C_{13}H_7Cl_2NO_3$	52.7	2.38	4.7	-	23.9	-
	MeOH	pale yellow	296.1	52.6	2.21	4.5	-	23.6	-
11c	152	42	$C_{13}H_8BrNO_3$	51.0	2.63	4.6	-	-	26.1
	MeOH	yellow	306.1	50.9	2.38	4.3	-	-	25.8
12	190	10	$C_{13}H_{12}Cl_2N_2O_4$	47.1	3.65	8.5	-	21.4	-
		colourless	331.2	47.0	3.41	8.3	-	21.2	-
13b	210	70	$C_{14}H_{10}O_5$	65.1	3.90	-	-	-	-
	MeOH	yellow	258.2	64.9	3.76	-	-	-	-
14	168	45	$C_{13}H_9SCl_2NO_2$	49.7	2.88	4.5	10.2	22.6	-
	MeOH	colourless	314.2	49.4	2.73	4.2	9.9	22.3	-
16a	222	40	$C_{20}H_{14}N_2O_6$	63.5	3.72	7.4	-	-	-
	MeOH	yellow	378.3	63.2	3.55	7.1	-	-	-
16b	234	45	$C_{20}H_{14}BrNO_4$	58.3	3.42	3.4	-	-	19.4
	MeOH	yellow	412.2	58.0	3.19	3.1	-	-	19.0

Table 2: Molluscicidal activity[a] of the tested products[b]

Compound No.	Number of snails killed after an exposure period of 24 h by a concentration of:			
	10 ppm	5 ppm	2 ppm	1 ppm
S	10	10	10	10
1a	8	4	2	0
1b	10	7	3	0
1c	10	5	2	0
2b	4	1	0	0
4a	5	3	0	0
4b	7	4	0	0
7a	5	2	0	0
7b	6	3	0	0
8a	10	4	2	0
8b	10	6	4	1
9a	10	6	4	0
9b	10	8	6	1
10a	10	6	3	0
10b	10	10	10	8
10c	10	9	7	4
11a	10	5	3	0
11b	10	8	6	3
11c	10	6	4	1
13b	4	2	0	0
13c	5	3	0	0
14	8	5	2	0

a) The test was carried out by dissolving 0.1 g of the compound in 10 ml of acetone and adding the appropriate volume of the solution to one L of water to get the required concentration. Ten snails were used in each experiment. 2,5-Dichloro-4-nitrosalicylanilide (S) was used as a standard[1]. Reference experiments: 10 ml of acetone/L water.

b) Compounds showing unsatisfactory results at 10 ppm were omitted from the table.

5-(2-Furoylethenyl) salicylanilides **16a,b**

A mixture of **13b** (0.01 mol) and SO_2Cl (0.05 mol) was heated under reflux in dry benzene (20 ml) for 1 h. The mixture was evaporated under vacuum and the residual oil was dissolved in dry benzene (25 ml), 4-bromo or 4-nitro-aniline (0.01 mol) and triethylamine (0.01 mol) in dry benzene (15 ml) were added dropwise while stirring in an ice bath for 15 min. After further 5 h the mixture was poured onto water, the separated org. layer was dried (Na_2SO_4) and concentrated. The separated solid was crystallized from the proper solvent.

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[Ph92]