Arch. Pharm. Res. Vol. 17, No. 2, pp. 66-70, 1994

Oxazole, Pyrazole and Piperidine Derivatives Having an o-Hydroxyaryl Moiety with Anticipated Molluscicidal Activity

Galal A. M. Nawwar, Randa H. Swellem and Amal M. Ibrahim

Pesticides Laboratory, National Research Centre, Dokki, Gairo, Egypt

(Received March 30, 1993)

The condensation reactions of hippuric acid and its furyl derivative with salicylaldehydes or that of salicylhippuric acid analogues with furaldehyde led to the corresponding oxazoles. These were subsequently treated with hydrazine hydrate, hydroxylamine or subjected to alkaline hydrolysis to yield new o-hydroxyaryl or salicyl containing derivatives. 5-Substituted salicylanilides were treated with piperidine and formaldehyde in a Mannich type reaction affording the corresponding 3-(N-piperidinomethyl) salicylanilides. It was noticed that the presence of an electron donating group in position 3 in the salicylanilide moiety decreases the molluscicidal activity.

Key words: Salicylanilides, Oxazoles, Pyrazoles, Mannich reaction, Molluscicidal activity.

INTRODUCTION

Several compounds containing the salicyl moiety had shown promising molluscicidal activity (Nawwar, 1993; Assad *et al.*, 1988). Recently, we have reported a structure-activity relationship of some newly synthesized salicyl derivatives (Nawwar *et al.*, 1993) and we concluded that the conjugation illustrated in Fig. 1 in this special arrangement is probably the active core in this class of compounds. In continuation, new compounds bearing the same structural features were synthesized here in and their molluscicidal activity discussed.

MATERIALS AND METHODS

General

Melting points were uncorrected and measured on Buchi 510 melting point apparatus, IR spectra (KBr) were measured on Pye Unicam Sp-1000 spectorometer. NMR spectra were determined on Varian EM 390 (90 MHz) and GEMINI-200 (200 MHz) spectrometers. Chemical shifts are reported in δ ppm relative to tetramethylsilane. Mass spectra were obtained on a varian MAT 311A mass spectrometer (70 eV). Analytical data were performed in Central Service Laboratory at National Research Centre.

The 5-chloro and 5-nitroethenylsalicyloyl chlorides were prepared following literature procedure (Nawwar *et al.*, 1993; Nawwar *et al.*, 1991).

Correspondence to: Galal A. M. Nawwar, National Resarch Center, Pesticides Lab., Tahrir St. Dokki, Giza, Egypt

Synthesis of 2-Substituted aryl-4-substituted arylidene oxazolin-5-ones (2,4,7)

General procedure: A mixutre of each of **1a-d** (1 mmole) and furaldehyde, 5-formylsali-cylaldehyde or 3,5-dichlorosalicylaldehyde (1 mmole) was boiled under reflux in 30 ml acetic anhydride in presence of sodium acetate (1 mole) for 3 hours. The reaction mixture was then cooled, poured into crushed ice and the solid thus formed was filtered off and crystallized.

2-(2-Acetoxy-5-chlorophenyl)-4-(2-furylidene)oxazolin-5-one (2a): Yellow crystals from methanol; 60% yield; m.p. 140℃; IR: 1760 (CO acetyl), 1705 (CO oxazolinone), 1650 (C=N). NMR: 2.2 (s, 3H, acetyl), 7.0-8.2 (m, 6H, ArH), 8.7 (s, 1H, ylidene H). $C_{16}H_{10}ClNO_5$ (331.7): Calc. C 57.9, H 3.0, N 4.2, Cl 10.7, Found C 57.7, H 2.9, N 3.8, Cl 10.4.

2-(2-Acetoxy-5-nitroetheylphenyl)-4-(2-furyliden) oxazolin-5-one (2b): Yellow crystals from methanol; 55% yield; m.p. 125℃; IR: 1760 (CO acetyl), 1710 (CO oxazolinone). NMR: 2.2 (s, 3H, acetyl), 7.0-8.2 (m, 8H, ArH and nitroethenyl olefinic H), 8.7 (s, 1H, ylidene H). $C_{18}H_{12}N_2O_7$ (368.3): Calc. C 58.7, H 3.3, N 7.6, Found C 58.4, H 3.1, N 7.4.

2-Phenyl-4-(3-formyl-4-acetoxybenzylidene)oxazolin-5-one (4): Yellow crystals from methanol; 72% yield;

m.p. 185℃; IR: 1760 (CO acetyl), 1745 (CO oxazolinone), 1705 (CO carboxylic), 1650 (C=N). NMR: 2.2 (s, 3H, acetyl), 7.2-7.7 (m, 6H, Ph, salicylate H-3), 8.1 (m, 2H, salicylate H-4, H-6), 8.7 (s, 1H, ylidene H), 8.9 (s, 1H, OH). $C_{19}H_{13}NO_6$ (351.3): Calc. C 65.0, H 3.7, N 4.0, Found C 64.7, H 3.6, N 3.7.

2-Phenyl-4-(2-acetoxy-3,5-dichlorobenzylidene)oxazolin-5-one (7a): Yellow crystals from methanol; 65% yield; m.p. 125℃; IR: 1765 (CO acetyl), 1705 (CO oxazolinone). NMR: 2.1 (s, 3H, acetyl), 7.1-8.0 (m, 7H, ArH), 8.7 (s, 1H, ylidene H). $C_{18}H_{11}Cl_2NO_4$ (376.2): Calc. C 57.5, H 3.0, N 3.7, Cl 18.9, Found C 57.3, H 2.8, N 3.4, Cl 18.5.

2-(2-Furyl)-4-(2-acetoxy-3,5-dichlorobenzylidene) oxazolin-5-one (7b): Yellow crystals from methanol; 70% yield; m.p. 135℃; IR: 1755 (CO acetyl), 1705 (CO oxazolinone), 645 (C=N). NMR: 2.2 (s, 3H, acetyl), 7.2-8.0 (m, 5H, ArH), 8.6 (s, 1H, ylidene H). $C_{16}H_9Cl_2NO_5$ (366.2): Calc. C 52.5, H 2.5, N 3.8, Cl 19.4, Found C 52.3, H 2.3, N 3.5, Cl 19.1.

Synthesis of 2-substituted aryl-4-substituted arylidene oxazolin-5-one (3 and 11)

General Procedure: A mixture of each of **2a, b** or **7a, b** (1 mmole) and hydroxylamine hydrochloride (7 mg, 1 mmole) was boiled under reflux in 30 ml ethanol for 4 hours in presence of 1 ml triethylamine. The solution was then concentrated, cooled and left to precipitate. The solid product thus formed was collected and crystallized.

2-(2-Hydroxy-5-chlorophenyl)-4-(2-furylidene)oxazolin-5-one (3a): Yellow crystals from methanol; 65% yield; m.p. 191℃; IR: 3500 (OH), 1700 (CO oxazolinone), $C_{14}H_8ClNO_4$ (289.7): Calc. C 58.1, H 2.8, N 4.8, Cl 12.2, Found C 57.8, H 2.6, N 4.6, Cl 11.9.

2-(2-Hydroxy-5-nitroethenylphenyl)-4-(2-furylidene) oxazolin-5-one (3b): Yellow crystals from methanol; 65% yield; m.p. 183℃; IR: 3500 (OH), 1705 (CO oxazolinone). NMR: 7.0-8.0 (m, 6H, ArH), 8.2 (m, 2H, nitro-ethenyl protons), 8.7 (s, 1H, ylidene H), 11.1 (s, 1H, OH). $C_{16}H_{10}N_2O_6$ (326.3): Calc. C 58.9, H 3.1, N 8.6, Found C 58.7, H 3.0, N 8.3.

2-Phenyl-4-(2-hydroxy-3,5-dichlorobenzylidene)oxazolin-5-one (11a): Yellow crystals from methanol; 45% yield; m.p. 163℃; IR: 3500 (OH), 1700 (CO oxazolinone). NMR: 7.3-7.5 (m, 5H, C_6H_5), 7.8, 8.0 (2d, J=3 Hz, 2H, C_6H_2), 8.6 (s, 1H, ylidene H), 10.3 (s, 1H, OH). $C_{16}H_9Cl_2NO_3$ (330.2): Calc. C 58.2, H 2.7, N 4.2, Cl 21.5, Found C 57.9, H 2.6, N 3.9, Cl 21.2.

2-(2-Furyl)-4-(2-hydroxy-3,5-dichlorobenzylidene) oxazolin-5-one (11b): Yellow crystals from methanol; 60% yield; m.p. 178℃;' IR: 3450 (OH), 1700 (CO). NMR: 6.9 (m, 2H, furan H-3 and H-4), 7.8-8.0 (m, 3H, furan H-5 and hydroxyaryl protons), 8.7 (s, 1H, ylidene H), 10.4 (s, 1H, OH). $C_{14}H_7Cl_2NO_4$ (324.1): Calc. C 51.9, H 2.2, N 4.3, Cl 21.9, Found C 51.8, H 2.1, N 4.1, Cl 21.3.

Synthesis of 2-chloro-4-nitro-5'-(2-phenyl-Δ^2-oxazolin-5-one-4-ylidene) salicylanilide (5)

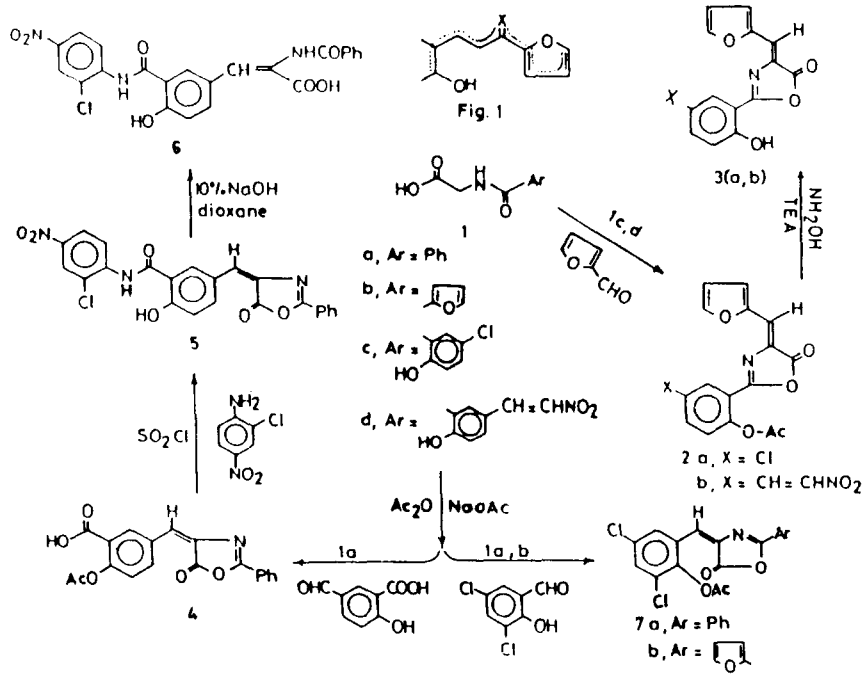
Compound **4** (35 mg, 1 mmole) was heated in 20 ml thionyl chloride at 80℃ for 2 hours. Thionyl chloride was then evaporated under reduced pressure and the acid chloride, thus formed, was dissolved in 20 ml dry toluene and cooled in an ice bath. A solution of 2-chloro-4-nitro-aniline (17 mg, 1 mmole) and 1 ml triethylamine in 20 ml dry benzene was added dropwise while stirring to the acid chloride solution at such a rate that the temperature did not rise above 5℃. The stirring was continued at the bath temperature for 1 hour, then at room temperature (25℃ for 2 hours. A solid precipitate was formed, filtered off, washed with water, yellow crystals from toluene (45% yield), m.p. 280℃. IR: 3400 (OH), 3300 (NH), 1755 (CO oxazolinone), 1660 (CO amide). NMR: 7.1-7.8 (m, 7H, C_6H_5, aniline H-6 and salicylate H-3), 8.0-8.2 (m, 4H, aniline H-3, H-5, salicylate H-4, H-6), 8.6 (s, 1H, ylidene H). $C_{23}H_{14}ClN_3O_6$ (463.8): Calc. C 59.6, H 3.1, N 9.1, Cl 7.6, Found C 59.4, H 3.0, N 8.9, Cl 7.4.

Syntheis of the salicylanilide (6) and the acrylic acid derivatives (10a,b)

Gernal Procedure: To a solution of **5** or **7a, b** (5 mmole) in 10 ml dioxane, 25 ml of 10% aqueous sodium hydroxide was added and stirred at room temperature (25℃) for 5 hours. The solution was acidified with dilute hydrochloric acid, then extracted with ethyl acetate. The organic layer washed with water, dried over anhydrous sodium sulfate, then concentrated; the solid precipitate obtained was filtered off and crystallized.

5'-(2-Benzamidoacrylic acid)-2-chloro-4-nitrosalicylanilide (6): Yellow crystals from dioxane; 50% yield; m.p. 178℃; IR: (br) 3500-3200 (phenolic OH, carboxylic OH and amides NH), 1700 (CO carboxylic), 1660, 1650 (amides CO). NMR: 7.3-7.5 (m, 7H, C_6H_5, salicylate H-3 and aniline H-6), 7.8-8.3 (m, 5H, aniline H-3, H-5, salicylate H-4, H-6 and ylidene H), 11.2 (br s, 1H, NH), 12.1 (s, 1H, OH), 13.1 (s, 1H, carboxylic OH). $C_{23}H_{16}ClN_3O_7$ (481.8): Calc. C 57.3, H 3.4, N 8.7, Cl 7.4, Found C 57.1, H 3.2, N 8.5, Cl 7.2.

2-Benzamido-1-(2-hydroxy-3,5-dichlorophenyl)acrylic acid (10a): Colorless crystals from dioxane; 80% yield; m.p. 200℃; IR: (br) 3500-3200 (phenolic OH, carboxylic OH and NH), 1650 (CO amide). NMR: 6. 9-7.5 (m, 5H, Ph), 7.8 (d, J=3 Hz, 1H, salicylate H-



Scheme I

3), 8.2 (m, 2H, acrylic H and salicylate H-5), 12.1 (s, 1H, OH), 13.2 (br s, 1H, OH carboxylic). $C_{16}H_{11}Cl_2NO_4$ (352.1): Calc. C 54.5, H 3.1, Cl 20.1, N 3.9, Found C 54.2, H 3.0, Cl 19.8, N 3.7.

2-Furylamido-1-(2-hydroxy-3,5-dichlorophenyl)acrylic acid (10b): Colorless crystals from ethanol; 80% yield; m.p. 194°C; IR: (br) 3500-3250 (phenolic OH, carboxylic OH and NH), 1655 (CO amide). NMR: 6.9-7.1 (m, 2H, furan H-3 and H-4), 7.8 (d, J=3 Hz, 1H, salicylate H-3), 7.9-8.1 (m, 3H, acrylic H, furan H-5 and salicylate H-5), 12.0 (s, 1H, OH), 13.1 (br s, 1H, OH carboxylic). $C_{14}H_9Cl_2NO_5$ (342.1): Calc. C 49.1, H 2.6, Cl 20.7, N 4.0, Found C 48.9, H 2.5, Cl 20.1, N 3.9.

Synthesis of 1-acetyl-3-(2-hydroxy-3,5-dichlorophenyl)-4-arylamido-5-hydroxypyrazole (9a, b)

General Procedure: A solution of each of **7a, b** (1 mmole) in 25 ml ethanol was treated with an equimolecular amount of hydrazine hydrate (80%) under reflux for 6 hours. The reaction mixture was then left to cool, the precipitate obtained was filtered off and identified as the azine **8** (m.p. and mixed m.p. 242°C) (Miller and Greenfield, 1974). To the remaining filtrate, water was added dropwise till precipitation commenced. The product, thus formed, was collected and identified as the pyrazoles **9**.

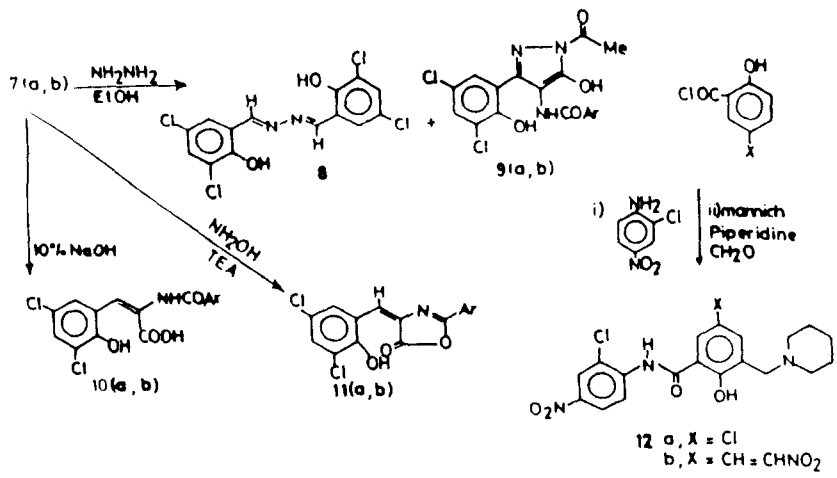
(9a): Yellow crystals from ethanol; 45% yield; m.p. 220°C; IR: 3450-3300 (2OH and NH), 1660-1650 (2CO amide). NMR: 2.2 (s, 3H, acetyl), 7.4-7.6 (m, 5H, C_6H_5), 7.9, 8.1 (2d, J=3 Hz, 2H, C_6H_2), 10.4 (s, 1H, OH), 11.2 (br s, 1H, NH). $C_{18}H_{13}Cl_2N_3O_4$ (406.2) Calc. C 53.2 H 3.2 Cl 17.4 N 10.3 Found C 52.9 H 3.1 Cl 17.1 N 10.2.

(9b): Yellow crystals from dioxane; 40% yield; m.p. 212°C; IR: 3450-3300 (2OH and NH), 1660-1650 (2CO amide). $C_{16}H_{11}Cl_2N_3O_5$ (396.1): Calc. C 48.4, H 2.7, Cl 17.9, N 10.6, Found C 48.2, H 2.5, Cl 17.3, N 10.2.

Synthesis of 2-chloro-4-nitro-3'-(N-piperidinomethyl)-5'-substituted salicylanilide derivatives (12a, b)

General Procedure: The 5-chloro and 5-nitroethenylsalicyloyl chlorides were treated each with 2-chloro-4-nitroaniline according to the reported methods (Nawwar, 1993; Latif *et al.*, 1985) to prepare the corresponding anilides. A solution of each of these anilides (3 mmole) in 30 ml ethanol was treated with piperidine acetate (3 mmole) and 40% formalin (3 mmole). The reaction mixture was refluxed for 5 hours and left to stand overnight at room temperature. The mixture was diluted with 60 ml water and basified with ammonia to pH 8. The product, thus separated, was filtered off and crystallized from the appropriate solvent.

3'-(N-piperidinomethyl)2,5'-dichloro-4-nitrosalicylanilide (12a): Bright yellow crystals from ethanol; 65% yield; m.p. 234°C; IR: 3400-2890 (OH, NH and N-piperidinomethyl group), 1650 (CO). NMR: 1.1 (m, 6H, piperidine protons), 3.2 (m, 4H, N-piperidinomethyl), 3.4 (s, 2H, N-CH_2), 7.9-8.3 (m, 5H, C_6H_3 and salicylate protons), 12.2 (s, 1H, OH). $C_{19}H_{19}Cl_2N_3L_4$ (424.31): Calc.



Scheme II

C 53.8, H 4.5, N 9.9, Cl 16.7, Found C 53.5, H 4.3, N 9.5, Cl 16.4.

2-Chloro-3'-(N-piperidinomethyl)-5'-nitroethenyl-4-nitrosalicylanilide (12b): Bright yellos crystals from methanol; 55% yield; m.p. 256°C; IR: 3410-2890 (OH, NH and aliphatic protons of N-piperidinomethyl group), 1655 (CO). NMR: 1.1 (s, 6H, piperidine protons), 3.1 (m, 4H, N-piperidinomethyl), 3.3 (s, 2H, exocyclic N-piperidinomethyl), 7.5-8.3 (m, 7H, C_6H_3, salicylate H and nitroethenyl protons), 11.8 (s, 1H, OH). $C_{21}H_{21}ClN_4O_6$ (460.9): Calc. C 54.7, H 4.6, N 12.2, Cl 7.7, Found C 54.6, H 4.4, N 12.0, Cl 7.4.

RESULTS AND DISCUSSION

On condensing the salicyloyl amino acid conjugates **1c, d** with furaldehyde in the presence of sodium acetate, the acetylated oxazolinone derivatives **2a, b** were obtained which subsequently reacted with NH_2OH to afford their deacetylated analogues **3a, b.**

The 5-formylsalicylic acid also condensed with **1a** to give a product with a molecular formula $C_{19}H_{13}NO_6$ ($M^{+\cdot}$ m/z=351) which is compatible with the salicylidene oxazolinone structure **4.** Similar condensation of hippuric acid with aromatic aldehydes has been previously reported (Armstrong, 1948).

When the acid chloride of compound **4** was treated with 2-chloro-4-nitroaniline, the expected salicylanilide **5** was obtained in a fairly good yield.

It is assumed that the subsequent deacetylation which occurred in compound **5** is due to the aminolysis by the aniline present in the reaction medium.

Upon treatment with 10% NaOH, the oxazolinone **5** was hydrolyzed to the corresponding salicylanilide derivative **6** which showed a molecular formula compatible with $C_{23}H_{16}ClN_3O_7$ ($M^{+\cdot}$ m/z=481) in its mass spectrum.

In addition, hippuric acid and its furyl derivative **1a, b** condensed with 3,5-dichlorosalicylaldehyde, under similar reaction conditions used to prepare compounds **2** and **4**, affording **7a, b** in good yield.

Compounds **7a, b** were treated with hydrazine hydrate affording the corresponding pyrazoles **9a, b** together with a second product-obtained in both cases-identified as the azine **8** (Miller and Greenfield, 1974).

The structure assignment of the pyrazoles **9** was deduced from its analytical and spectral data. Thus, they gave positive $FeCl_3$ test in contrast to their parent compounds **7** and their NMR spectra showed no ylidene protons which were detected as singlets at δ 8.6-8.7 ppm in compounds **7.**

When treated with 10% NaOH, compounds **7a, b** were hydrolysed affording the acrylic acid derivatives **10a, b** in satisfactory yield.

On reacting the oxazolinones **7** with NH_2OH, new products were obtained showing NMR spectra similar to that of the starting compounds except the absence of the acetyl protons signals detected in the latter at δ 2.2 ppm; they also gave positive $FeCl_3$ test. Accordingly, the deacetylated structure **11** was given to these products.

In continuation, the 5-chloro and 5-nitroethenylsalicyloyl chlorides reacte with 2-chloro-4-nitroaniline, following literature procedure (Assad *et al.*, 1988; Latif *et al.*, 1985) to prepare the corresponding salicylanilides which when treated with formaldehyde and piperidine in a Mannich type reaction afforded the 3-(N-piperidino-methyl)salicylanilides **12a, b.** Their NMR spectra revealed the characteristic piperidine protons pattern (El-Kholy *et al.*, 1981) beside the N-benzyl protons as singlet at δ 3.4 ppm. The mass spectral data of **12a** added further proof to the suggested structure; it gave a molecular formula compatible with $C_{19}H_{19}Cl_2N_3O_4$ ($M^{+\cdot}$ m/z=424).

Table I. Molluscicidal activity[a] of the tested products[b]

Compound No.	Number of snails killed after an exposure period of 24 h a concentraiton of:			
	10 ppm	5 ppm	2 ppm	1 ppm
A	10	10	10	10
3a	4	1	0	0
3b	4	1	0	0
6	3	0	0	0
8	8	4	0	0
9a	6	3	0	0
9b	8	5	2	0
10b	3	0	0	0
11a	6	2	0	0
11b	10	6	2	0
12a	10	8	5	2
12b	10	8	5	1

[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 concentratikon. Ten snails were used in each experiment. 2,5'-Dichloro-4-nitrosalicylanilide (A) was used as a standard (Gonnert, 1961). Reference experiments: 10 ml of acetone/L water.

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

Molluscicidal Activity

The toxicity of the products to Biomphalaria alexandria snails, the intermediata host of schistosoma mansoni in Egypt was evaluated. The results shown in Table 1 indicates that the salicylanilides containing the N-piperidinomethyl moiety **12a, b** are the most effective compounds synthesized in the present work; although they proved to be toxic in concentration down to 1 ppm yet their activity is inferior to their parent salicylanilides (Latif *et al.*, 1985; Gonnert, 1961) and other derivatives of this family having electronegative substitutent (NO_2) at position **3** (Assad *et al.*, 1988).

In spite of its structural ressemblance with Bylocid (the known molluscicide) (Gonnert, 1961), compound **6** showed only marginal activity at 10 ppm meaning that the replacement of the electronegative chlorine atom in Bylocid with a less electronegative conjugated residue destroys the activity markedly.

Accordingly, it could be deduced that electronegative substituents at positions 3 or/and 5 in the salicylanilide moiety increases the activity and vice versa. This could be considered an additional parameter in our molluscicidal structure activity relationship study of salicylanilides and their related compounds (Nawwar, 1993; Nawwar *et al.*, 1993; Assad *et al.*, 1988; Nawwar *et al.*, 1991).

Regarding the oxazolinones, derivative **11b** was the most effective one. This result is in accordance with our previous report (Nawwar *et al.*, 1993) about the suggested active core illustrated in Fig. 1. Also, the activity of the azine **8** is in accordance with this view.

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