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Full Length Research Paper

Synthesis and molluscicidal activity of some new substituted-furan and furo[2,3-d]pyrimidine derivatives

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1-benzoyl-3-bromo-2-phenylpropenedinitrile derivative 1 reacted with potassium hydroxide to afford the furan derivatives 4 and 5. The furan derivative 5 reacted with formamide, phenyl isothiocyanate, malononitrile, and trichloroacetonitrile to afford the furo[2,3-d]pyrimidine derivatives 6, 8, 11 and 16 respectively. The reaction of 5 with ethyl cyanoacetate afforded however the furo[2,3-b]pyridine derivative 15. The molluscicidal activity of the synthesized compounds towards *Biomphalaria alexanrina* snails (the intermediate host of *Schistosoma mansoni*) was investigated and showed weak to moderate activity.

Key words: 1-benzoyl-3-bromo-2-phenylpropenedinitrile, furans, furo [2, 3-d] pyrimidines.

INTRODUCTION

In the last few years we have been involved in a program aiming at the synthesis of heterocyclic compounds of expected biological activity to be used as biodegradable agrochemicals from laboratory available starting material (Abdelrazek et al., 2004, 2006). *Schistosomiasis (bilharziasis)* still represents one of the major national health problems in Egypt as well as most of the third world countries; and great national and international efforts are made to combat this disease. Although praziquantel has been successfully used as chemical therapy in Egypt and other places, however the habits of the Egyptian farmers which necessitate their contineous and daily contact with canal-water during the irrigation process, specially in the Nile Delta, where nile water canals and streems are widespread, and even the habits of the school pupils who dive and swimm in these streems led to repeated infection. Therefore snail control through molluscicides, is considered not only complementary but essential in *Schistsomal* control. Copper sulfate and niclosamide were used tentatively in Egypt within a program developed by Bayer AG, however, due to their hazardous enviromental effects (Andrews et al., 1983; Dobrat and Martijin, 1995; WHO, 2002) it was stopped. Therefore the search for- and need to synthetic, or naturally occuring molluscicides is still ongoing.

In an earlier work it has been found that some furo[2,3-b]pyrimidine derivatives showed moderate molluscicidal activity against *Biomphalaria alexandrina* snails, the intermediate host of the infective phase of *Schistosoma mansonni* (Abdelrazek and Nawwar, 1991). In the context of this program, some novel furo [2, 3-d] pyrimidine derivatives were required for molluscicidal activity evaluation. Most recently we have reported the synthesis and some reactions of 1-benzoyl-3-bromo-2-phenylpropenedinitrile derivative 1 (Abdelrazek et al., 2007) (Scheme 1). In the present work we further explore the synthetic potential of 1 to prepare the required title compounds.

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 (if not mentioned otherwise) 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 by the Microanalytical Center at Cairo University. Molluscicidal activity tests were conducted in the Research Institute for Tropical Medicine, Cairo, Egypt.

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The reaction of 1 with potassium hydroxide: 1-Benzoyl-3-bromo-2-phenylpropenedinitrile 1 (10.5 g; 30 mmole) was dissolved in ethanol (~ 50 ml) and the mixture is heated gently till complete dissolution. This solution was filtered off to remove any insoluble material. To the clear filtrate was added drop wise at room temperature a concentrated water solution of potassium hydroxide (1.7 g; ~30 mmole in the minimum amount of distilled water). After complete addition (~5 minutes) the reaction mixture was left to stand overnight under stirring then poured on ice cold water and neutralized with acetic acid. The precipitated solid thus formed was collected by filtration, washed with water and left to dry. TLC analysis of the product revealed two components which were separated by column chromatography on silica gel with petroleum ether / ethyl acetate (5:1) as eluent. Compound 5 was collected first followed by 4. The overall yield of the reaction is 78% with a ratio of 1:1.

3,5-Diphenyl-furan-2,4-dicarbonitrile 4: Yellow crystalline solid 3.2 g (~39%), m.p. 207-208°C (EtOH/DMF). IR: ν_{max} (KBr) = 2220 and 2215 cm^{-1} (2 CN). ^1H NMR: 7.25-7.65 (m, arom-H); MS: *m/z* = $[M^+]$ (270). Analysis for $C_{18}H_{10}N_2O$: calcd. C 79.99, H 3.73, N 10.36; found: C 79.50, H 4.10, N 10.10.

5-Amino-4-benzoyl-3-phenyl-furan-2-carbonitrile 5: Yellow crystalline solid 3.4 g (~39%), m.p. 223-224°C (EtOH/DMF). IR: ν_{max} (KBr) = 3350-3280 (NH_2), 2217 (CN) and 1687 (CO) cm^{-1}. ^1H NMR: 5.7 (s, 2H, NH_2), 7.3-8.0 (m, 10H, arom-H); MS: *m/z* = $[M^+]$ (288). Analysis for $C_{18}H_{12}N_2O_2$: calcd. C 74.99, H 4.20, N 9.72; found: C 74.60, H 4.40, N 9.90.

4,5-Diphenyl-furo[2,3-d]pyrimidine-6-carbonitrile 6: A suspension of the furan derivative 5 (1.44 g; 5 mmole) in 15 ml of formamide was refluxed for 2 h whereby the color turns dark. After cooling to room temperature, the contents of the flask were poured on ice cold water and neutralized with acetic acid. The solid precipitate formed was filtered off and recrystallized to afford greenish yellow crystalline solid (yield 1 g; 65%), m.p. 237-238 °C (EtOH/DMF). IR: ν_{max} (KBr) = 2217 cm^{-1} (CN).^1H NMR: 7.2-7.55 (m, 10H, arom-H), 9.15 (s, 1H, pyrimidine H); MS: *m/z* = $[M^+]$ (297). Analysis for $C_{19}H_{11}N_3O$: calcd. C 76.76, H 3.73, N 14.13; found: C 76.50, H 3.60, N 14.30.

3,4,5-Triphenyl-2-thioxo-2,3-dihydro-furo[2,3-d]pyrimidine-6-carbonitrile 8: To a solution of 5 (1.44 g, 5 mmole) in dry acetone (15 ml) was added phenyl isothiocyanate (0.67 g; 5 mole) and a catalytic amount of piperidine. The reaction mixture was refluxed for 2 h then left to cool to room temperature. The precipitated solid that appeared was filtered off and recrystallized to afford brownish yellow crystalline solid (yield 1.37 g; 68%), m.p. 210-211°C (EtOH/DMF). IR: ν_{max} (KBr) = 2212 cm^{-1} (CN). ^1H NMR: 6.75-7.52 (m, arom-H); MS: *m/z* = $[M^+]$ (405). Analysis for $C_{25}H_{15}N_3OS$: calcd. C 74.05, H 3.73, N 10.36, S 7.91; found: C 74.30, H 3.60, N 10.70, S 8.1.

2-Cyanomethyl-4,5-diphenyl-furo[2,3-d]pyrimidine-6-carbonitrile 11: A mixture of 5 (1.44 g, 5 mmole) and malononitrile (0.33 g, 5 mmole) was fused on an oil bath at ~ 160°C. To the fused mixture was added few drops of triethylamine and heating was continued for 2 h. After cooling to room temperature, the obtained mass was triturated with ethanol, filtered off and then recrystallized to afford 11 as brown crystalline solid (yield 1.2 g; 72%), m.p.268-270°C (EtOH/Dioxan 1:1). IR: ν_{max} (KBr) = 2215 and 2220 (2 CN). ^1H NMR (DMSO-d_6): δ = 3.80 (s, 2H, CH_2) and 7.4-8.65 ppm (m, 10H, arom-H); MS: *m/z* = $[M^+]$ (336). Analysis for $C_{21}H_{12}N_4O$: calcd. C 74.99, H 3.60, N 16.66; found: C 74.60, H 3.70, N 16.50.

6-Oxo-3,4-diphenyl-6,7-dihydro-furo[2,3-b]pyridine-2,5-dicarbonitrile 15: To a mixture of 5 (1.44 g, 5 mmole) and ethyl cyanoacetate (0.56 g; 5 mmole) in 20 ml of absolute ethanol was added 3 drops of triethylamine. The reaction mixture was refluxed for 2 h and then evaporated under vacuum to about third its original volume and left to cool overnight. To the clear solution thus obtained was added few drops of acetic acid whereby a dark yellow solid precipitated, filtered off and washed thoroughly with cold water. The obtained product was then recrystallized from ethanol/dioxan mixture (1:1) to afford 15 as dark yellow fine crystals (yield 1.25 g, 75%), m.p. 255-256 °C. IR: ν_{max} (KBr) 3440 & 3270 (NH), 2212 & 2219 (2 CN) and 1665 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ = 7.3 - 7.6 ppm (m, 10H, arom-H) and 8.65 (s, 1H, NH); MS: *m/z* = $[M^+]$ (337). Analysis for $C_{21}H_{11}N_3O_2$: calcd. C 74.77, H 3.29, N 12.46; found: C 74.50, H 3.50, N 12.60.

4,5-Diphenyl-2-trichloromethyl-furo[2,3-d]pyrimidine-6-carbonitrile 16: To a solution of 5 (1.44 g, 5 mmole) in 20 ml of dry benzene was added 1 ml (10 mmole) of trichloroacetonitrile followed by few drops of piperidine catalyst. The reaction mixture was refluxed for 2 h, and then left to cool overnight. The precipitated solid was filtered off and recrystallized to afford 16 as yellowish brown crystalline solid (2.3 g; 75%), m.p. 179-181°C (Benzene). ^1H NMR: 7.25-7.75 (m, arom-H); MS: *m/z* = $[M^+]$ (413 and 415). Analysis for $C_{20}H_{10}Cl_3N_3O$: calcd. C 57.93, H 2.43, Cl 25.65, N 10.13; found: C 58.10, H 2.60, Cl 26.00, N 10.20.

Preparation of compounds 17a-c: Compound 16 (2 g; 5mmole) was refluxed in 20 ml of water, methanol or ethanol for 30 min., then left to cool to room temperature. The solid precipitates were collected by filtration and recrystallized from the proper solvent to give respectively:

2-Hydroxy-4,5-diphenylfuro[2,3-d]pyrimidine-6-carbonitrile 17a: Dark yellow crystalline solid (yield 1.1 g; 70%), m.p. 115-116°C (dioxane). IR: ν_{max} (KBr) = 3650 and 3340 (br. OH), 2218 (CN) cm^{-1}. ^1H NMR: 6.25 (s, 1H, OH), 7.25-7.75 (m, 10H, arom-H); MS: *m/z* = $[M^+]$ (313). Analysis for $C_{19}H_{11}N_3O_2$: calcd. C 72.84, H 3.54, N 13.41; found: C 73.10, H 3.60, N 13.30.

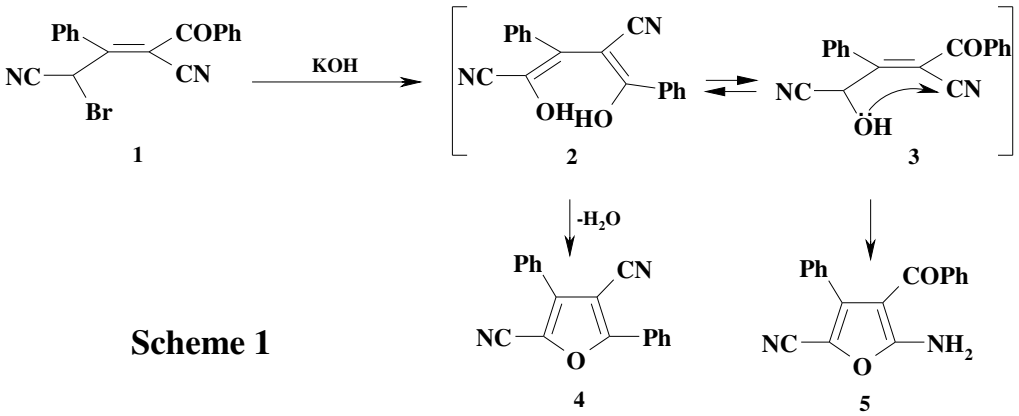
2-Methoxy-4,5-diphenylfuro[2,3-d]pyrimidine-6-carbonitrile 17b: Brownish crystalline solid (yield 1.1 g; 68%), m.p. 168-170°C (MeOH). IR: ν_{max} (KBr) = 2225, 2217 cm^{-1} (CN). ^1H NMR: 3.7 (s, 3H, CH_3), 7.25-7.60 (m, 10H, arom-H); MS: *m/z* = $[M^+]$ (327). Analysis for $C_{20}H_{13}N_3O_2$: calcd. C 73.38, H 4.00, N 12.84, found: C 73.50, H 3.90, N 13.10.

2-Ethoxy-4,5-diphenylfuro[2,3-d]pyrimidine-6-carbonitrile 17c: Light brown solid (yield 1.2 g; 71%), m.p. 133-134°C (EtOH). IR: ν_{max} (KBr) = 2207 cm^{-1} (CN). ^1H NMR: 1.3 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 7.25-7.65 (m, 10H, arom-H); MS: *m/z* = $[M^+]$ (341). Analysis for $C_{21}H_{15}N_3O_2$: calcd. C 73.89, H 4.43, N 12.31; found: C 73.70, H 4.50, N 12.20.

Preparation of compounds 18a,b: To a solution of compound 16 (2 g; 5mmole) in 25 ml of dioxane was added the molar equivalent of either hydrazine hydrate or phenyl hydrazine and the mixture was refluxed for 30 min., then left to cool to room temperature. The solid precipitates were collected by filtration and recrystallized from the proper solvent to give respectively:

2-Hydrazino-4,5-diphenylfuro[2,3-d]pyrimidine-6-carbonitrile 18a: Light brown crystalline solid (yield 1.2 g; 73%), m.p. 238-239°C (dioxane). IR: ν_{max} (KBr) = 3356 - 3148 (NH and NH_2), 2215 cm^{-1} (CN). ^1H NMR: 6.23 (s, 2H, NH_2), 7.23-7.78 (m, 10H, arom-H), 10.15 (s, 1H, NH); MS: *m/z* = $[M^+]$ (327). Analysis for $C_{19}H_{13}N_5O$: calcd. C 69.71, H 4.00, N 21.39; found: C 69.70, H 4.20, N 21.70.

4,5-Diphenyl-2-(N`-phenylhydrazino)furo[2,3-d]pyrimidine-6-carbonitrile 18b: Canary yellow solid (yield 1.5 g; 75%), m.p. 228-230°C (dioxane). IR: ν_{max} (KBr) = 3450 & 3345 (NH), 2216 cm^{-1}(CN). ^1H NMR: 7.25-7.75 (m, 15H, arom-H), 8.5 (s, 1H, NH), 10.05



Scheme 1

(s, 1H, NH); MS: *m/z* = [M$^+$] (403). Analysis for $C_{25}H_{17}N_5O$: calcd. C 74.43, H 4.25, N 17.36; found: C 74.50, H 4.40, N 17.00.

Molluscicidal activity tests

The molluscicidal activity tests were carried out by determination of the half and full-lethal doses LC_{50} , and LC_{100} for each compound under investigation. *B. alexandrina* snails (ca. 7 mm shell diameter) were collected from the field (water canals) and maintained under laboratory conditions for a period of 10 days before the test and fed daily by lettuce leaves. Six concentrations of each compound under investigation were prepared ranging from 1 to 15 ppm. The required amount of the compound under investigation was mixed thoroughly with few drops of Tween 20 and 2 mL of DMSO to render the compounds completely soluble, followed by addition of the appropriate volume of untreated raw water (taken directly from the Nile River or its subsidiary branches/canals) to get a homogeneous suspension with the requisite concentration and placed in glass jar vessels 15 × 25 × 20 cm dimensions fitted with air bubblers. Ten snails were used in each experiment and maintained in the test solution under laboratory conditions at 25^{o}C for 24 h. Each experiment was repeated three times, and the mean number of killed snails was taken for each concentration (as shown in Table 1). A control group was taken by placing 10 snails in water containing 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 W.H.O guidelines (WHO Technical Report 1993) slightly modified by using two mixed solvents to dissolve the compounds

RESULTS AND DISCUSSION

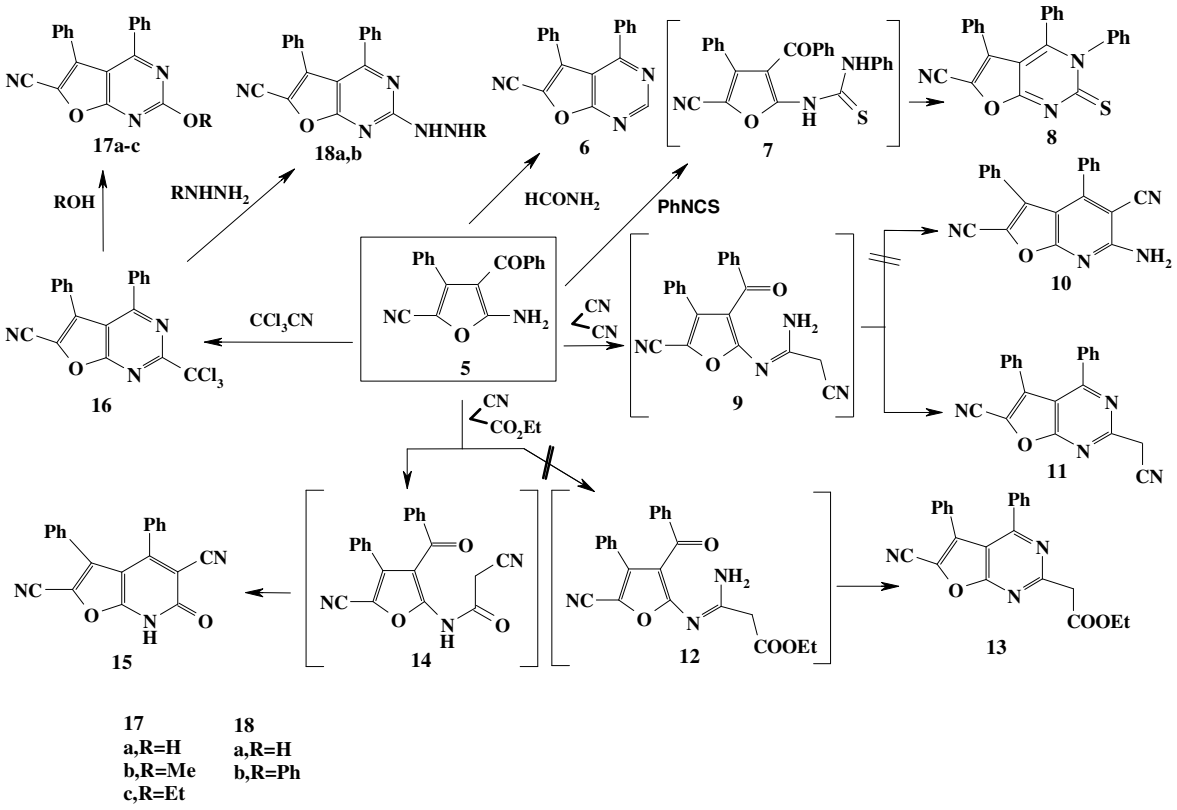
Compound 1 reacted with potassium hydroxide to afford a solid product. TLC analysis showed two compounds which could be separated by fractional crystallization, one of them has a melting point 207^{o}C and the other has 223^{o}C. The lower melting point product showed only one absorption band in the functional group region at *v* 2220 and 2215 cm^{-1} corresponding to two CN groups. The ^{1}H NMR spectrum of this product revealed only an aromatic multiplet at δ 7.25-7.65 ppm. Based on the spectral as well as analytical data (see experimental) the furan structure 4 was assigned to this product (Scheme 1). The IR spectrum of the higher melting product showed absorption bands at *v* 3350-3280, 2217 and 1687 cm^{-1} corresponding to NH_2, CN and C=O groups respectively. The ^{1}H-NMR spectra of this compounds revealed a broad singlet at δ 5.7 (2H) and a multiplet (10H) at δ 7.3-8.0 ppm assignable to NH_2 and the aromatic protons. On the basis of these data as well as elemental analyses structure 5 was assigned to this product. It is assumed that the bromine atom in compound 1 is hydrolyzed under the effect of KOH to afford the acyclic hydroxy tautomeric intermediates 2 and 3 (Scheme 1). Elimination of water from 2 leads to the furan derivative 4, while cyclization of 3 via nucleophilic addition of the OH to the CN affords the furan derivative 5. A similar behavior has been earlier reported (Abdelrazek et al., 1995).

Enaminones and *o*-aminoketones are known to be useful precursors for the synthesis of fused heterocyclic systems. The enaminone moiety in compound 5 could be explored to fulfill our objective. Thus when compound 5 was refluxed in formamide a yellow product was obtained for which structure 6 was assigned. The reaction of 5 with phenyl isothiocyanate afforded the furo[2,3-d]pyrimidine-2-thione 8 presumably via the thiourea intermediate 7 (Scheme 2).

Compound 5 reacted with malononitrile to afford the cyanomethyl furo[2,3-d]pyrimidine derivative 11 presumably via the acyclic intermediate 9 which seemingly undergoes cyclization with the NH_2 group rather than the CH_2 which would have given the furo[2,3-b]pyridine 10.

Contrary to this behavior 5 reacted with ethyl cyanoacetate to afford the furo[2,3-b]pyridine derivative 15 instead of the expected furo[2,3-d]pyrimidine 13 (Scheme 2). It seems that the elimination of ethanol to afford the intermediate 14 is faster and easier than the addition of NH_2 to the CN to afford the intermediate 12 which would have given 13. In case of malononitrile both groups are CN and there is no choice.

Compound 5 reacted with trichloroacetonitrile in refluxing benzene to afford the 2-trichloromethyl furo[2,3-d]pyrimidine derivative 16. Being a good leaving group the trichloromethyl moiety in compound 16 could be easily substituted by OH, OMe, OEt, $NHNH_2$, or NHNHPh



Scheme 2

Table 1. The mean number of snails killed after an exposure time of 24 h at the given concentration.

Compd No	1	3	5	7	11	15 ppm
Bayluscide	10	10	10	10	10	10
4	0	1	3	5	8	10
5	0	1	3	5	6	7
6	0	0	0	0	3	4
8	0	0	0	1	3	4
11	0	1	2	2	4	5
15	0	0	1	3	5	8
16	0	1	3	5	8	10
17a	0	0	0	1	3	7
17b	0	0	1	1	2	5
17c	0	0	1	1	4	6
18a	0	2	5	7	10	10
18b	0	0	1	1	4	6

upon refluxing 16 in water, methanol, ethanol to afford compounds 17a-c, or in dioxane in presence of hydrazine hydrate or phenyl hydrazine to afford compounds 18a,b respectively. Ready substitution of the trichloromethyl moiety by nucleophiles is well established (Abdelrazek et. al., 1984; Gewald et al., 1985). All structures were assigned on the basis of the spectral and analytical data (*cf.* experimental).

Molluscicidal activity

The toxicity of compounds 4, 5, 6, 8, 11, 15, 16, 17a-c, 18a,b toward *B. alexandrina* snails was evaluated. An insight inspection of the results listed in Table 1 shows that all compounds have moderate to low effects on the snails, and they all showed very weak activity below 5 ppm. The half- and full-lethal doses (LC_{50} and LC_{100} in

Table 2. Molluscicidal activity of compounds 4, 5, 6, 8, 11, 15, 16, 17a-c, 18a,b expressed as LC_{50} and LC_{100} in ppm.

Compd No	LC_{50}	LC_{100}
Bayluscide	<1	1
4	7	15
5	7	>15
6	>15	>15
8	>15	>15
11	15	>15
15	11	>15
16	7	15
17a	13	>15
17b	15	>15
17c	13	>15
18a	5	11
18b	13	>15

ppm) for each compound was determined and is shown in Table 2.

The most effective of them are 18a, 4 and 16 (LC_{50} = 5, 7, and 7 ppm, respectively). The activity of 4 may be attributed mainly to the presence of two cyano groups. Compound 16 displays activity similar to 4 at the same concentration; although one cyano group is present however the trichloromethyl moiety seems to have influence. Compound 18a with the hydra-zide side chain showed the highest activity (LC_{50}= 5 and LC_{100}= 11 ppm) within the furo[2,3-d]pyrimidine series. The phenyl analog 18b is far less active (LC_{50} = 13 ppm). 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) (Andrews et al., 1983; WHO, 2002); showed that our compounds are still far inferior as molluscicidal agents. However, compound 18a looks promising after further structural modification which will be considered in a future study.

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