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NOVEL SYNTHESIS OF HYDRAZIDE-HYDRAZONE AND THEIR USES FOR THE SYNTHESIS 1,3,4-OXADIAZINE, 1,2,4-TRIAZINE, PYRAZOLE AND PYRIDAZINE DERIVATIVES WITH ANTIMICROBIAL AND ANTIFUNGAL ACTIVITIES

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ABSTRACT: The reaction of the cyanoacetylhydrazine (**1**) with α-bromoketones (**2a-c**) gave the hydrazide-hydrazone derivatives **3a-c**. The latter compounds underwent ready cyclization when heated in sodium ethoxide to form the 1,3,4-oxadiazine derivatives **4a-c**. The reaction of 3a with hydrazines gave the 1,3,4-triazine derivatives **7a,b**. Compounds **3a-c** and **7a,b** underwent some heterocyclizations when treated with some reagents to afford coumarin, 1,2,4-triazine, pyridazine and pyrazole derivatives. The antimicrobial and antifungal activities of the newly synthesized products were measured which showed that most of have high activities.

INTRODUCTION

Tuberculosis is presently regarded as the most dangerous infective disease world-wide and one of the major AIDS-associated infections. The simultaneous presence of HIV infection, the spread of drug resistant strains of *Mycobacterium tuberculosis*, and the scarce compliance with the lengthy complex therapies often complicate the treatment of tuberculosis [1]. Therefore, the search for new antituberculosis agents is required. This requirement had an impact on our further work on the synthesis and search for some new hydrazide–hydrazones with the antituberculosis activity.

It is well known that the hydrazone group plays an important role for the antimicrobial activity. Furthermore, a number of hydrazide–hydrazone claimed to possess interesting antibacterial-antifungal [2-4], anticonvulsant [5,7], anti-inflammatory [8,9], antimalarial [10] and antituberculosis activities [11-17]. With the aim of obtaining new hydrazide-hydrazones with such wide spectrum of pharamaceutical applications, we report here the synthesis of a series of hydrazide-hydrzones via the reaction of cyanoacetylhydrazine (**1**) with α-bromoketones (**2a-c**).

RESULTS AND DISCUSSION

The reaction of cyanoacetylhydrazine (**1**) with the α-haloketones **2a-c** in 1,4-dioxan at room temperature gave the α -bromohydrazone derivatives **3a-c**. The structures of the latter products were based on analytical and spectral data.

Thus, the ^{1}H NMR spectrum of **3a** showed the presence of two singlets at δ 4.80, 5.38 corresponding to two CH_2 groups, a multiplet at δ 7.28-7.38 corresponding to phenyl protons and a singlet at δ 8.80 (D_2O exchangeable) for an NH group. Compounds **3a-c** underwent ready cyclization when heated in sodium ethoxide solution in a boiling water bath to form the 1,3,4-oxadiazine derivatives **4a-c**. The analytical and spectral data obtained are in analogy with the proposed structures (see experimental section).

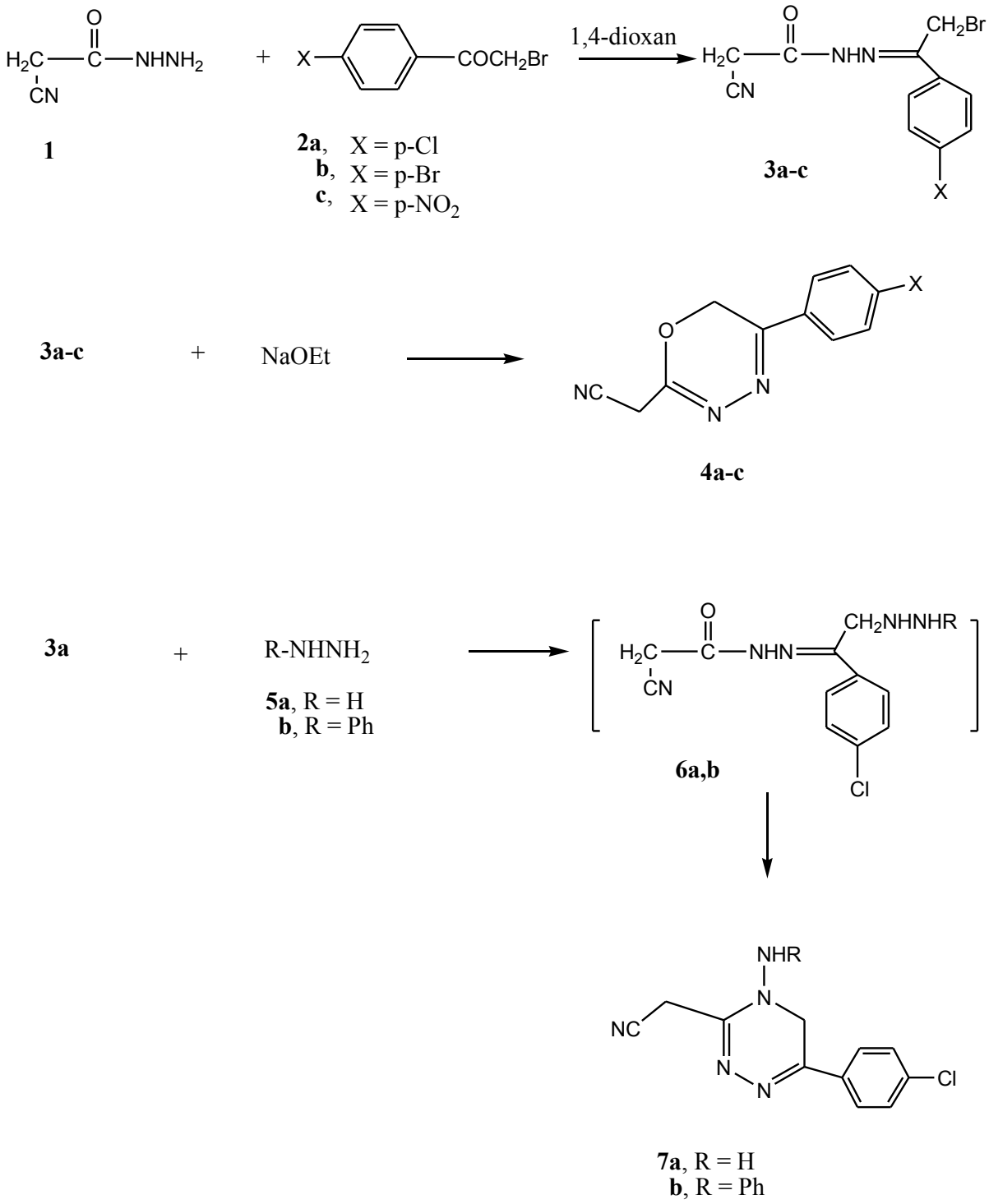
The reaction of **3a** with either hydrazine hydrate (**5a**) or phenylhydrazine (**5b**) gave the 1,2,4-triazine derivatives **7a** and **7b**, respectively. Formation of the latter products is explained interms of the intermediate formation of **6a,b** followed by dehydration. The elemental analysis and ^{1}H NMR spectra were the basis of structure elucidation. The 1,2,4-triazine derivatives **7a,b** bearing the acetonitrilo group showed a high reactivity towards aromatic aldehydes. Thus, the reaction of compounds **7a,b** with benzaldehyde (**8**) gave the benzal derivatives **9a** and **9b**, respectively. On the other hand, their reaction with salicylaldehyde gave the coumarin derivatives **11a,b**.

The reaction of compounds **3a-c** with benzaldehyde gave the 2-benzalacetonitrilo-1,3,4-oxadiazine derivatives **13a-c**. The structure of the latter products were based on the analytical and spectral data and on their synthesis using another reaction rout. Thus, the reaction of **4a-c** with benzaldehyde gave the same products **13a-c** (m.p. and mixed m.p.).

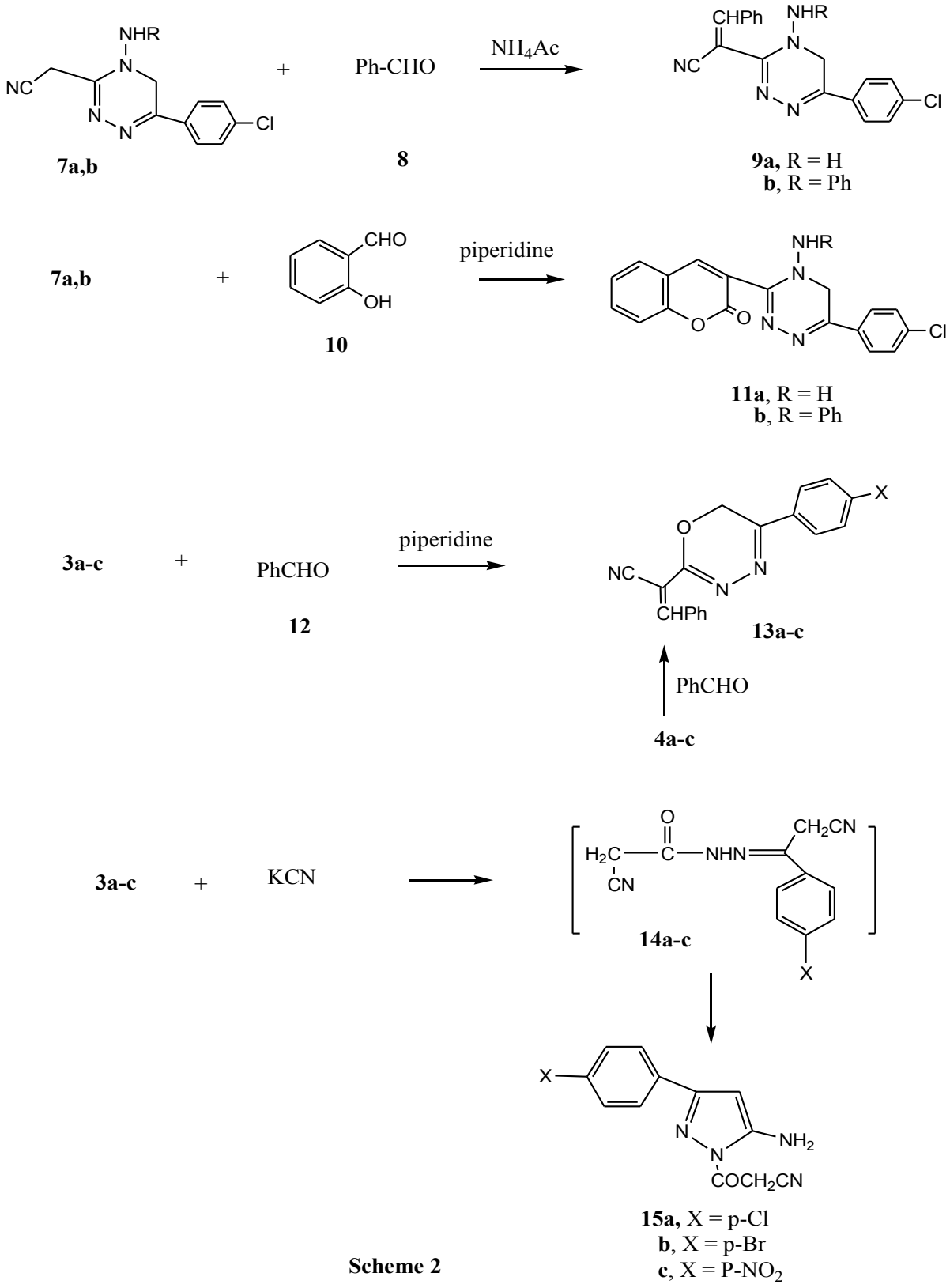
Compounds **3a-c** bearing the δ -bromomethyl group seemed to be reactive towards nucleophilic reagents. Thus, with potassium cyanide compounds **3a-c** gave the pyrazole derivatives **15a-c**. Formation of the latter products was based on the intermediate formation of **14a-c** followed by cyclization. Our trials to isolate the acyclic intermediates were failed (Scheme 2). The analytical and spectral data of **15a-c** are in agree with the proposed structures. On the other hand, the reaction of **3a-c** with either malononitrile (**16a**) or ethyl cyanoacetate (**16b**) gave the alkylated products **17a-f**. The structures of the latter products were based on analytical and spectral data. Thus, the ^{1}H NMR spectrum of **17a** showed a doublet at δ 3.78 for CH_2 group, a triplet at δ 4.21 for CH group, a singlet at δ 4.53 corresponding to CH_2 group, a multiplet at δ 7.31-7.38 corresponding to phenyl proons and a singlet (D_2O exchangeable) at δ 8.30 for NH group. Compounds **17a-f** underwent ready cyclization when heated in sodium ethoxide solution in a boiling water bath to give the 4-[H]-pyridazine derivatives **18a-f**. The analytical and spectral data of the isolated products are consistent with the proposed structures.

IN VITRO ANTIMICTOBIAL AND ANTIFUNGAL ACTIVITIES EVALUATION

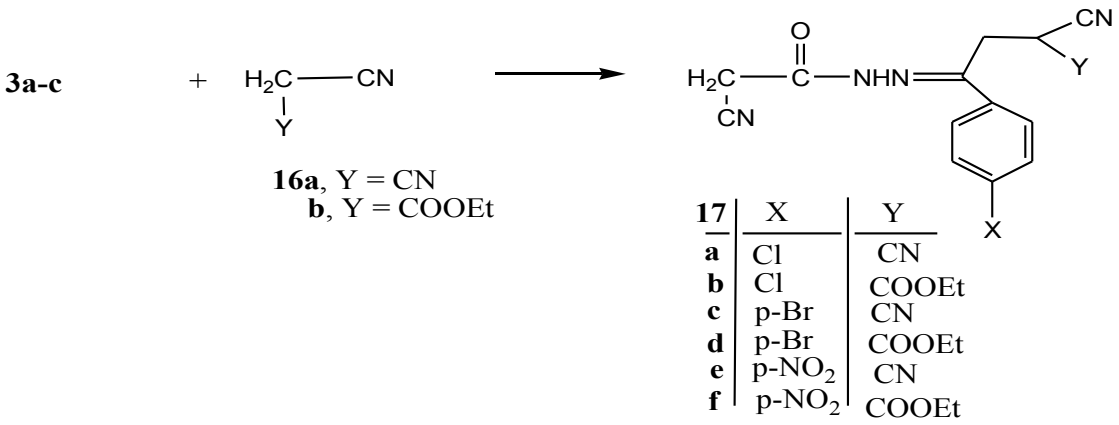
An evaluation of the antibacterial activity using two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram-positive bacteria (*Bacillus subtilis* and *Bacillus cereus*) and the antifungal activity using *Candida albicans* as a representative species of fungi was assessed for compounds. The minimal inhibitory concentration (MIC in g/mL) was determined using an adaptation of agar streak dilution method based on radial diffusion.[18,19] In the same conditions different concentrated solutions of ampicillin (antibacterial) and cycloheximide (antifungal) were used as standards. The MIC was considered to be the lowest concentration of the tested compound which inhibits growth of bacteria or fungi on the plate. The diameters of the inhibition zones corresponding to the MICs are presented in Table 1. The compounds tested are not active against *Pseudomonas aeruginosa* starting from DMSO solutions of 1000 µg/mL of each compound.


1,4-dioxan
1
2a, X = p-Cl
b, X = p-Br
c, X = p-NO2
3a-c
3a-c + NaOEt
4a-c
3a + R-NHNH2
5a, R = H
b, R = Ph
6a,b
7a, R = H
b, R = Ph

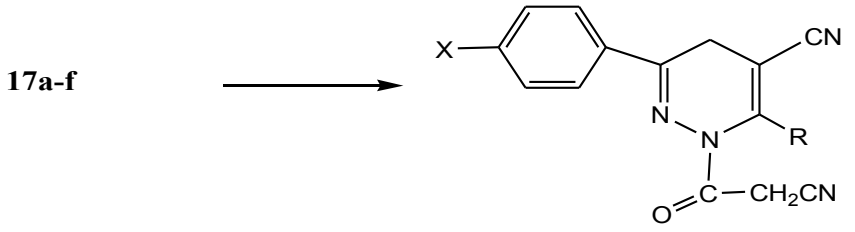
Scheme 1


NHR
NC
N
N
N
Cl
7a,b
+
Ph-CHO
8
NH4Ac
CHPh
NHR
NC
N
N
N
Cl
9a, R = H
b, R = Ph
7a,b
+
CHO
OH
10
piperidine
NHR
N
O
O
N
N
Cl
11a, R = H
b, R = Ph
3a-c
+
PhCHO
12
piperidine
O
X
NC
N
N
CHPh
13a-c
PhCHO
4a-c
3a-c
+
KCN
O
H2C
C
NHN
CH2CN
CN
14a-c
X
X
N
N
NH2
COCH2CN
15a, X = p-Cl
b, X = p-Br
c, X = P-NO2

Scheme 2



17	X	Y
a	Cl	CN
b	Cl	COOEt
c	p-Br	CN
d	p-Br	COOEt
e	p-NO_2	CN
f	p-NO_2	COOEt



18	X	R
a	p-Cl	NH_2
b	p-Cl	OH
c	p-Br	NH_2
d	p-Br	OH
e	p-NO_2	NH_2
f	p-NO_2	OH

Scheme 3

From the analysis of Table 1 it is possible to establishsome SARs. The only active compounds against *E. coli* in the concentrations tested are **3a**, **3b**, **3c**, **7a**, **7b**, **11b**, **17a**, **17b**, and **17d** (MIC 6.25 µg/mL), the substituted pyrazole moiety being responsible for the activity. However, the hydrazide-hydrazone derivative **3a** showed the lowest activity and **17d** showed the highest activity. Comparing **3a-c** with **17a-f** (Both are hydrazide-hydrazone), compounds **17a-c** appear to be more active against *B. Cereus* (MIC 3.13 µg/mL) and *B. subtilis*. Compounds **17f** and **17c** (pyridazine derivative) showed the highest activity against *B. Subtilis*. Compound **17a** showed the highest activity against *B. Cereus*.

Table 1: The antitmicrobial and antifungal activities of compounds **3a-18f**

Compound	MIC in µg/mL (zone of inhibition in mm)			
	E. coli ECT 101	*B. Cereus* CECT 148	*B. subtilis* CECT 498	*C. albicans* CECT 1394
3a	16.64	6.06 (2)	6.33 (5)	8.65 (4)
3b	14.8	8.05 (9)	3.13 (10)	0.61 (6)
3c	16.50 (6)	20 (8)	6.25 (4)	50 (11)
4a	Not active	4.25 (15)	18 (8)	30 (6)
4b	Not active	12.34 (7)	6.13 (4)	0.40 (5)
4c	Not active	18.32 (5)	6.22 (2)	0.40 (10)
7a	16.2	20.15 (4)	23.16 (9)	100 (5)
7b	14.8	12.32 (3)	16.32 (8)	14.40 (4)
9a	Not active	6.05 (6)	12.42 (2)	4.55 (10)
9b	Not active	12.30 (4)	4.22 (6)	12.55 (12)
11a	Not active	25 (8)	23 (6)	26 (3)
11b	10.46 (4)	8.66 (6)	25.33 (5)	12.22 (8)
13a	Not active	4.25 (3)	6.23 (8)	6.44 (6)
13b	Not active	0.08 (2)	2.22 (5)	6.44 (8)
13c	Not active	7.03 (8)	0.68 (2)	20.50 (5)
15a	Not active	0.08 (2)	2.22 (5)	6.44 (8)
15b	Not active	7.39 (4)	4.33 (5)	12.77 (5)
15c	Not active	6.22 (5)	12.89 (4)	18.42 (9)
17a	10.3	0.01 (3)	0.48	25.60 (6)
17b	8.8	1.03 (8)	0.68 (2)	20.50 (5)
17c	Not active	0.55 (3)	0.48	25.60 (6)
17d	6.6	4.06 (4)	4.33 (5)	12.77 (5)
17e	Not active	10.23 (6)	2.56 (4)	28.60 (8)
17f	Not active	0.61 (3)	0.48	25.60 (6)
18a	Not active	6.22 (5)	12.89 (4)	18.42 (9)
18b	Not active	7.03 (8)	0.68 (2)	20.50 (5)
18c	Not active	7.39 (4)	12.89 (4)	18.42 (9)
18d	Not active	6.22 (5)	4.33 (5)	12.77 (5)
18e	Not active	0.08 (2)	6.44 (8)	2.22 (5)
18f	Not active	22.01 (3)	25.60 (6)	4.16(5)
Ampicillin	6.25	3.13	12.50 (10)	-
Cycloheximide	-	-	-	12.50

For the in vitro antimicrobial activity, suspensions of the microorganism were prepared to contain approximately 108 cfu/mL and the plates were inoculated. A stock solution of the synthesized compound (1000 µg/mL) in DMSO was prepared and graded dilutions of the tested compounds were incorporated in a cavity (depth 3 mm, diameter 4 mm) made in the center of the petridish (nutrient agar for antibacterial activity and Sabouraud vs dextrose agar medium for antifungal activity). The plates were incubated at 37ºC (for bacteria) and at 30ºC (for fungi) for 24 h in duplicate. Positive control using only inoculation and negative control using only DMSO in the cavity were carried out.

EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected . IR spectra were measured using KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}HNMR spectra ware measured on a varian EM390-200 MHz instrument in CD_3SOCD_3 as solvent using TMS as internal standard, and chemical shifts are expressed as δ ppm.

α-Bromo(p-chloroacetophenone)-α-cyanoacetylhydrazone (3a), α-bromo(p-bromoacetophenone)-α-cyanoacetylhydrazone (3b) and α-bromo(p-nitroacetophenone)-α-cyanoacetylhydrazone (3a),

A solution of cyanoacetylhydrazine (**1**) (0.99 g, 0.01 mol), in 1,4-dioxan (40 mL) either of p-chlorophenacylbromide (**2a**) (2.35 g, 0.01 mol), p-bromophenaclbromide (**2b**) (2.80 g, 0.01 mol) or p-nitrophenacylbromide (2.46 g, 0.0.1 mol) was added. The reaction mixture was kept at room temperature with stirring for 2h and the formed solid product was filtrated off.

Compound **3a**: Pale yellow crystals were recovered from ethanol in a yield 80 % (2.49 g) and with a mp 165-7°C; *Calculated for* $C_{11}H_9BrClN_3O$ (312.96): C, 42.00; H, 2.88; N, 13.36. Found: C, 42.31; H, 3.09; N, 13.39. IR (δcm^{-1}) = 3477-3334 (NH), 3054 (CH aromatic), 2883 (CH_2), 2263 (CN), 1684 (C=O), 1662 (C=N), 1639 (C=C). ^{1}H NMR δ = 4.80, 5.38 (2s, 4H, 2 CH_2), 7.28-7.38 (m, 4H, C_6H_4), 8.80 (s, 1H, NH).

Compound **3b**: Pale yellow crystals were recovered from ethanol in a yield 72 % (2.59 g) and with a mp 175-8°C; *Calculated for* $C_{11}H_9Br_2N_3O$ (359.02): C, 36.80; H, 2.53; N, 11.70. Found: C, 36.52; H, 2.85; N, 11.55. IR (υ/cm^{-1}) = 3466-3339 (NH), 3050 (CH aromatic), 2887 (CH_2), 2260 (CN), 1689 (C=O), 1664 (C=N), 1634 (C=C). ^{1}H NMR δ = 4.74, 5.40 (2s, 4H, 2 CH_2), 7.26-7.35 (m, 4H, C_6H_4), 8.83 (s, 1H, NH).

Compound **3c**: Orange crystals were recovered from ethanol in a yield 88 % (2.84 g) and with a mp 227-30°C; *Calculated for* $C_{11}H_9BrN_4O_3$ (323.99): C, 40.64; H, 2.79; N, 17.23. Found: C, 40.38; H, 3.17; N, 17.09. IR (υ/cm^{-1}) = 3465-3326 (NH), 3056 (CH aromatic), 2888 (CH_2), 2263 (CN), 1685 (C=O), 1661 (C=N), 1634 (C=C). ^{1}H NMR δ = 4.79, 5.44 (2s, 4H, 2 CH_2), 7.31-7.39 (m, 4H, C_6H_4), 8.80 (s, 1H, NH).

5-(p-Cloropheny)l-2-acetonitrilo-1,3,4-oxadiazine (4a), 5-(p-bromo-phenyl)-2-acetonitrilo-1,3,4-oxadiazine (4b), 5-(p-nitrophenyl)-2-acetonitrilo-1,3,4-oxadiazine (4c).

A suspension of either **3a** (3.12 g, 0.01 mol), **3b** (3.65 g, 0.01 mol) or **3c** (3.24 g, 0.01 mol) in sodium ethoxide [prepared by dissolving sodium metal (0.46 g, 0.02 mol) in absolute ethanol (25 mL)] was heated in a boiling water bath for 4h then left to cool. The solid product formed upon pouring into ice/water containing hydrochloric acid (till pH_7) was collected by filtration.

Compound **4a**: Pale yellow crystals were recovered from 1,4-dioxan in a yield 70 % (1.63 g) and with a mp 255-8 °C; *Calculated for* $C_{11}H_8ClN_3O$ (233.04): C, 56.54; H, 3.45; N, 17.98. Found: C, 56.78; H, 3.27; N, 18.31. IR(υ/cm^{-1}): 3060 (CH aromatic), 2870 (CH_2), 2245 (CN), 1660 (C=N), 1638 (C=C); ^{1}HNMR (δ ppm): 4.82 (s, 2H, CH_2), 5.70 (s, 2H, ring CH_2), 7.33-7.41 (m, 4H, C_6H_4).

Compound **4b**: Pale orange crystals were recovered from 1,4-dioxan in a yield 78 % (2.17 g) and with a mp 280-5 °C; *Calculated for* $C_{11}H_8BrN_3O$ (278.12): C, 47.51; H, 2.90; N, 15.11. Found: C, 47.58; H, 3.33; N, 14.79. IR(υ/cm^{-1}): 3066 (CH aromatic), 2877 (CH_2), 2249 (CN), 1663 (C=N), 1635 (C=C); ^{1}HNMR (δ ppm): 4.77 (s, 2H, CH_2), 5.73 (s, 2H, ring CH_2), 7.31-7.40 (m, 4H, C_6H_4).

Compound **4c**: Pale orange crystals were recovered from 1,4-dioxan in a yield 63 % (g) and with a mp 220-4 °C; *Calculated for* $C_{11}H_8N_4O_3$ (244.06): C, 54.10; H, 3.30; N, 22.94. Found: C, 53.89; H, 3.36; N, 23.42. IR(υ/cm^{-1}): 3068 (CH aromatic), 2869 (CH_2), 2253 (CN), 1660 (C=N), 1641 (C=C); ^{1}HNMR (δ ppm): 4.79 (s, 2H, CH_2), 5.79 (s, 2H, ring CH_2), 7.34-7.46 (m, 4H, C_6H_4).

3-Acetonitrilo-4-amino-6-phenyl-1,2,4-triazine (7a) and 3-acetonitrilo-4-phenylamino-6-phenyl-1,2,4-triazine (7b)

General procedure: To a solution of **3a** (3.12 g, 0.01 mol) in 1,4-dioxan (40 mL) either hydrazine hydrate (0.50 g, 0.01 mol) or phenylhydrazine (1.08 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 hr then left to cool. The solid product formed upon pouring onto ice/water containing few drops of hydrochloric acid was collected by filtration.

Compound **7a**: Yellow crystals were recovered from 1,4-dioxan in a yield 60 % (1.48 g) and with a mp 164-6 °C; *Calculated for* $C_{11}H_{10}ClN_5$ (247.06): C, 53.34; H, 4.07; N, 28.28. Found: C, 53.79; H, 4.09; N, 28.39. IR (υ /cm^{-1}) = 3059 (CH aromatic), 2890 (CH_2), 2225 (CN), 1660 (C=N), 1635 (C=C). ^{1}H NMR υ = 4.45 (s, 2H, CH_2), 4.95 (s, 2H, NH_2), 5.68 (s, 2H, triazine CH_2), 7.31-7.36 (m, 4H, C_6H_4).

Compound **7b**: Yellow crystals were recovered from 1,4-dioxan in a yield 68 % (2.19 g) and with a mp 198 °C; *Calculated for* $C_{17}H_{14}ClN_5$ (323.09): C, 63.06; H, 4.36; N, 21.63. Found: C, 62.88; H, 4.86; N, 21.72. IR (υ /cm^{-1}) = 3055 (CH aromatic), 2883 (CH_2), 2221 (CN), 1662 (C=N), 1637 (C=C). ^{1}H NMR υ = 4.47 (s, 2H, CH_2), 4.83 (s, 2H, NH_2), 5.68 (s, 2H, triazine CH_2), 7.33-7.38 (m, 4H, C_6H_4), 8.37 (s, 1H, NH).

3-α-Benzalacetonitrilo-4-amino-6-(p-chlorophenyl)-1,2,4-triazine (9a), and 3-α-benzalacetonitrilo-4-phenylamino-6-(p-chlorophenyl)-1,2,4-triazine (9b).

General Procedure: To an equimolecular amounts of dry solid of either **7a** (2.47 g, 0.01 mol) or **7b** (3.23 g, 0.01 mol), benzaldehyde (1.08 g, 0.01 mol) and ammonium acetate (1.0 g) was added. The whole reaction mixture was heated in an oil bath at 120 °C for 15 min then left to cool. The solid product formed upon triturating the remaining product wit ethanol was filtered off.

Compound **9a**: Pale yellow crystals were recovered from acetic acid in a yield 72 % (2.41 g) and with a mp 155-7 °C; *Calculated for* $C_{18}H_{14}ClN_5$ (335.09): C, 64.38; H, 4.20; N, 20.86. Found: C, 64.84; H, 4.41; N, 21.22. IR (υ /cm^{-1}) = 3054 (CH aromatic), 2883 (CH_2), 2218 (CN), 1656 (C=N), 1639 (C=C). ^{1}H NMR υ = 4.86 (s, 2H, NH_2), 5.64 (s, 2H, triazine CH_2), 6.61 (s, 1H, CH=C), 7.28-7.36 (m, 9H, C_6H_5, C_6H_4).

Compound **9b**: Orange crystals were recovered from 1,4-dioxan in a yield 69 % (2.83 g) and with amp 210-3 °C; *Calculated for* $C_{24}H_{18}ClN_5$ (411.13): C, 69.98; H, 4.40; N, 17.00. Found: C, 70.24; H, 4.66; N, 16.78. IR (μ/cm^{-1}) = 3058 (CH aromatic), 2876 (CH_2), 2219 (CN), 1660 (C=N), 1643 (C=C). ^{1}H NMR υ = 5.74 (s, 2H, triazine CH_2), 6.33 (s, 1H, CH=C), 7.27-7.38 (m, 14H, $2C_6H_5$, C_6H_4), 8.21 (s, 1H, NH).

3-(Coumarin-3-yl)-4-amino-6-(p-clorophenyl)-1,2,4-triazine (11a) and 3-(coumarin-3-yl)-4-phenylamino-6-(p-chlorophenyl)-1,2,4-triazine (11a)

To a solution of either **7a** (2.47 g, 0.01 mol) or **7b** (3.23 g, 0.01 mol) in 1,4-dioxan (40 mL) containing piperidine (0.5 mL), salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 hr then evaporated under vacuum. The remaining product was triturated with ethanol and the solidified product was collected by filtration.

Compound **11a**: Pale yellow crystals were recovered from acetic acid in a yield 62 % (2.18 g) and with a mp 180-4°C; *Calculated for* $C_{18}H_{13}ClN_4O_2$ (354.08): C, 61.28; H, 3.71; N, 15.88. Found: C, 61.52; H, 4.06; N, 16.45. IR (υ /cm^{-1}) = 3060 (CH aromatic), 1690 (CO), 1673 (C=N), 1644 (C=C). ^{1}H NMR υ = 4.67 (s, 2H, NH_2), 5.81 (s, 2H, triazine CH_2), 6.88 (s, 1H, coumarin H-4), 7.32-7.39 (m, 8H, $2C_6H_4$).

Compound **11b**: Pale brown crystals were recovered from acetic acid in a yield 57 % (2.43 g) and with a mp 210-3°C; *Calculated for* $C_{24}H_{17}ClN_4O_2$ (428.10): C, 67.21; H, 4.00; N, 13.06. Found: C, 67.09; H, 3.85; N, 13.39. IR (υ /cm^{-1}) = 3055 (CH aromatic), 1688 (CO), 1665 (C=N), 1644 (C=C). ^{1}H NMR υ = 4.42 (s, 2H, NH_2), 5.77 (s, 2H, triazine CH_2), 6.90 (s, 1H, coumarin H-4), 7.28-7.38 (m, 8H, $2C_6H_4$).

2-α--5-p-chlorophenyl-1,3,4-oxadiazine (13a), 2-α-benzalacetonitrilo-5-p-bromophenyl-1,3,4-oxadiazine (13b) and 2-α-benzalacetonitrilo-5-p-nitrophenyl-1,3,4-oxadiazine (13c)

General procedure: To a solution of either **3a** (3.12 g, 0.01 mol), **3b** (3.65 g, 0.01 mol), **3c** (3.24 g, 0.01 mol), **4a** (2.33 g, 0.01 mol), **4b** (2.79 g, 0.01 mol) or **4c** (2.44 g, 0.01 mol) in 1,4-dioxan (40 mL) containing piperidine (1.0 mL) benzaldehyde (1.08 g, 0.01 mol) was added. The reaction mixture was heated under refux for 6 hr then poured onto ice/water containing few hydrops of hydrochloric acid. The solid product, formed in each case, was collected by filtration to afford the respective products.

Compound **13a**: Yellow crystals were recovered from methanol in a yield 63 %, from **3a** (2.02 g), 70 % (2.25) from **4a** and with a mp 155-7 °C; *Calculated for* $C_{18}H_{12}ClN_3O$ (322.06): C, 67.19; H, 3.76; N, 13.06. Found: C, 67.33; H, 4.06; N, 12.74. IR(υ/cm^{-1}): 3055 (CH aromatic), 2220 (CN), 1656 (C=N), 1640 (C=C). ^{1}HNMR (δ ppm): 5.59 (s, 2H, oxadiazine CH_2), 6.21 (s, 1H, CH=C), 7.31-7.38(m, 9H, C_6H_5, C_6H_4).

Compound **13b**: Orange-red crystals were recovered from methanol/dioxan mixture in a yield 66% (2.41 g) and with a mp 175-9 °C; *Calculated for* $C_{18}H_{12}BrN_3O$ (365.02): C, 59.03; H, 3.30; N, 11.47.Found: C, 58.88; H, 3.72; N, 11.85. IR(υ/cm^{-1}): 3057 (CH aromatic), 2223 (CN), 1660 (C=N), 1638 (C=C). ^{1}HNMR (δ ppm): 5.79 (s, 2H, oxadiazine CH_2), 6.26 (s, 1H, CH=C), 7.27-7.34 (m, 9H, C_6H_5, C_6H_4).

Compound **13c**: Orange crystals were recovered from 1,4-dioxan in a yield 70 % (2.32 g) and with a mp 258-62 °C; *Calculated for* $C_{18}H_{12}N_4O_3$ (332.09): C, 65.06; H, 3.64; N, 16.86. Found: C, 64.88; H, 4.42; N, 16.55. IR (υ/cm^{-1}): 3063 (CH aromatic), 2223 (CN), 1656 (C=N), 1638 (C=C); ^{1}HNMR (δ ppm): 5.80 (s, 2H, ring CH_2), 6.21 (s, 1H, CH=C), 7.32-7.46 (m, 9H, C_6H_4).

5-Amino-1-cyanoacetyl-3-(p-chlorophenyl)-pyrazole (15a), 5-Amino-1-cyanoacetyl-3-(p-bromophenyl)-pyrazole (15b) and 5-Amino-1-cyanoacetyl-3-(p-nitrophenyl)-pyrazole (15c)

General procedure: To a solution of either **3a** (3.12 g, 0.01 mol), **3b** (3.65 g, 0.01 mol) or **3c** (3.24 g, 0.01 mol) in ethanol (40 mL), a solution of potassium cyanide (2.8 g, 0.05 mol) was added. The reaction mixture, in each case, was heated in a warm water bath at 60 ºC for 30 min., then left with stirring at room temperature overnight. The solid product formed upon pouring onto ice/water containing hydrochloric acid (till pH 6) was collected by filtration.

Compound **15a**: Orange crystals were recovered from 1,4-dioxan in a yield 74 % (1.92 g) and with a mp 175-8 °C; *Calculated for* $C_{12}H_9ClN_4O$ (260.05): C, 55.29; H, 3.48; N, 21.49; Found: C, 55.43; H, 4.08; N, 21.26. IR υ : 3460-3377 (NH_2), 3050 (CH aromatic), 2250 (CN), 1688 (C=O), 1650 (C=N), 1636 (C=C). ^{1}H NMR υ : 4.64 (s, 2H, CH_2), 4.90 (s, 2H, NH_2), 6.52 (s, 1H, pyrazole H-4), 7.28-7.34 (m, 4H, C_6H_4).

Compound **15b**: Brown crystals were recovered from 1,4-dioxan in a yield 70 % (2.13 g) and with a mp 180-4 °C; *Calculated for* $C_{12}H_9BrN_4O$ (305.13): C, 47.24; H, 2.97; N, 18.36; Found: C, 47.08; H, 3.22; N, 18.73. IR υ : 3455-3349 (NH_2), 3055 (CH aromatic), 2243 (CN), 1690 (C=O), 1655 (C=N), 1638 (C=C). ^{1}H NMR υ : 4.65 (s, 2H, CH_2), 4.75 (s, 2H, NH_2), 6.49 (s, 1H, pyrazole H-4), 7.26-7.38 (m, 4H, C_6H_4).

Compound **15c**: Dark orange crystals were recovered from 1,4-dioxan in a yield 64 % (1.73 g) and with a mp 195-9 °C; *Calculated for* $C_{12}H_9N_5O_3$ (271.07): C, 53.14; H, 3.34; N, 25.82; Found: C, 52.88; H, 3.20; N, 25.43. IR υ : 3459-3354 (NH_2), 3052 (CH aromatic), 2239 (CN), 1688 (C=O), 1657 (C=N), 1636 (C=C). ^{1}H NMR υ : 4.67 (s, 2H, CH_2), 4.79 (s, 2H, NH_2), 6.52 (s, 1H, pyrazole H-4), 7.29-7.36 (m, 4H, C_6H_4).

α-Cyano- β-(4-chlorobenzoyl)-propiononitrilo- β-cyanoacetylhydrazone (17a), ethyl β-(4-chlorobenzoyl)- β -cyanoacetylhydrazonopropiononitrilo- β -carboxylate (17b), β-Cyano-β-(4-bromobenzoyl)-propiononitrilo-β-cyano-acetylhydrazone (17c), ethyl β-(4-bromobenzoyl)- β-cyanoacetyl-hydrazonopropiononitrilo- β-carboxylate (17d), β-Cyano- β -(4-nitrobenzoyl)-propiononitrilo- β-cyanoacetylhydrazone (17e), ethyl β -(4-nitrobenzoyl)-β -cyanoacetylhydrazonopropiononitrilo-α-carboxylate (17f)

General procedure: To a solution of either **3a** (3.12 g, 0.01 mol), **3b** (3.65 g, 0.01 mol) or **3c** (3.24 g, 0.01 mol) in 1,4-dioxan (40 mL) containing triethylamine (0.50 mL) either malononitrile (0.66 g, 0.01mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The whole reaction mixture was heated under reflux for 5 hrs then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **17a**: Yellow crystals were recovered from 1,4-dioxan in a yield 68 % (2.03 g) and with a mp 177-80 °C; *Calculated for* $C_{14}H_{10}ClN_5O$ (299.06): C, 56.10; H, 3.36; N, 23.37; Found: C, 55.88; H, 3.76; N, 23.78. IR ῡ: 3437-3322 (NH), 3053 (CH aromatic), 2245, 2227, 2220 (3 CN), 1687 (C=O), 1663 (C=N), 1642 (C=C). ^{1}H NMR δ: 3.78 (d, J = 4.22 Hz, 2H, CH_2), 4.21 (t, J = 4.22 Hz, 1H, CH), 4.53 (s, 2H, CH_2), 7.31-7.38 (m, 4H, C_6H_4), 8.30 (s, 1H, NH).

Compound **17b**: Yellow crystals were recovered from 1,4-dioxan in a yield 68 % (2.03 g) and with a mp 144 °C; *Calculated for* $C_{16}H_{15}ClN_4O_3$ (346.08): C, 55.42; H, 4.36; N, 16.16; Found: C, 55.76; H, 4.76; N, 16.55. IR ῡ: 3446-3318 (NH), 3058 (CH aromatic), 2258, 2229, 2222, 2220 (3 CN), 1689, 1681 (2C=O), 1667 (C=N), 1637 (C=C). ^{1}H NMR δ: 1.35 (t, J = 7.04 Hz, 3H, CH_3), 3.75 (d, J = 4.07 Hz, 2H, CH_2), 4.21 (t, J = 4.07 Hz, 1H, CH), 4.22 (q, J = 7.04 Hz, 2H, CH_2), 4.53 (s, 2H, CH_2), 7.33-7.39 (m, 4H, C_6H_4), 8.27 (s, 1H, NH).

Compound **17c**: Yellow crystals were recovered from 1,4-dioxan in a yield 68 % (2.03 g) and with a mp 190-3 °C; *Calculated for* $C_{14}H_{10}BrN_5O$ (343.01): C, 48.86; H, 2.93; N, 20.35; Found: C, 49.31; H, 3.22; N, 20.74. IR ῡ: 3455-3336 (NH), 3056 (CH aromatic), 2258, 2227, 2220 (3 CN), 1689 (C=O), 1666 (C=N), 1643 (C=C). ^{1}H NMR δ: 3.80 (d, J = 4.28 Hz, 2H, CH_2), 4.19 (t, J = 4.28 Hz, 1H, CH), 4.57 (s, 2H, CH_2), 7.27-7.35 (m, 4H, C_6H_4), 8.28 (s, 1H, NH).

Compound **17d**: Pale yellow crystals were recovered from 1,4-dioxan in a yield 55 % (2.14 g) and with a mp 210-3 °C; *Calculated for* $C_{16}H_{15}BrN_4O_3$ (390.03): C, 49.12; H, 3.86; N, 14.32; Found: C, 49.33; H, 4.43; N, 14.07. IR ῡ: 3446-3322 (NH), 3056 (CH aromatic), 2257, 2229, 2221 (3 CN), 1690, 1688 (2C=O), 1662 (C=N), 1639 (C=C). ^{1}H NMR δ: 1.36 (t, J = 7.44 Hz, 3H, CH_3), 3.76 (d, J = 4.51 Hz, 2H, CH_2), 4.24 (t, J = 4.51 Hz, 1H, CH), 4.25 (q, J = 7.44 Hz, 2H, CH_2), 4.76 (s, 2H, CH_2), 7.27-7.36 (m, 4H, C_6H_4), 8.24 (s, 1H, NH).

Compound **17e**: Orange crystals were recovered from acetic acid in a yield 83 % (2.57 g) and with a mp 188-90 °C; *Calculated for* $C_{14}H_{10}N_6O_3$ (310.08): C, 54.20; H, 3.25; N, 27.09; Found: C, 53.87; H, 3.61; N, 26.91. IR ῡ: 3449-3321 (NH), 3050 (CH aromatic), 2889 (CH_2), 2258, 2228, 2222, 2220 (3 CN), 1683 (C=O), 1663 (C=N), 1640 (C=C). ^{1}H NMR δ: 3.83 (d, J = 4.22 Hz, 2H, CH_2), 4.10 (t, J = 4.22 Hz, 1H, CH), 4.50 (s, 2H, CH_2), 7.27-7.35 (m, 4H, C_6H_4), 8.32 (s, 1H, NH).

Compound **17f**: Orange crystals were recovered from acetic acid in a yield 73 % (2.60 g) and with a mp 230-3 °C; *Calculated for* $C_{16}H_{15}N_5O_5$ (357.11): C, 53.78; H, 4.23; N, 19.60; Found: C, 53.88; H, 4.34; N, 19.75. IR □: 3460-3325 (NH), 3060 (CH aromatic), 2256, 2228, 2221 (3 CN), 1693, 1686 (2C=O), 1660 (C=N), 1636 (C=C). ^{1}H NMR ῡ: 1.34 (t, J = 7.27 Hz, 3H, CH_3), 3.69 (d, J = 4.25 Hz, 2H, CH_2), 4.21 (t, J = 4.25 Hz, 1H, CH), 4.25 (q, J = 7.44 Hz, 2H, CH_2), 4.71 (s, 2H, CH_2), 7.29-7.38 (m, 4H, C_6H_4), 8.28 (s, 1H, NH).

6-Amino-5-cyano-1-cyanoacetyl-3-(4-p-chlorophenyl)-4-[H]-pyridazine (18a), 5-cyano-1-cyanoacetyl-6-hydroxy-3-(4-p-chlorophenyl)-4-[H]-pyridazine (18b), 6-amino-5-cyano-1-cyanoacetyl-3-(4-p-bromophenyl)-4-[H]-pyridazine(18c),5-cyano-1-cyanoacetyl-6-hydroxy-3-(4-p-bromophenyl)-4-[H]-pyridazine (18d) and 6-amino-5-cyano-1-cyanoacetyl-3-(4-p-nitrophenyl)-4-[H]-pyridazine (18e), 5-cyano-1-cyanoacetyl-6-hydroxy-3-(4-p-nitrophenyl)-4-[H]-pyridazine (18f)

General procedure: A suspension of either **17a** (2.99 g, 0.01 mol), **17b** (3.46 g, 0.01 mol), **17c** (3.43 g, 0.01 mol), **17d** (3.90 g, 0.01 mol), **17e** (3.10 g, 0.01 mol) or **17f** (3.57 g, 0.01 mol) in sodium ethoxide (0.01 mol) [prepared by dissolving sodium metal (2.30 g, 0.01 mol) in absolute ethanol (40 mL) was heated in a boiling water bath for 8 hrs. The cold reaction mixture was poured onto ice/water mixture containing hydrochloric acid (till pH 6) and the formed solid product was collected by filtration.

Compound **18a**: Pale yellow crystals were recovered from methanol in a yield 60 % (1.80 g) and with a mp >300 °C; *Calculated for* $C_{14}H_{10}ClN_5O$ (299.06): C, 56.10; H, 3.36; N, 23.37; Found: C, 56.31; H, 3.46; N, 22.87. IR ῡ: 3433-3316 (NH_2), 3058 (CH aromatic), 2231, 2222 (2 CN), 1684 (C=O), 1662 (C=N), 1638 (C=C). ^{1}H NMR δ: 4.72 (s, 2H, CH_2), 5.33 (s, 2H, NH_2), 6.42 (s, 2H, pyridazine CH_2), 7.33-7.42 (m, 4H, C_6H_4).

Compound **18b**: Pale yellow crystals were recovered from methanol in a yield 55 % (1.65 g) and with a mp 277-81 °C; *Calculated for* $C_{14}H_9ClN_4O_2$ (300.04): C, 55.92; H, 3.02; N, 18.63; Found: C, 55.54; H, 2.79; N, 18.55. IR ῡ: 3573-3322 (OH), 3052 (CH aromatic), 2233, 2220 (2 CN), 1687 (C=O), 1663 (C=N), 1630 (C=C). ^{1}H NMR δ: 4.71 (s, 2H, CH_2), 6.63 (s, 2H, pyridazine CH_2), 7.27-7.41 (m, 4H, C_6H_4), 10.32 (s, 1H, OH).

Compound **18c**: Yellow crystals were recovered from methanol/dioxin mixture in a yield 63 % (2.16 g) and with a mp 210-14 °C; *Calculated for* $C_{14}H_{10}BrN_5O$ (343.01): C, 48.86; H, 2.93; N, 20.35; Found: C, 49.22; H, 3.41; N, 20.09. IR ῡ: 3466-3323 (NH_2), 3052 (CH aromatic), 2235, 2223 (2 CN), 1687 (C=O), 1660 (C=N), 1638 (C=C). ^{1}H NMR δ: 4.73 (s, 2H, CH_2), 4.83 (s, 2H, NH_2), 6.68 (s, 2H, pyridazine CH_2), 7.29-7.36 (m, 4H, C_6H_4).
Compound **18d**: Pale brown crystals were recovered from 1,4-dioxan in a yield 62 % (2.12 g) and with a mp 255-8 °C; *Calculated for* $C_{14}H_9BrN_4O_2$ (343.99): C, 48.72; H, 2.63; N, 16.23; Found: C, 48.51; H, 2.44; N, 15.99. IR ῡ: 3546-3325 (OH), 3055 (CH aromatic), 2233, 2222 (2 CN), 1688 (C=O), 1660 (C=N), 1636 (C=C). ^{1}H NMR δ: 4.73 (s, 2H, CH_2), 6.67 (s, 2H, pyridazine CH_2), 7.30-7.37 (m, 4H, C_6H_4), 10.30 (s, 1H, OH).

Compound **18e**: Pale orange crystals were recovered from 1,4-dioxan in a yield 77 % (2.38 g) and with a mp 177-80 °C; *Calculated for* $C_{14}H_{10}N_6O_3$ (310.08): C, 54.20; H, 3.25; N, 27.09; Found: C, 54.09; H, 3.54; N, 27.35. IR ῡ: 3438-3322 (NH_2), 3062 (CH aromatic), 2233, 2228 (2 CN), 1687 (C=O), 1661 (C=N), 1635 (C=C). ^{1}H NMR δ: 4.72 (s, 2H, CH_2), 4.87 (s, 2H, NH_2), 6.64 (s, 2H, pyridazine CH_2), 7.30-7.39 (m, 4H, C_6H_4).

Compound **18f**: Pale orange crystals were recovered from 1,4-dioxan in a yield 79 % (2.45 g) and with a mp 231-4 °C; *Calculated for* $C_{14}H_9N_5O_4$ (311.07): C, 54.02; H, 2.91; N, 22.50; Found: C, 53.79; H, 3.34; N, 22.73. IR ῡ: 3660-3322 (OH), 3063 (CH aromatic), 2233, 2222 (2 CN), 1688 (C=O), 1657 (C=N), 1641 (C=C). ^{1}H NMR δ: 4.75 (s, 2H, CH_2), 6.65 (s, 2H, pyridazine CH_2), 7.26-7.39 (m, 4H, C_6H_4), 10.26 (s, 1H, OH).

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