Hydrazide-Hydrazones in the Synthesis of 1,3,4-Oxadiazine, 1,2,4-Triazine and Pyrazole Derivatives with Antitumor Activities

Rafat M. Mohareb*[,a,b], Rehab A. Ibrahim[c] and Hosam E. Moustafa[d]

[a]*Faculty of Pharmacy, Organic Chemistry Department, October University of Modern Sciences & Arts, October City, A. R. Egypt*

[b]*Faculty of Science, Chemistry Department, Cairo University, Giza, A.R. Egypt*

[c]*Chemistry Department, Faculty of Engineering, New Cairo Academy, El-Tagemmoe El-Khames, Egypt*

[d]*Applied Medical Sciences Department, Community College in Quaryat, Al jouf University, Saudi Arabia*

Abstract: The reaction of cyanoacetyl hydrazine (**1**) with the α-haloketones **2a-2c** in 1,4-dioxane afforded the hydrazide-hydrazone derivatives **3a-3c**. The latter products were used in a series of heterocyclization to give 1,3,4-oxadiazine, 1,2,4-triazine and pyrazole derivatives. All compounds synthesized through this work are new products and their antitumor evaluation towards three human tumor cell lines representing different tumor types, namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268). Some of the synthesized products showed high inhibitory effect towards the three cell lines.

Keywords: Antitumor, hydrazide-hydrazone, 1,3,4-oxadiazine, 1,2,4-triazine, pyrazole.

INTRODUCTION

It is well known that the hydrazone group plays an important role for the antimicrobial activity. Thus, a number of hydrazide–hydrazone possessed interesting antibacterial-antifungal [1-4], 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 pharmaceutical applications, we report here the synthesis of a series of hydrazide-hydrazones **3a-3c** *via* the reaction of cyanoacetylhydrazine **1** with α-bromoketones (**2a-2c**). Moreover, the synthesized hydrazide-hydrazone derivatives were used in a series of heterocyclic transformations to give 1,3,4-oxadiazine, 1,2,4-triazine and pyrazole derivatives [18-21].

RESULTS AND DISCUSSION

The reaction of cyanoacetyl hydrazine **1** with the α-haloketones **2a-2c** in 1,4-dioxane at room temperature gave the α-bromohydrazone derivatives **3a-3c** (Scheme **1**). The structures of the latter were elucidated through analytical and spectral data. Thus, the ^{1}H NMR spectrum of **3a** showed the presence of two singlets at 4.77. 5.38 ppm corresponding to two CH_2 groups, a multiplet at 7.27-7.40 ppm corresponding to phenyl protons and a singlet at 8.88 ppm (D_2O exchangeable) for an NH group. Moreover, the ^{13}C NMR of **3a** showed the presence of δ: 27.0, 64.6 corresponding to the two CH_2 groups together with other signals which are consistent with the proposed structure (see experimental section).

Compounds **3a-3c** underwent ready cyclization when heated in a boiling water bath with sodium ethoxide in ethanol solution to form the 1,3,4-oxadiazine derivatives **4a-4c** (Scheme **2**). The analytical and spectral data obtained for the synthesized compounds were are in agreement 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** or **7b**, respectively (Scheme **3**). Formation of the latter is explained in terms of the non-isolable intermediate formation of **6a** or **6b** followed by dehydration. The elemental analysis and ^{1}H NMR spectra were the basis of structure elucidation.

The 1,2,4-triazine derivatives **7a** and **7b** bearing the cyanomethyl group showed a high reactivity towards aromatic aldehydes. Thus, the reaction of compounds **7a** and **7b** with benzaldehyde **8** gave the derivatives **9a** and **9b** (Scheme **4**). On the other hand, their reaction with salicylaldehyde **10** gave the coumarin derivatives **11a** and **11b**.

The reaction of compounds **3a-3c** with benzaldehyde gave the 2-benzalcyanomethyl-1,3,4-oxadiazine derivatives **13a-13c** (Scheme **5**). The structures of the obtained products were elucidated on the basis of analytical and spectral data. The same compounds **13a-13c**, respectively were obtained through reaction of **4a-4c** with benzaldehyde.

Compounds **3a-3c** bearing the α-bromomethyl group seemed to be reactive towards nucleophilic reagents. Thus, their reaction with potassium cyanide gave the pyrazole derivatives **15a-15c** (Scheme **6**). Formation of these products was based on the formation of the non isolable intermediates **14a-14c** followed by cyclization. Our trials to isolate the acyclic intermediates failed. The analytical and spectral data of compounds **15a-15c** were in agreement with the proposed structures. Thus, the ^{1}H NMR spectrum of **15a** showed a

*Address correspondence to this author at the Faculty of Pharmacy, Organic Chemistry Department, October University of Modern Sciences & Arts, October City, A. R. Egypt; Tel: 002012-3406896; Fax: 002025676570; E-mail: raafat_mohareb@yahoo.com

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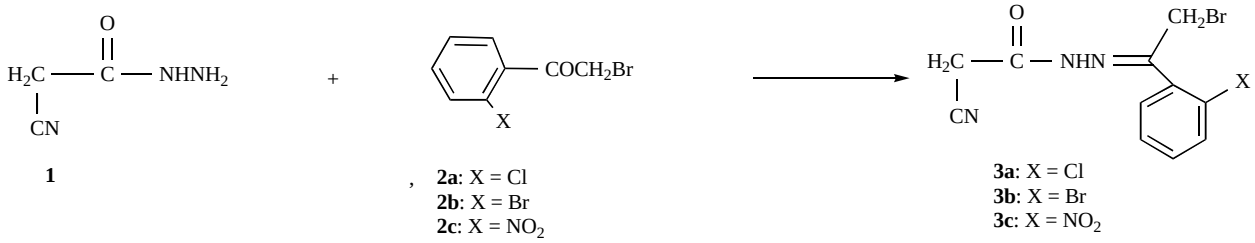
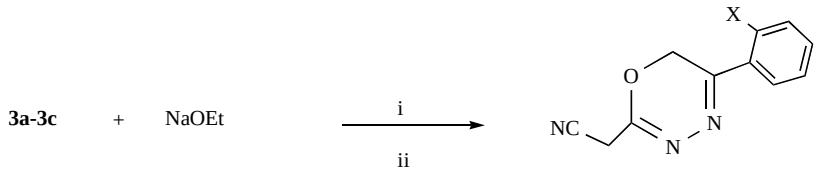


1 , **2a**: X = Cl
2b: X = Br
2c: X = NO_2

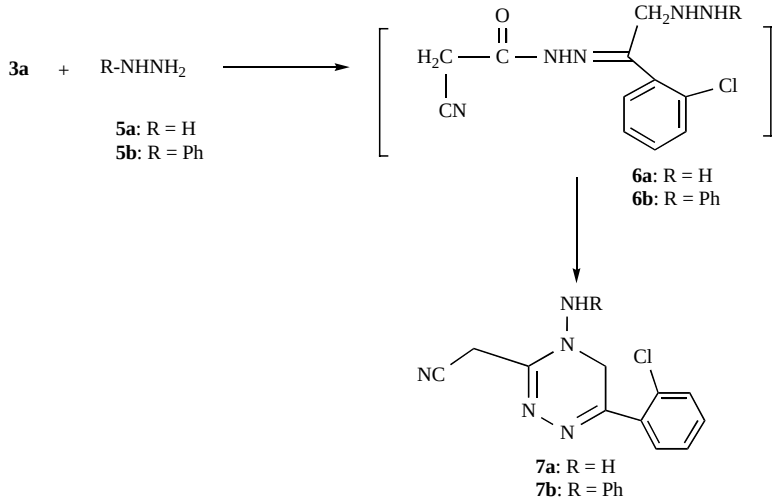
3a: X = Cl
3b: X = Br
3c: X = NO_2

Scheme 1. Reagents and conditions: 1,4-dioxane (0.01 mole equiv.), heat 2h, stirring at r.t. 2 h, yield 80% (**3a**), 72 % (**3b**), 88 % (**3c**).



4a: X = Cl
4b: X = Br
4c: X = NO_2

Scheme 2. Reagents and conditions:(i) NaOEt, EtOH (0.01 equiv.), heat in a boiling water bath 4 h (ii) HCl in ice/water, pH 7, 70 % (**4a**), 78 % (**4b**), 63 % (**4c**).

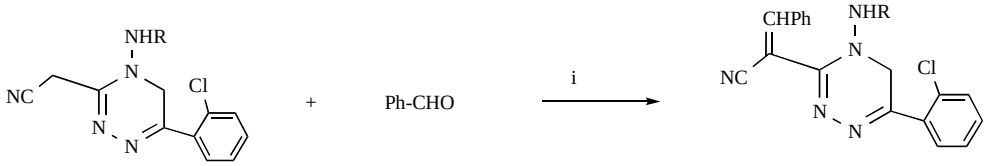


5a: R = H
5b: R = Ph

6a: R = H
6b: R = Ph

7a: R = H
7b: R = Ph

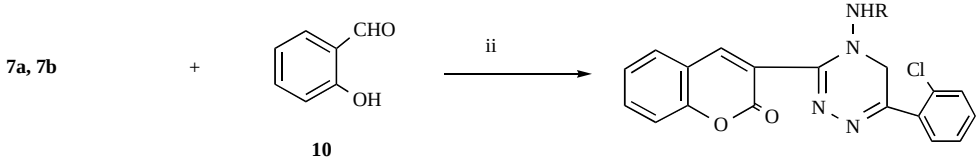
Scheme 3. Reagents and conditions: 1,4-dioxane (0.01 equiv.), heat 3 h, ice/water with HCl, 60 % (**7a**), 68 % (**7b**).



7a: R = H
7b: R = Ph

8

9a: R = H
9b: R = Ph

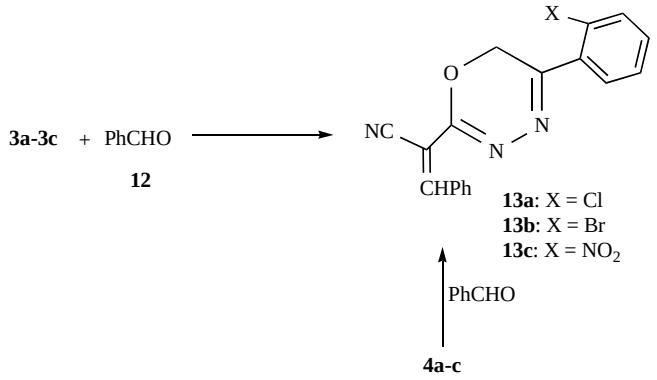


10

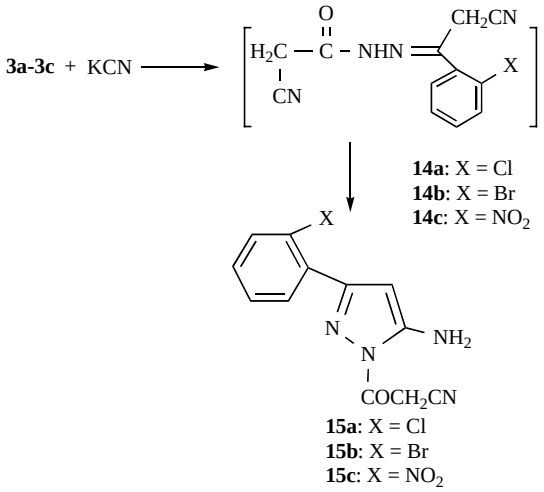
11a: R = H
11b: R = Ph

Scheme 4. Reagents and conditions: (i) NH_4OAc, Oil bath 120 ºC, 15 min. (0.01 equiv.), EtOH, 72 % (**9a**), 69 % (**9b**). (ii) 1,4-dioxane (0.01 equiv.), piperidine, heat 4 h, EtOH, 62 % (**11a**), 57 % (**11b**).

singlet at 4.64 ppm corresponding to CH_2 group, a singlet at 4.90 ppm corresponding to an NH_2 group, a singlet at 6.52 ppm corresponding to the pyrazolic proton H-4 and a multiplet at 7.28-7.34 ppm for the protons of C_6H_4 group. Moreover, the ^{13}C NMR showed signals that are in agreement with the structure of **15a** (see experimental section).



Scheme 5. Reagents and conditions: 1,4-dioxane (0.01 mole equiv.), piperidine, heat 6 h, HCl in ice/water, 63 % (**13a**), 66 % (**13b**), 70 % (**13c**).



Scheme 6. Reagents and conditions: EtOH (0.01 mole equiv.), water bath at 60 ºC, 0.5 h, HCl in ice/water pH 6, 74 % (**15a**), 70 % (**15b**), 64 % (**15c**).

Effect of the Synthesized Compounds on the Growth of Human Tumor Cell Lines

The effect of compounds **3a-15c** was evaluated on the *in vitro* growth of three human tumor cell lines representing different tumor types, namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268), after a continuous exposure of 48 h. The results are summarized in Table **1**.

All the tested compounds were able to inhibit the growth of the human tumor cell lines in a dose-dependent manner (data not shown). The 1,3,4-oxadiazine derivative **4c**, the 1,2,4-triazine derivative **11a** and the pyrazole derivative **15c** showed the highest inhibitory effect of the tested compounds, exhibiting an equivalent potency in all the three tumor cell lines. However, their activity is largely lesser than the positive control. While compounds **3b**, **3c**, **7a**, **9a**, **13b**, **15a** showed moderated growth inhibitory effect relative to compounds **4c, 11a** and **15c**. On the other hand, compounds **3a**, **4a**, **4b**, **9b**, **11b**, **13a** and **15b** showed the lowest inhibitory effect relative to the tested compounds. It is convenient to observe that the pyrazole derivative **15c** with its *o*-nitrophenyl group showed the maximum inhibitory effect through the three cell lines. Comparing the activities of compounds **4a**, **4b** and **4c**, it is observed that the *o*-chlorophenyl-1,3,4-oxazine **4a** presents a weaker growth inhibitory effect while the o-nitrophenyl-1,3,4-oxazine **4c** showed high inhibitory effect although the results in NCI-H460 cell line are comparable.

EXPERIMENTAL SECTION

General Information

Melting points were determined in open capillaries and are uncorrected. I.R spectra were measured using KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}HNMR & ^{13}C NMR spectra were measured on a Varian EM390-200 MHz instrument in DMSO-d_6 as solvent and using TMS as internal standard, and chemical shifts (δ) are expressed in ppm. Elemental analyses were determined on a Yanaco CHN Corder elemental analyzer (Japan).

α-Bromo(o-chloroacetophenone)-α-cyanoacetylhydrazone 3a, β-bromo(o-bromoacetophenone)-α-cyanoacetylhydrazone 3b and β-bromo(o-nitroacetophenone)-α-cyanoacetylhydrazone 3c

To a solution of cyanoacetyl hydrazine **1** (0.99 g, 0.01 mol), in 1,4-dioxane (40 mL) either of *o*-chlorophenacylbromide **2a** (2.3 g, 0.01 mol), *o*-bromophenacylbromide **2b** (2.80 g, 0.01 mol) or o-nitrophenacylbromide (2.46 g, 0.0.1 mol) was added. The reaction mixture was kept at room temperature with stirring for 2 h and the formed solid product was filtrated off.

Compound **3a**: Pale yellow crystals were recovered from ethanol in a yield of 80 % (2.49 g); mp: 177-179°C. I.R (υ/cm^{-1}) = 3480-3334 (NH), 3054 (CH aromatic), 2887 (CH_2), 2260 (CN), 1684 (C=O), 1666 (C=N), 1641 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.77 (s, 2H, CH_2), 5.38 (s, 2H, CH_2) 7.27-7.40 (m, 4H, C_6H_4), 8.88 (s, 1H, NH). ^{13}C NMR (200 MHz, DMSO-d_6) δ 27.0 (CH_2), 64.6 (CH_2), 116.3 (CN), 126.8, 127.0, 128.7, 130.0, 138.4 (C_6H_5), 157.3 (C=N), 172.7 (C=O). Calculated for $C_{11}H_9BrClN_3O$: 314.57, C: 42.00, H: 2.88, N: 13.36). Found, C: 42.09, H: 3.11, N: 13.40.

Compound **3b**: Pale yellow crystals were recovered from ethanol in a yield of 72 % (2.59 g); mp: 202-205°C. I.R (υ/cm^{-1}) = 3463-3329 (NH), 3050 (CH aromatic), 2887 (CH_2), 2260 (CN), 1690 (C=O), 1666 (C=N), 1636 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.74 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 7.26-7.35 (m, 4H, C_6H_4), 8.83 (s, 1H, NH). ^{13}C NMR (200 MHz, DMSO-d_6) δ 27.2 (CH_2), 64.5 (CH_2), 116.0 (CN), 126.0, 126.8, 127.0, 128.7, 133.0, 139.4 (C_6H_5), 157.0 (C=N), 172.9 (C=O). Calculated for $C_{11}H_9Br_2N_3O$: 359.02, C: 36.80, H: 2.53, N: 11.70. Found, C: 36.66, H: 2.49, N: 11.38.

Compound **3c**: Orange crystals were recovered from ethanol in a yield of 88 % (2.84 g) ; mp: 210-214°C. I.R (υ/cm^{-1}) = 3465-3326 (NH), 3056 (CH aromatic), 2888

Table 1. Effect of Compounds 3-15c on the Growth of Three Human Tumor Cell Lines

Compound No.	GI_{50} (μM)		
	MCF-7	**NCI-H460**	**SF-268**
3a	66.6 ± 12.2	12 ± 6.2	24.8 ± 3.2
3b	20 ± 0.4	24.3 ± 0.8	32 ± 0.8
3c	30 ± 0.6	17.3 ± 1.4	22.3 ±1.5
4a	40.6 ± 12.6	32.6 ± 8.6	60.4 ± 14.8
4b	72.7 ± 17.5	40.2 ± 12.8	50.0 ± 9.01
4c	11.8 ± 0.6	14.5 ± 0.8	16.7 ± 1.6
7a	35.4 ± 10.2	24.1 ± 0.8	18.9 ± 6.8
7b	38.0 ± 1.8	44.0 ± 0.8	20.5 ± 1.1
9a	22.0 ± 0.2	30.6 ± 1.4	38.4 ± 0.6
9b	50.1 ± 0.7	23.2 ± 4.8	18.4 ± 1.8
11a	11.9 ± 0.5	14.1 ± 0.6	20.3 ± 0.5
11b	70.9 ± 0.9	43.6 ± 1.8	56.8 ± 0.8
13a	66.6 ± 16.9	38.9 ± 10.8	50.8 ± 8.6
13b	40.6±12.2	32.6±8.6	60.4±14.8
13c	22.0±0.2	30.6±1.4	38.4±0.6
15a	20 ±0.4	24.3±0.8	32±0.8
15b	70.9±0.9	43.6±1.8	56.8±0.8
15c	2.5 ± 0.5	10.4 ± 0.6	8.0 ± 0.4
Doxorubicin	0.0428 ± 0.008	0.0940 ± 0.008	0.0940 ± 0.007

Results are given in concentrations that were able to cause 50 % of cell growth inhibition (GI_{50}) after a continuous exposure of 48 h and show means ± SEM of three-independent experiments performed in duplicate.

(CH_2), 2263 (CN), 1685 (C=O), 1661 (C=N), 1634 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.79 (s, 3H, CH_2) , 5.44 (s, 2H, CH_2), 7.31-7.39 (m, 4H, C_6H_4), 8.80 (s, 1H, NH). ^{13}C NMR (200 MHz, DMSO-d_6) δ 27.1 (CH_2), 64.6 (CH_2), 116.6 (CN), 126.2, 127.6, 128.9, 130.8, 138.1 (C_6H_5), 157.2 (C=N), 172.5 (C=O). . Calculated for $C_{11}H_9BrN_4O_3$: 323.99, C: 40.64, H: 2.79, N: 17.23. Found, C: 40.40, H: 3.09, N: 17.11.

5-(p-Clorophenyl)l-2-cyanomethyl-1,3,4-oxadiazine 4a 5-(p-bromo-phenyl)-2-acetonitrilo-1,3,4-oxadiazine 4b and 5-(p-nitrophenyl)-2-cyanomethyl-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 4 h 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-dioxane in a yield of 70 % (1.63 g); mp: 262-265°C. I.R (υ/cm^{-1}) = 3060 (CH aromatic), 2870 (CH_2), 2245 (CN), 1660 (C=N), 1638 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.65 (s, 2H, CH_2), 5.89 (s, 2H, ring CH_2), 7.30-7.38 (m, 4H, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ 19.8 (CH_2), 64.6 (ring CH_2), 116.8 (CN), 126.0, 127.3, 129.9, 130.8, 138.0 (C_6H_5), 164.2, 164.8 (2 C=N). Calculated for $C_{11}H_8ClN_3O$: 233.04, C: 56.54, H: 3.45, N: 17.98. Found, C: 56.51, H: 3.60, N: 18.02.

Compound **4b**: Pale orange crystals were recovered from 1,4-dioxane in a yield of 78 % (2.17 g); mp: 266-269°C. I.R (υ/cm^{-1}) = 3066 (CH aromatic), 2880 (CH_2), 2222 (CN), 1660 (C=N), 1635 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.77 (s, 2H, CH_2), 5.73 (s, 2H, ring CH_2), 7.31-7.40 (m, 4H, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ19.8 (CH_2), 64.6 (ring CH_2), 116.6 (CN), 126.3, 127.0, 129.6, 130.4, 138.2 (C_6H_5), 164.0, 164.6 (2 C=N). Calculated for $C_{11}H_8BrN_3O$: 278.12, C: 47.51, H: 2.90, N: 15.11. Found, C: 47.44, H: 3.30, N: 14.92.

Compound **4c**: Pale orange crystals were recovered from 1,4-dioxane in a yield of 63 % (1.53g); mp: 246-249°C. I.R (υ/cm^{-1}) = 3066 (CH aromatic), 2871 (CH_2), 2226 (CN), 1660 (C=N), 1639 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.77 (s, 2H, CH_2), 5.80 (s, 2H, ring CH_2), 7.30-7.38 (m, 4H, C_6H_4). 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.

3-cyanomethyl-4-amino-6-phenyl-1,2,4-triazine 7a and 3-cyanomethyl-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-dioxane (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 h 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-dioxane in a yield of 60 % (1.48 g); mp: 164-166°C. I.R (υ/cm^{-1}) = 3059 (CH aromatic), 2890 (CH_2), 2225 (CN), 1660 (C=N), 1635 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.46 (s, 2H, CH_2), 4.87 (s, 2H, NH_2), 5.66 (s, 2H, triazine CH_2), 7.28-7.34 (m, 4H, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ19.7 (CH_2), 64.6 (ring CH_2), 116.4 (CN), 126.8, 127.3, 129.5, 129.9, 138.0 (C_6H_5), 164.3, 164.8 (2 C=N). 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.

Compound **7b**: Yellow crystals were recovered from 1,4-dioxane in a yield of 68 % (2.19 g); mp: 198 °C. I.R (υ/cm^{-1}) = 3055 (CH aromatic), 2883 (CH_2), 2221 (CN), 1662 (C=N), 1637 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.47 (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). ^{13}C NMR (200 MHz, DMSO-d_6) δ19.7 (CH_2), 64.6 (ring CH_2), 116.4 (CN), 126.8, 127.3, 129.5, 129.9, 138.0 (C_6H_5), 164.3, 164.8 (2 C=N). 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.

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) were added. The whole reaction mixture was heated in an oil bath at 120 ^{o}C for 15 min then left to cool. The solid product formed upon triturating the remaining product with ethanol was filtered off.

Compound **9a**: Pale yellow crystals were recovered from acetic acid in a yield of 72 % (2.41 g); mp: 190-193°C. I.R (υ/cm^{-1}) = 3056 (CH aromatic), 2873 (CH_2), 2220 (CN), 1653 (C=N), 1639 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.99 (s, 2H, NH_2), 5.64 (s, 2H, triazine CH_2), 6.61 (s, 1H, CH=C), 147.2 (CH=<u>C</u>), 7.30-7.39 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ19.7 (CH_2), 64.6 (ring CH_2), 116.8 (CN), 96.9 (<u>CH</u>=C), 145.7 (CH=<u>C</u>), 126.6, 127.0, 129.1, 129.9, 130.5, 132.8, 138.8 (C_6H_5, C_6H_4), 164.0, 164.9 (2 C=N). Calculated for $C_{18}H_{14}ClN_5$: 335.09, C: 64.38, H: 4.20, N: 20.86. Found, C: 64.54, H: 4.49, N: 21.08.

Compound **9b**: Orange crystals were recovered from 1,4-dioxane in a yield of 69 % (2.83 g); mp: 180-183°C. I.R (υ/cm^{-1}) = 3058 (CH aromatic), 2876 (CH_2), 2219 (CN), 1660 (C=N), 1643 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ5.74 (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). ^{13}C NMR (200 MHz, DMSO-d_6) δ19.9 (CH_2), 64.5 (ring CH_2), 116.2 (CN), 96.3 (<u>CH</u>=C), 145.6 (CH=<u>C</u>), 126.6, 127.3, 129.0, 129.9, 130.2, 131.7, 134.0, 136.9, 138.6 ($2C_6H_5$, C_6H_4), 164.2, 164.3 (2 C=N). 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.

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-dioxane (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 h 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 of 62 % (2.18 g); mp: 180-184°C. IR (υ/cm^{-1}) = 3060 (CH aromatic), 1690 (CO), 1673 (C=N), 1644 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.67 (s, 2H, NH_2), 5.81 (s, 2H, triazine CH_2), 6.88 (s, 1H, coumarin H-4), 7.32-7.39 (m, 8H, $2C_6H_4$). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.5 (ring CH_2), 96.0 (coumarin H-4), 120.3, 122.6, 124.0, 125.9, 127.0, 129.3, 129.9, 130.2, 131.7, 134.0, 136.9, 138.0 (2 C_6H_4), 159.0 (C=O), 164.3, 164.6 (2 C=N). 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.

Compound **11b**: Pale brown crystals were recovered from acetic acid in a yield of 57 % (2.43 g); mp: 210-213°C. I.R (υ/cm^{-1}) = 3055 (CH aromatic), 1688 (CO), 1665 (C=N), 1644 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.42 (s, 2H, NH_2), 5.77 (s, 2H, triazine CH_2), 6.90 (s, 1H, coumarin H-4), 7.28-7.38 (m, 8H, $2C_6H_4$). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.0 (ring CH_2), 96.3 (coumarin H-4), 120.6, 121.9, 123.6, 125.5, 127.4, 128.7, 129.3, 130.0, 131.9, 134.8, 135.7, 138.3, 144.2, 146.9 (C_6H_5, 2 C_6H_4), 158.8 (C=O), 164.1, 164.5 (2 C=N). 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.

2-α-5-p-chlorophenyl-1,3,4-oxadiazine 13a, 2-α-benzalcyanomethyl-5-p-bromophenyl-1,3,4-oxadiazine 13b and 2-α-benzalcyanomethyl-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-dioxane (40 mL) containing piperidine (1.0 mL) benzaldehyde (1.08 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then poured onto ice/water containing few drops 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 of 63 % (2.02 g), from **3a** and 70 % (2.25) from **4a**; mp: 180-182°C. I.R (υ/cm^{-1}) = 3055 (CH aromatic), 2220 (CN), 1656 (C=N), 1640 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ5.60 (s, 2H, oxadiazine CH_2), 6.30 (s, 1H, CH=C), 7.30-7.39(m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.4 (ring CH_2), 95.0 (<u>CH</u>=C), 118.0 (CH=<u>C</u>), 120.3, 121.5, 123.2, 125.0, 127.4, 129.3, 130.0, 134.8, 135.0, 144.0 (C_6H_5, C_6H_4), 164.0, 164.2 (2 C=N). 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.

Compound **13b**: Orange-red crystals were recovered from methanol/dioxane mixture in a yield of 66% (2.41 g); mp: 210-212°C. I.R (υ/cm^{-1}) = 3060 (CH aromatic), 2226 (CN), 1665 (C=N), 1621 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ5.77 (s, 2H, oxadiazine CH_2), 6.20 (s, 1H, CH=C), 7.29-7.39 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.6 (ring CH_2), 95.2 (CH=C), 118.3 (CH=C), 120.0, 120.2, 121.6, 123.2, 127.4, 128.0, 130.2, 132.6, 134.2, 140.4 (C_6H_5, C_6H_4), 164.1, 164.8 (2 C=N). Calculated for $C_{18}H_{12}BrN_3O$: 365.02, C: 59.03, H: 3.30, N: 11.47. Found, C: 58.92, H: 3.55, N: 11.51.

Compound **13c**: Orange crystals were recovered from 1,4-dioxane in a yield of 70 % (2.32 g); mp: 233-236°C. I.R (υ/cm^{-1}) = 3063 (CH aromatic), 2223 (CN), 1656 (C=N), 1638 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ5.80 (s, 2H, ring CH_2), 6.21 (s, 1H, CH=C), 7.32-7.46 (m, 9H, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.3 (ring CH_2), 95.5 (CH=C), 118.1 (CH=C), 120.0, 120.5, 121.6, 123.2, 125.9, 126.8, 130.8, 132.9, 133.9, 141.0 (C_6H_5, C_6H_4), 164.3, 164.5 (2 C=N). MS: m/e = 332 (M^+). 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.

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 ^{o}C for 0.5 h 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-dioxane in a yield of 74 % (1.92 g); mp: 175-178°C. I.R (υ/cm^{-1}) = 3460-3377 (NH_2), 3050 (CH aromatic), 2250 (CN), 1688 (C=O), 1650 (C=N), 1636 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.64 (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). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.6 (ring CH_2), 95.2 (CH=C), 118.0 (CH=C), 120.3, 120.9, 121.4, 123.0, 124.9, 126.9, 138.8, 130.9, 133.9, 140.2 (C_6H_5, C_6H_4), 164.2, 164.8 (2 C=N). MS: m/e = 260 (M^+). Calculated for $C_{12}H_9ClN_4O$: 260.05, C: 55.29, H: 3.48, N: 21.49. Found, C: 55.43, H: 3.68, N: 21.26.

Compound **15b**: Brown crystals were recovered from 1,4-dioxane in a yield of 70 % (2.13 g); mp: of 177-180°C. I.R (υ/cm^{-1}) = 3455-3349 (NH_2), 3055 (CH aromatic), 2243 (CN), 1690 (C=O), 1655 (C=N), 1638 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.65 (s, 2H, CH_2), 4.75 (s, 2H, NH_2), 6.49 (s, 1H, pyrazole H-4), 7.29-7.38 (m, 4H, C_6H_4). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.3 (ring CH_2), 95.2 (CH=C), 118.4 (CH=C), 120.6, 120.3, 121.0, 123.3, 124.7, 126.9, 138.8, 130.9, 133.9, 140.9 (C_6H_5, C_6H_4), 164.0, 164.8 (2 C=N). 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.

Compound **15c**: Dark orange crystals were recovered from 1,4-dioxane in a yield of 64 % (1.73 g); mp: 195-199 °C. I.R (υ/cm^{-1}) = 3459-3354 (NH_2), 3052 (CH aromatic), 2239 (CN), 1688 (C=O), 1657 (C=N), 1636 (C=C). ^{1}H NMR (200 MHz, DMSO-d_6) δ4.67 (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). ^{13}C NMR (200 MHz, DMSO-d_6) δ60.3 (ring CH_2), 95.2 (CH=C), 118.0 (CH=C), 120.3, 120.9, 121.4, 123.0, 124.9, 126.9, 138.8, 130.9, 133.9, 138.2 (C_6H_5, C_6H_4), 164.5, 164.7 (2 C=N). MS: m/e = 271 (M^+). 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.

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