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REACTION OF PHENYLHYDRAZO ETHYLACETOACETATE WITH CYANO ACETYL HYDRAZINE: NOVEL SYNTHESIS OF PYRIDAZINE AND PYRAZOLE DERIVATIVES AND THEIR ANTI-TUMOR EVALUATIONS

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ABSTRACT: The reaction of phenylhydrazoethyl acetoacetate (1) with cyanoacetyl hydrazine (2) in an oil bath in the presence of ammonium acetate gave the pyridazine derivative 4. However, carrying the same reaction but in ethanolic/Et_3N gave the pyrazole derivative 5. Compounds 4 and 5 were used in a series of heterocyclization reactions to afford products that showed anti-tumor activities towards three cell lines namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268).

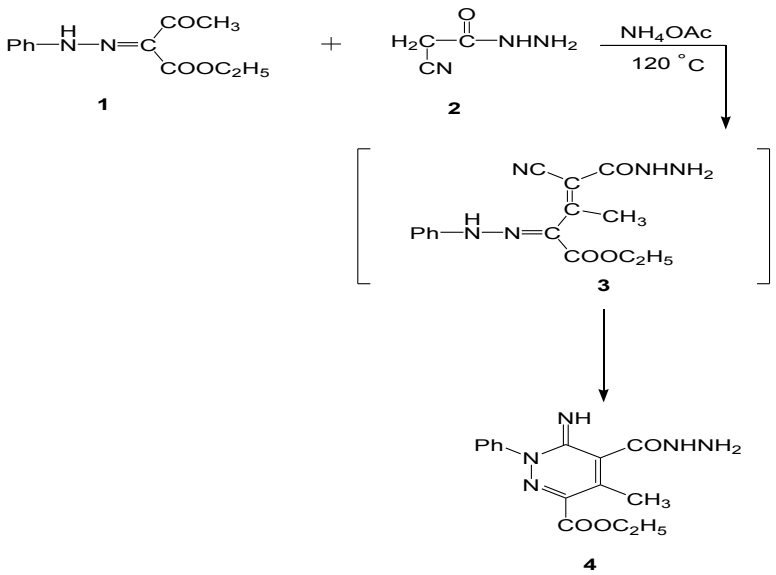
Keywords: Pyridazine, pyrazole, coumarin, pyran, anti-tumor.

INTRODUCTION

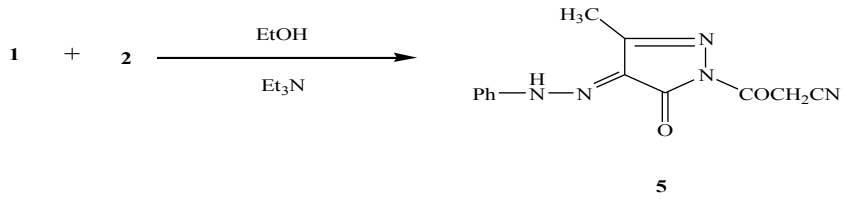
Recently infectious diseases have dramatically increased and become a major threat to public health, despite tremendous progress in medicinal chemistry. The impact is more acute in developing countries due to non availability of desired medicines and emergence of widespread drug resistance [1]. Infections caused by fungal species are common in immunocompromised patients and carry significant treatment cost and mortality [2]. Antibacterial resistance is a growing problem which necessitates the discovery of newer antibiotics with activity against resistant strains [3]. Hydrazide derivatives have been claimed to possess antimicrobial [4], antimycobacterial [5], antitumour [6], anti-inflammatory [7], trypanocidal [8], antimalarial [9] and anti-HIV activities [10,11].

RESULTS AND DISCUSSION

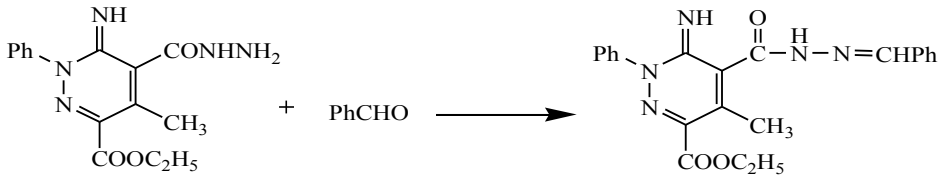
In this work, we are studying the reaction of phenylhydrazo ethyl acetoacetate (1) with cyanoacetylhydrazide (2) in different conditions in order to get either hydrazide or hydrazide-hydrazone derivatives followed by their uses to form heterocyclic derivatives incorportating . Thus, the reaction of (1) with (2) in ammonium acetate at 120°C gave the pyridazine derivative (4). The reaction took place via the intermediate formation of (3) followed by Michael addition to afford the pyridazine derivative (4). The structure of compound (4) was based on analytical data. Thus, the ^{1}H NMR spectrum of the reaction product showed the presence of a triplet at δ 1.36 corresponding to the ester CH_3 group, a singlet at δ 2.81 for CH_3 group, a quartet at δ 4.20 for CH_2, a singlet at δ 4.57 for NH_2 group a multiplet at δ 7.29-7.38 for C_6H_5 and two singlets at δ 8.22, 8.39 ppm for the two NH groups.



On the other hand , carrying the same reaction in absolute ethanol and the presence of a catalytic amount of triethylamine gave the pyrazole derivative (5). The analytical and spectral data of compound (5) are consistent with the proposed structure. Thus ^{1}H NMR spectrum of compound (5) showed a singlet at δ 2.78 correcponding to CH_3 group, a singlet at δ 3.87 for the CH_2 group, a multiplet at δ 7.23-7.43 for the phenyl protons and a singlet at δ 8.89 for the NH group.

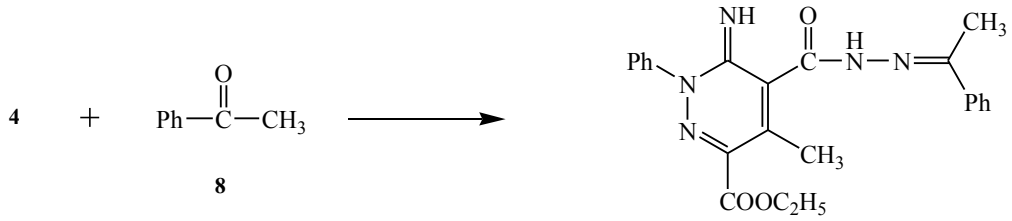


Further confirmation for structures of compound (4) and (5) were obtained through studying the reactivates of them towards some chemical reagents. Thus, compound (4) reacted with benzaldehyde (6) to give the benzal derivative (7).



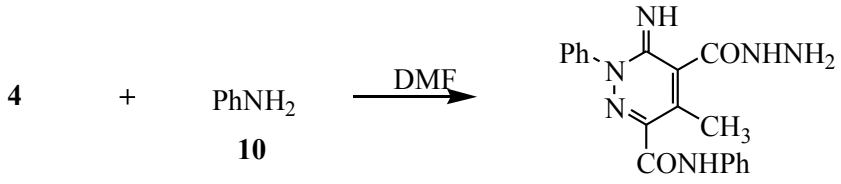
4 **6** **7**

Similarly, the reaction of compound (4) with acetophenone (8) gave the hydrazide-hydrazone derivative (9). Formation of hydrazide-hydrazone derivatives have been recently reported [12,13]. The ^{1}H NMR spectrum of compound (9) showed a triplet at δ 1.13 corresponding to the ester CH_3 group a singlet at δ 2.80 for the CH_3 group, a quartet at δ 4.20 for the ester CH_2 group and a multiplet at δ 7.26-7.36 corresponding to the two phenyl groups and two singlets at δ 8.89, 9.70 for the two NH groups.



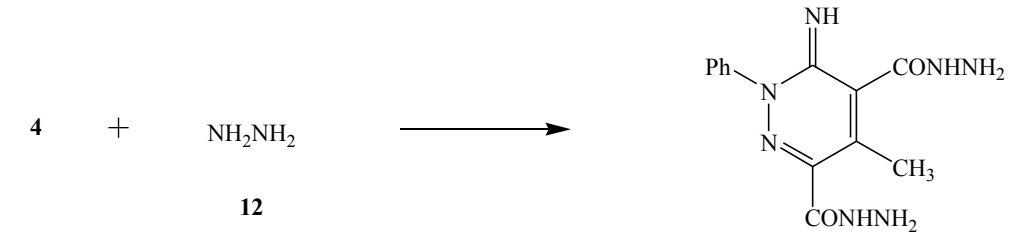
8 **9**

On the other hand, the reaction of compound **(4)** with aniline **(10)** in dimethyl formamide gave the anilide derivative **(11).**



4 **10** **11**

The reaction of compound (4) with hydrazine hydrate (12) gave the 3,5-dihydrazide derivative (13). The analytical and spectral data are consistent with the structure of the reaction product.



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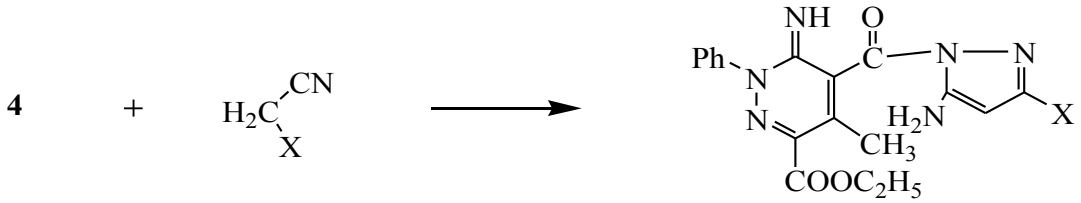
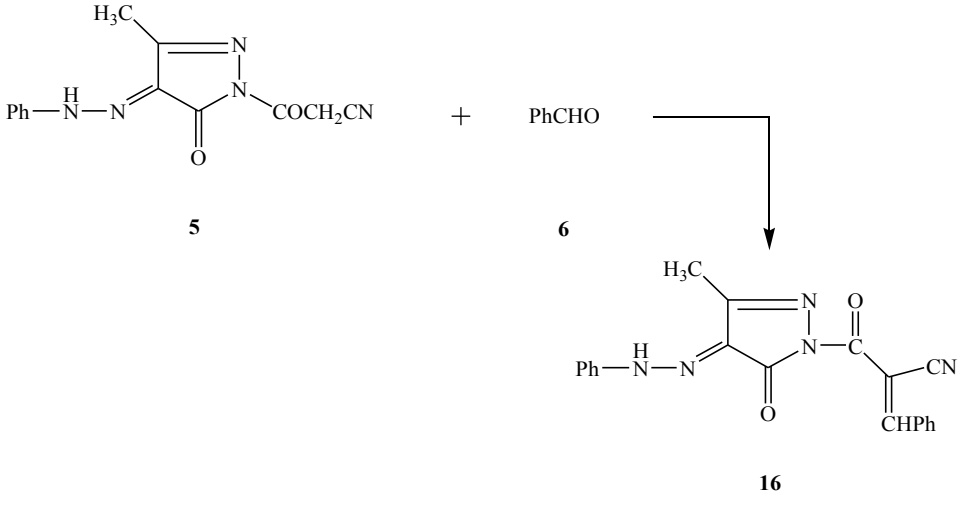
Compound **(14)** reacted with either malononitrile **(14a)** or ethyl cyanoacetate **(14b)** to give the pyrazole derivatives **(15a)** and **(15b)**, respectively.



14a, X= CN
b, X= $COOC_2H_5$

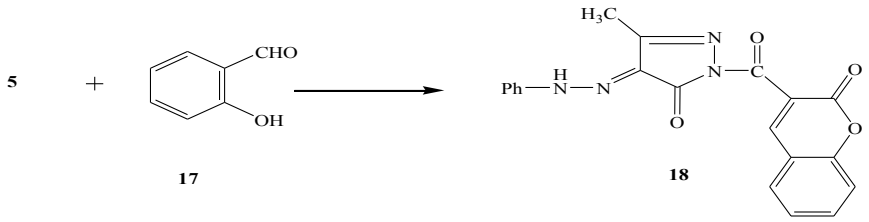
15a, X= NH_2
b, X= OH

Compound **(5)** reacted with benzaldehyde **(6)** to give the benzal derivative **(16).** On the other hand its reaction with salicaldehyde **(17)** gave the coumarin derivative **(18).**

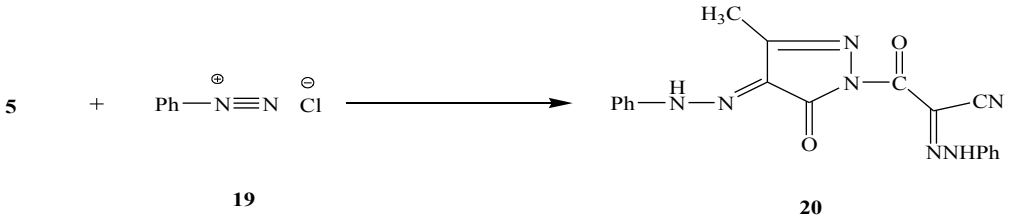


5 **6**

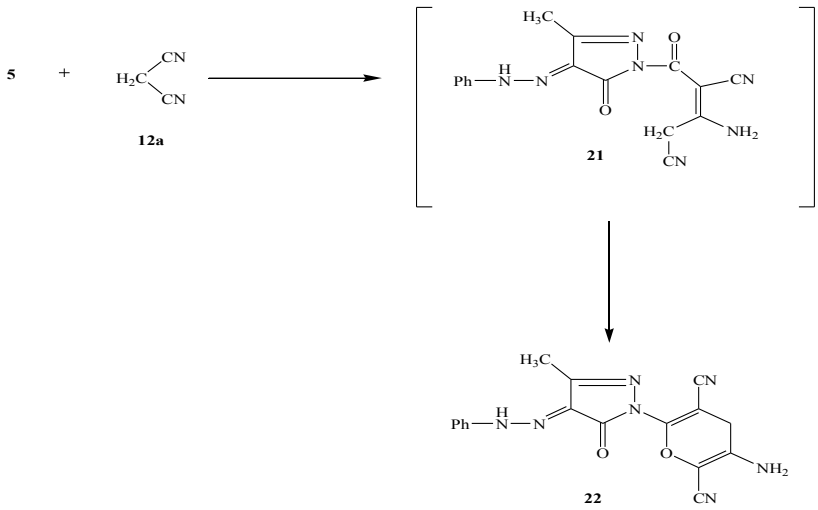
16



The reaction of compound **(5)** with benzenediazoniom chloride **(19)** at 0-5°C gave the phenylhydrazo derivative **(20).**



On the other hand , the reaction of compound **(5)** with malononitrile **(14a)** gave the pyrazole derivative **(22).** The reaction took place via the intermediate formation of **(21).** The ^{1}H NMR spectrum of **(22)** showed a singlet at δ 2.76 corresponding to CH_3, a singlet at δ 2.91 for the pyran CH_2 group, a multiplet at δ 7.28-7.36 for the phenyl protons and a singlet at δ 8.86 for the NH group.



All newly synthesized products were evaluated for antitumor activities, some of them showed high activities.

Effect on the growth of human tumor cell lines.

The effect of compounds 4-22 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 compounds were able to inhibit the growth of the human tumor cell lines in a dose-dependent manner. Compounds 13, 20 and 22 showed the better results, exhibiting an equivalent potency in all the three tumor cell lines, while compounds 4, 5, 16 and 18 showed only a moderated growth inhibitory effect. Comparing the activities of 15a and 15b it is observed that the two amino groups of 15a showed a weaker growth inhibitory effect towards the three cell lines while substitution of one NH_2 group by the OH as in 15b showed higher inhibitory effect towards the three cell lines.

Table 1: Effect of the newly synthesized products on the growth of three human tumor cell lines.

Compound	GI_{50} (δ M)		
	MCF-7	NCI-H460	SF-268
4	30 □± 0.6	17.3 ± 1.4	22.3 ±1.5
5	20 □± 0.4	24.3 ± 0.8	32 ± 0.8
7	70.6 ± 16.9	38.9 ± 10.8	50.8 ± 8.6
9	40.6 ± 12.6	32.6 ± 8.6	60.4 ± 14.8
11	35.4 ± 10.2	24.1 ± 0.8	18.9 ± 6.8
13	0.8 ± 0.6	1.5 ± 0.8	1.7 ± 0.6
15a	72.7 ± 17.5	40.2 ± 12.8	50.0 ± 9.01
15b	50.1 ± 0.7	23.2 ± 4.8	18.4 ± 1.8
16	22.0 ± 0.2	30.6 ± 1.4	38.4 ± 0.6
18	38.0 ± 1.8	44.0 ± 0.8	20.5 ± 1.1
20	1.1 ± 0.7	4.2 ± 0.8	2.4 ± 0.8
22	2.0 ± 0.2	1.6 ± 0.8	2.4 ± 0.6
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.

Material, methods and Reagents

Reagents: Fetal bovine serum (FBS) and L-glutamine, were from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma Chemical Co. (Saint Louis, USA). Samples: Stock solutions of compounds 4-22 were prepared in DMSO and kept at -20ºC. Appropriate dilutions of the compounds were freshly prepared just prior the assays. Final concentrations of DMSO did not interfere with the cell growth.

Cell cultures: Three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) were used. MCF-7 was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and NCI-H460 and SF-268 were kindly provided by the National Cancer Institute (NCI, Cairo, Egypt). They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 5% heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 □g/mL), at 37 ºC in a humidified atmosphere containing 5% CO_2. Exponentially growing cells were obtained by plating 1.5 X 10^5 cells/mL for MCF-7 and SF-268 and 0.75 X 10^4 cells/mL for NCI-H460, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all the experiments by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

Tumor cell growth assay: The effects of compounds 4-22 on the in vitro growth of human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the '*In vitro* Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B to assess cell growth [14]. Briefly, exponentially, cells growing in 96-well

Plates were then exposed for 48 h to five serial concentrations of each compound, starting from a maximum concentration of 150 lM. Following this exposure period adherent cells were fixed, washed, and stained. The bound stain was solubilized and the absorbance was measured at 492 nm in a plate reader (Bio-Tek Instruments Inc., Powerwave XS, Wincoski, USA). For each test compound and cell line, a dose–response curve was obtained and the growth inhibition of 50% (GI50), corresponding to the concentration of the compounds that inhibited 50% of the net cell growth, was calculated as described elsewhere [15]. Doxorubicin was used as a positive control and tested in the same manner.

EXPERIMENTAL

Analysis and measurements

The reagents used in this work were of Merck products. Spectroscopic grade solvents were used for spectral measurements. The carbon, hydrogen and nitrogen contents in each sample were performed at RSIC, CDRI Lucknow. The IR spectra were recorded on a Perkin-Elmer 783 spectrophotometer KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DRX 300 (300MHz) FT spectrometer in CD_3SOCD_3 using TMS as internal reference. Chemical shifts are reported in ppm downfield from TMS as internal reference. Elemental analyses were carried out in the Elementar VarioEL III instrument. Melting points were determined on a VEB Wagetechink Rapio PHMK05 instrument and are uncorrected.

Ethyl 6-imino-5-hydrazido-4-methylpyridazin-3-carboxylate (4)

To a dry solid of phenylhydrazoethyl acetoacetate [prepared by the addition of benzenediazonium chloride (1.40 g, 0.01 mol) to a cold solution 0-5 °C of ethyl acetoacetate (1.30 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (2.54 g, 0.03 mol) with continuous stirring] cyanoacetyl hydrazine (1.0 g, 0.01 mol) was added. The whole reaction mixture was heated in an oil bath at 140 °C for 20 min then left to cool. The remaining product was triturated with ethanol and the formed solid product was collected by filtration.

Pale yellow needles, m.p. 155 °C; IR cm^{-1}: 3450-3320 (NH_2, 2NH), 3045 (CH aromatic), 2987, 2889 (CH_2, CH_3), 1745, 1698 (2 C=O), 1660 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 1.36 (t, J = 7.02 Hz, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.20 (q, J = 7.02 Hz, 2H, CH_2), 4.57 (s, 2H, NH_2), 7.29-7.38 (m, 5H, C_6H_5), 8.22, 8.39 (2s, 2H, 2NH). Mol. Formula $C_{12}H_{17}N_5O_3$, Mol. Wt.: 315.33, Calculated C, 57.13; H, 5.43; N, 22.21, found C, 57.01; H, 5.32; N, 22.53.

3-(4-(2Phenylhydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)-3-oxopropanenitrile (5)

To a solution of phenylhydrazoethyl acetoacetate (2.34 g, 0.01mol) in absolute ethanol (40 mL) containing triethylamine (0.5 mL) cyanoacetyl hydrazine (1.0 g, 0.01mol) was added. The whole reaction mixture was heated under reflux for 3 h then left to cool. The solid product formed upon pouring into ice/water containing hydrochloric acid was collected by filtration.

Yellow crystals, m.p. 200-203 °C; IR cm^{-1}: 3430-3312 (NH_2, 2NH), 3042 (CH aromatic), 2980, 2877 (CH_2, CH_3), 1723, 1686 (2 C=O), 1663 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.78 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 7.23-7.43 (m, 5H, C_6H_5), 8.89 (s, 1H,, NH). Mol. Formula $C_{13}H_{11}N_5O_2$, Mol. Wt.: 269.26, Calculated C, 57.99; H, 4.12; N, 26.01, found C, 57.73; H, 4.32; N, 25.88.

Ethyl 5-(benzylideneaminocarbamoyl)-1, 6-dihydro-6-imino-4-methyl-1-phenylpyridazine-3-carboxylate (7)

To a solution of compound 4 (3.15 g, 0.01 mol) in 1, 4-dioxan (30 mL), benzaldehyde (1.06 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 was collected by filtration.

White crystals, m.p. 155-157 °C; IR cm^{-1}: 3441-3327 (2NH), 3055 (CH aromatic), 2987, 2893 (CH_2, CH_3), 1705, 1689 (2 C=O), 1666 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 1.16 (t, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.22 (q, 2H, CH_2), 5.95 (s, 1H, N=CH), 7.28-7.39 (m, 10H, $2C_6H_5$), 8.87, 9.73 (2s, 2H,, 2NH). Mol. Formula $C_{22}H_{21}N_5O_3$, Mol. Wt.: 404.16, Calculated C, 65.50; H, 5.25; N, 17.36, found C, 65.31; H, 5.32; N, 17.72.

Ethyl 5-(1-phenylethylideneaminocarbamoyl)-1, 6-dihydro-6-imino-4-methyl-1-phenylpyridazine-3-carboxylate (9)

To a solution of compound 4 (3.15 g, 0.01 mol) in 1, 4-dioxan (30 mL) acetophenone (1.20 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then poured onto ice water and the formed solid product was collected by filtration.

White crystals, m.p. 194-197 °C; IR cm^{-1}: 3448-3331 (2NH), 3053 (CH aromatic), 2989, 2890 (CH_2, CH_3), 1712, 1686 (2 C=O), 1660 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 1.13 (t, 3H, J = 6.99 Hz, CH_3), 2.80 (s, 3H, CH_3), 4.20 (q, 2H, J = 6.99 Hz, CH_2), 7.26-7.36 (m, 10H, $2C_6H_5$), 8.89, 9.70 (2s, 2H,, 2NH). Mol. Formula $C_{23}H_{23}N_5O_3$, Mol. Wt.: 417.46, Calculated C, 66.17; H, 5.55; N, 16.78, found C, 66.33; H, 5.42; N, 17.03.

6-(Phenylcarbaml)-2,3-dihydro-3-imino-5-methyl-2-phenylpyridazin-4-carbohydrazide (11)

To a solution of compound 4 (3.15 g, 0.01 mol) in dimethylformamide (40 mL), aniline (0.94 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then left to cool. The whole mixture was poured onto ice/water containing few drop of hydrochloric acid and the formed solid product was collected by filtration.

White crystals, m.p. 184-188 °C; IR cm^{-1}: 3436-3329 (3NH), 3066 (CH aromatic), 2992 (CH_3), 1710, 1689 (2 C=O), 1663 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.83 (s, 3H, CH_3), 7.26-7.39 (m, 10H, $2C_6H_5$), 8.56, 8.92, 9.70 (3s, 3H, 3NH). Mol. Formula $C_{19}H_{18}N_6O_2$, Mol. Wt.: 362.39, Calculated C, 62.97; H, 5.01; N, 23.19, found C, 63.30; H, 5.12; N, 23.03.

1, 6-Dihydro-6-imino-4-methyl-1-phenylpyridazine-3, 5-dicarbo-hydrazide (13)

To a solution of compound **4** (3.15 g, 0.01 mol) in 1, 4-dioxan (30 mL) hydrazine hydrate (0.1 g, 0.02 mol) was added. The reaction mixture was heated under reflux for 2 h then poured into ice water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.
White crystals, m.p. 210-214 °C; IR cm^{-1}: 3432-3315 ($2NH_2$, 3NH), 3050 (CH aromatic), 2986, 2891 (CH_2, CH_3), 1710, 1684 (2 C=O), 1663 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.89 (s, 3H, CH_3), 4.82, 5.41 (2s, 4H, $2NH_2$), 7.26-7.36 (m, 5H, C_6H_5), 8.86, 8.92, 9.61 (3s, 3H, 3NH). Mol. Formula $C_{13}H_{15}N_7O_2$, Mol. Wt.: 301.30, Calculated C, 51.82; H, 5.02; N, 32.54, found C, 52.05; H, 4.92; N, 32.39.

Ethyl 6-imino-1-phenyl-4-methyl-5-(3,5-diaminopyrazol-1-carbonyl)-pyridazine (15a) and ethyl 6-imino-1-phenyl-4-methyl-5-(3-amino-5-hydroxypyrazol-1-carbonyl)pyridazine (15b)

General procedure: To a solution of compound **4** (3.15 g, 0.01 mol) in 1,4-dioxan (30 mL) either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 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 into ice/water was collected by filtration.
15a: Yellow crystals, m.p. 164-166 °C; IR cm^{-1}: 3465-3326 ($2NH_2$, NH), 3033 (CH aromatic), 2990, 2883 (CH_2, CH_3), 1705, 1687 (2 C=O), 1665 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 1.15 (t, 3H, J = 7.02 Hz, CH_3), 2.85 (s, 3H, CH_3), 4.21 (q, 2H, J = 7.02 Hz, CH_2), 4.77, 4.90 (2s, 4H, $2NH_2$), 7.25-7.39 (m, 5H, C_6H_5), 8.72 (s, 1H, NH). Mol. Formula $C_{18}H_{19}N_7O_2$, Mol. Wt.: 381.39, Calculated C, 56.69; H, 5.02; N, 25.71, found C, 56.45; H, 4.89; N, 25.53.

15b: Yellow crystals, m.p. 230-235 °C; IR cm^{-1}: 3565-3326 (OH, NH_2, NH), 3043 (CH aromatic), 2986, 2891 (CH_2, CH_3), 1703, 1688 (2 C=O), 1663 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.91 (s, 3H, CH_3), 4.23 (q, 2H, J = 7.30 Hz, CH_2), 4.66 (s, 2H, NH_2), 7.29-7.38 (m, 5H, C_6H_5), 8.93, (s, 1H, NH), 10.25 (s, 1H, OH). Mol. Formula $C_{18}H_{18}N_6O_4$, Mol. Wt.: 382.14, Calculated C, 56.54; H, 4.74; N, 21.98, found C, 52.39; H, 4.62; N, 22.32.

3(4-(2-Phenylhydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)-3-oxo-a-benzalpropanenitrile (16) and 4-(2-Phenylhydrazono)-1-(coumarin-3-oyl)-3-methyl-1H-pyrazol-5-(4H)-one (18)

General procedure: To a solution of compound **5** (2.69 g, 0.01 mol) in 1,4-dioxan (40 mL) containing piperidine (0.50 mL) either benzadehyde (1.06 g, 0.01 mol) or salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 2 h then evaporated under vacuum. The remaining product was triturated with ethanol and the formed solid product was collected by filtration.

16: Orange crystals, m.p. 145-146 °C; IR cm^{-1}: 3468-3328 (NH), 3056 (CH aromatic), 2989, 2875 (CH_2, CH_3), 1699, 1686 (2 C=O), 1660 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.79 (s, 3H, CH_3), 6.22 (s, 1H, CH=C), 7.26-7.35 (m, 10H, $2C_6H_5$), 8.74 (s, 1H, NH). Mol. Formula $C_{20}H_{15}N_5O_2$, Mol. Wt.: 357.37, Calculated C, 67.22; H, 4.23; N, 19.60, found C, 67.01; H, 4.46; N, 19.82.

18: Orange crystals, m.p. 170-173 °C; IR cm^{-1}: 3463-3331 (NH), 3050 (CH aromatic), 2985, 2893 (CH_2, CH_3), 1689-1686 (3 C=O), 1662 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.81 (s, 3H, CH_3), 6.01 (s, 1H, coumarin H-4), 7.23-7.39 (m, 9H, C_6H_5, C_6H_4), 8.88 (s, 1H, NH). Mol. Formula $C_{20}H_{14}N_4O_4$, Mol. Wt.: 374.34, Calculated C, 64.17; H, 3.77; N, 14.97, found C, 64.03; H, 4.01; N, 14.68.

2-(2-Phenylhydrazono)-3-(4(2-phenylhydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)-3-oxopropanenitrile (20)

A cold solution of compound **5** (2.69 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (5 mL, 10 %) benzenediazonium chloride (prepared by adding sodium nitrite solution (0.7 g, 0.01 mol) to a cold solution (0-5 °C) of aniline (0.94 g, 0.01 mol) in concentrated hydrochloric acid (18 mL) with continuous stirring) was added with stirring. The reaction mixture was left at room temperature for 3 h and the formed solid product was collected by filtration. **20**: Reddish brown crystals, m.p. 145-147 °C; IR cm^{-1}: 3456-3343 (2NH), 3062 (CH aromatic), 2980, 2891 (CH_2, CH_3), 1693-1684 (2 C=O), 1665 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.80 (s, 3H, CH_3), 7.26-7.40 (m, 10H, $2C_6H_5$), 8.82, 9.01 (2s, 2H, 2NH). Mol. Formula $C_{19}H_{15}N_7O_2$, Mol. Wt.: 373.37, Calculated C, 61.12; H, 4.05; N, 26.26, found C, 61.34; H, 4.28; N, 26.08.

6-(4-(2-Phenylylhydrazono)-4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)-3-amino-4H-pyran-2,5-dicarbonitrile (22)

To a solution of compound **5** (2.69 g, 0.01 mol) in 1,4-dioxan (40 mL) containing triethylamine (0.50 mL), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 8 h then left to cool. The formed solid product upon pouring onto ice/water containing few drops of hydrochloric acid was collected by filtration. **22:** Yellow crystals, m.p. 248-251 °C; IR cm^{-1}: 3473-3342 (NH_2, NH), 3053 (CH aromatic), 2979, 2866 (CH_2, CH_3), 2227, 2221 (2 CN), 1689 (C=O), 1660 (exocyclic C=N). ^1H NMR (400 MHz, CD_3SOCD_3): 2.76 (s, 3H, CH_3), 2.91 (s, 2H, pyran CH_2), 4.88 (s, 2H, NH_2), 7.28-7.36 (m, 5H, C_6H_5), 8.86 (s, 1H, NH). Mol. Formula $C_{17}H_{13}N_7O_2$, Mol. Wt.: 347.33, Calculated C, 58.79; H, 3.77; N, 28.23, found C, 58.66; H, 3.96; N, 28.09.

CONCLUSION

In conclusion we have developed a convenient method for the synthesis of novel pyridazine and pyrazole derivatives in excellent yields. The antitumor activities of the newly synthesized products against the three cell lines namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268)

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