Sameh A. Rizk,[a] Salwa S. Abdelwahab,[a,b]* and Eman Elrazaz[c]

[a]Department of Chemistry, Faculty of Science, Ain Shams University, Cairo 11566, Egypt
[b]Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt, Cairo 11835, Egypt
[c]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt
*E-mail: salwa_elsayed@ymail.com

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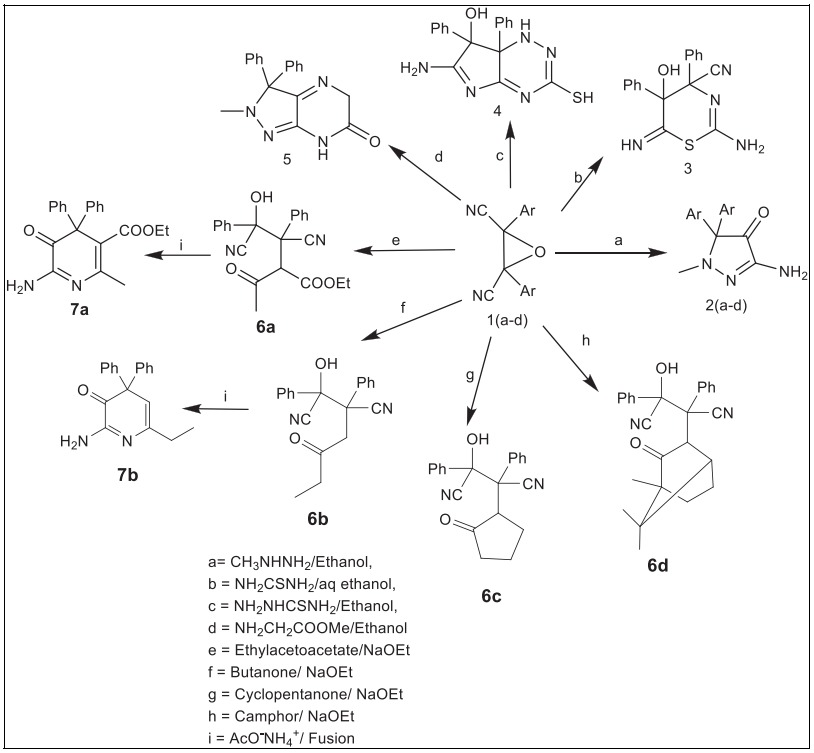

2,3-Diaryloxirane-2,3-dicarbonitriles have employed in heterocyclic synthesis in many organic reactions. Authors highlight its use as intermediate in the synthesis of various organic compounds through the reaction with different nitrogen nucleophiles as methyl hydrazine, thiourea, thiosemicarbazide, methylglycinate, and others to furnish new heterocyclic derivatives. They are also used as key starting materials to construct some important heterocycles. Structures of all newly synthesized products are substantiated by studying their micro analytical and spectral data. Some of newly synthesized compounds were evaluated for their *in vitro* cytotoxic effects against a panel of three human tumor cell lines, namely, Hep-G2, Hela, and MCF-7. Most of the newly synthesized compounds (**1a**, **2a**, **2d**, **3**, **4**, **5**, **6a**, **6c**, **6d**, **7a**, and **7b**) inhibited cell proliferation with IC_{50} values in range of 0.52–5.21 μM. For activity against HepG2 cell line, compounds **5**, **6a**, **6d**, and **7b** emerged as the most active members. The Hela cell line showed highest sensitivity toward compounds **2a**, **2d**, and **6c** whereas compounds **2d** and **6c** showed the highest inhibitory activity against MCF-7 cell line.

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INTRODUCTION

2,3-Diaryloxirane-2,3-dicarbonitriles is a versatile, convenient, and key synthetic intermediate [1–3]. The target intermediate with substituted pyrazole and azolehydrazone moieties has received tremendous attention and reported diverse synthetic methods in the previous articles; example pyrazoles and their derivatives represent an important class of compounds that are used extensively in the pharmaceutical and agrochemical industries [4], herbicide fluazolate [5], cyclooxygenase-2 (COX-2) inhibitor celecoxib [6], fungicide pyraclostrobin [7], and e HIV-1 reverse transcriptase inhibitor PNU-32945 [8].

They also have anticancer effects [9]. Literature review reveals that these derivatives exhibit diverse pharmacological activities [10–12] such as potential cytotoxic agents.

Pyrazolopyrazines derivatives are an interesting variety of heterocyclic compounds of great importance. They are used as bone metabolism improvers, anti-inflammatory, anti-aggregation of blood platelets, and antitumoral agents [13,14]. Nitrogen-containing heterocycles such as pyridines and their derivatives are one of the most prevalent heterocycles found in natural products. It has great synthetic interest because of its high cytotoxicity against cancer cell lines. It constitutes an important class of compounds in the field of agricultural and medicinal chemistry [15–17]. Pyridines are among the most prevalent heterocyclic structural units in pharmaceutical and materials science [18]. Therefore, because of their broad spectrum of the biological activities, we decided to use 2,3-diaryloxirane-2,3-dicarbonitriles as a key starting materials for the idea of preparing some innovative heterocyclic compounds [19].

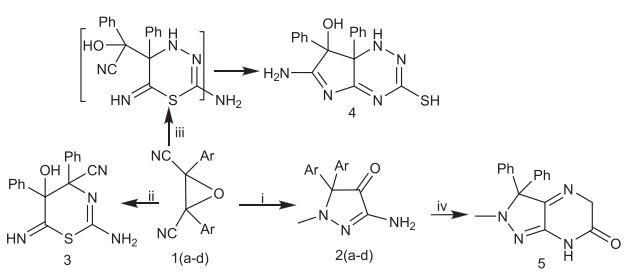
RESULTS AND DISCUSSION

Chemistry. The synthetic route of *E*-1-(4-aroyl) 2-oxirane carboxylic acid was synthesized as previously described [20]. Small systematic chemical variations were made by introducing different functional groups at oxirane derivatives by replacing the carbonyl and carboxylic groups with dicyano and aryl groups. Compounds based on modifications at the dicyano an aryl ring (**1**) were synthesized as described [2]. Herein, authors reported the behavior of 2,3-diaryloxirane-2,3-dicarbonitriles **1** because of different kinds of its electrophilic centers that can be allowed to react with simply binucleophiles, for example, methyl hydrazine, thiourea, thiosemicarbazide, and active methylene to afford some important heterocyclic compounds (Scheme 1). An equimolar mixture of compounds $\mathbf{1_{a–d}}$ (0.01 mol) and the methyl hydrazine, (0.01 mol) in 50-mL ethanol was refluxed for 6 h.

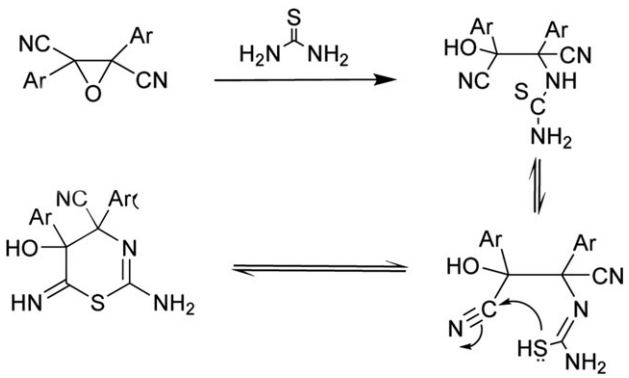
The solid that separated after cooling was filtered off, washed with petroleum ether (bp 40–60°C), dried, and then crystallized from ethanol [9] that afforded amino-2-methyl-4-oxo-4,5-dihydro-pyrazole derivatives (**2a–d**). In one pot reaction of 2,3-diaryloxirane-2,3-dicarbonitrile **1a** with thiourea in boiling aq ethanol afforded\derivative **3**. A reasonable mechanism for the synthesis of compound **3** is revealed in (Scheme 2). In the same manner, reaction of **1a** with thiosemicarbazide afforded the pyrrolo[2,3-*e*] triazine derivative **4** *via* aminothiadiazine heterocyclic interconversion (Scheme 3). Moreover, when the isomers **2**a were treated with methylglycinate afforded the oily products **5a**.

2,3-Diaryloxirane-2,3-dicarbonitrile ($\mathbf{1_{a–d}}$) were also conducted to react with different carbon acids, for example, ethylacetoacetate, ethylmethylketone, cyclopentanone, and/or camphor in the presence of sodium ethoxide; these reactions afforded the adducts $\mathbf{6_{a–d}}$. The isolated

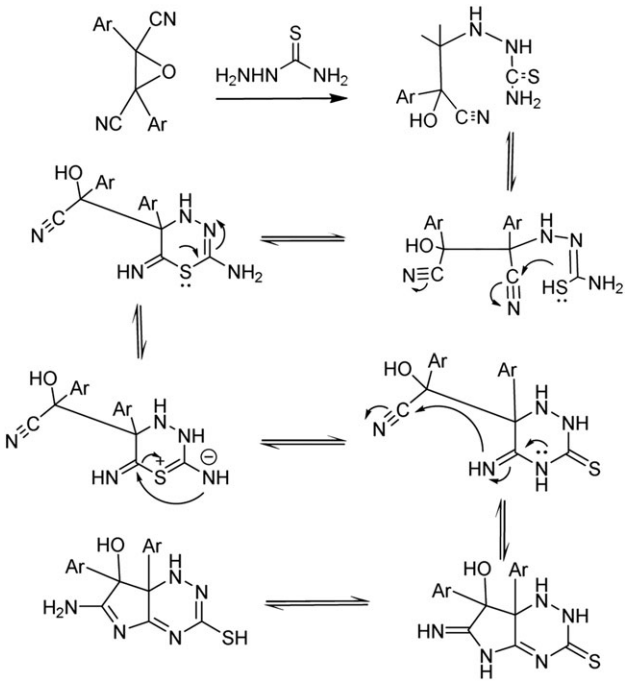
Scheme 1. i = CH3NHNH2/Ethanol, ii = NH2CSNH2/aq ethanol, iii = NH2NHCSNH2/Ethanol, iv = NH2CH2COOMe/Ethanol



Scheme 2. Outline the proposal mechnism of Compund 3



Scheme 3. Outline the proposal mechnism of Compund 4



adducts $\mathbf{6_{a,b}}$ were cyclized by boiling in molten ammonium acetate to afford the target 3-pyridone derivatives **7a**,**b**. The challenge of organic synthesis was the isolation of pure one of the tautomer of 3-pyridone. In fact, it was reported that it is impossible for the presence of the lactam form of the 3-hydroxypyridine and the tautomer is present 100% phenolic group in position 3, that is, 2-pyridone and 4-pyridone are present in lactam–lactim dynamic equilibrium but 3-pyridone is not formed. Authors achieved isolation of 100% of 3-pyridones **7** (Scheme 4).

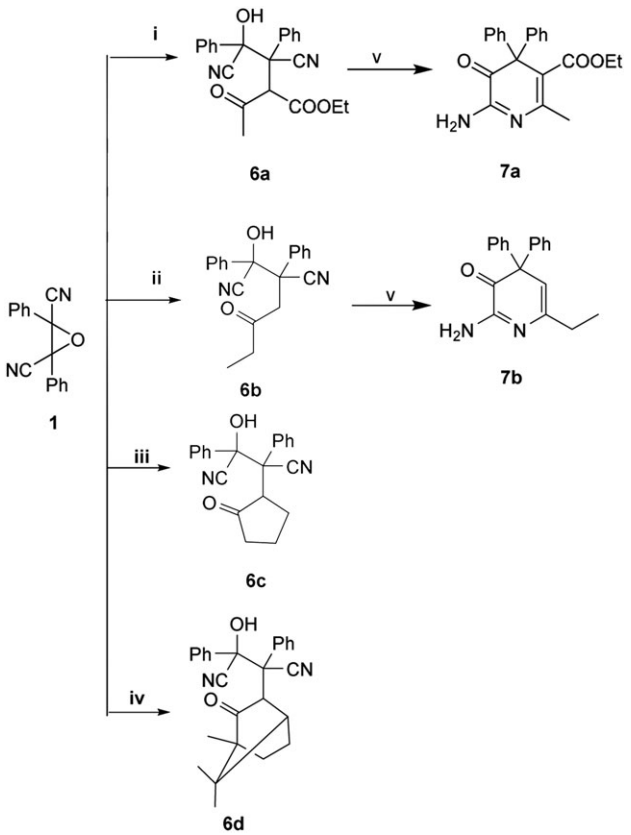
Cytotoxicity of the synthesized compounds. The cytotoxicity activity of target compounds (**1a**, **2a**, **2d**, **3**, **4**, **5**, **6a**, **6c**, **6d**, **7a**, and **7b**) against a panel of three human tumor cell lines, namely, Hep-G2, Hela, and MCF-7, was measured by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Erlotinib was selected as standard drug. The IC_{50} values were summarized in Table 1. As for activity against HepG2 cell line, all the compounds inhibited cell proliferation with IC_{50} values in range of 0.52–5.21 μM. It was observed that among the synthesized compounds, compounds **5**, **6a**, **6d**, and **7b** displayed much higher antiproliferation activity than standard erlotinib against cell line. Compounds **2a** and **7a** showed good inhibitory activity against Hep-G2 cell line more than erlotinib itself. Compounds **3** and **6c** displayed activity comparable with erlotinib. Compounds **1**, **2d**, and **4** revealed the lowest cytotoxic activity inhibitory activity against Hep-G2 cell line. The Hela cell line showed highest sensitivity toward compounds **2a**, **2d**, and **6c** whereas compounds **2d** and **6c** showed the highest inhibitory activity against MCF-7 cell line (Fig. 1).

Table 1

In vitro anticancer activity (IC_{50}) of the compounds expressed in μM.

Compd.	Hep-G2 IC_{50} μM	Hela IC_{50} μM	MCF-7 IC_{50} μM
1	5.21	5.64	4.46
2a	1.19	2.18	3.85
2d	4.17	1.58	2.89
3	2.89	3.25	4.13
4	4.02	22.65	25.83
5	0.68	9.65	11.58
6a	0.52	4.76	6.74
6c	3.12	2.06	2.94
6d	0.87	3.12	3.67
7a	1.92	6.56	6.88
7b	0.59	8.96	8.13
Erlotinib	2.97	1.95	2.53

Scheme 4. i= Ethylacetoacetate/NaOEt; ii= Butanone/NaOEt; iii= Cyclopentanone/ NaOEt; iv= Camphor/NaOEt; v= $AcO^-NH_4^+$/Fusion



QSAR study. The QSAR study was performed using Discovery Studio 2.5 Software. The training set was composed of the 10 synthesized compounds (**1**, **2a**, **2d**, **3**, **4**, **5**, **6a**, **6d**, **7a**, and **7b**). The internal validation for the QSAR model used employed leave one-out cross-validation, external validation using test set composed of erlotinib and one of the synthesized compounds (**6c**), as well as residuals between the predicted and experimental activity of the training set and test set.

"Calculate Molecular Properties" module was used in calculating the 2D molecular properties as well as energies of highest occupied and lowest unoccupied molecular orbitals [21] of each of the training set compounds were determined. 2D Descriptors involved AlogP, fingerprints, molecular properties, surface area and volume, molecular properties as molecular formula, molecular composition, molecular weight, molecular solubility, pKa, molecular property counts as HBA_Count, HBD_Count, Num_Aromatic rings, and Num_Rotatable bonds, and topological descriptors [22].

Genetic function approximation model was employed to search for optimal QSAR models that combine high quality binding pharmacophores with other molecular descriptors and being capable of correlating bioactivity variation across the used training set collection. The trials were held while changing the independent properties till the best model with the least variables was obtained.

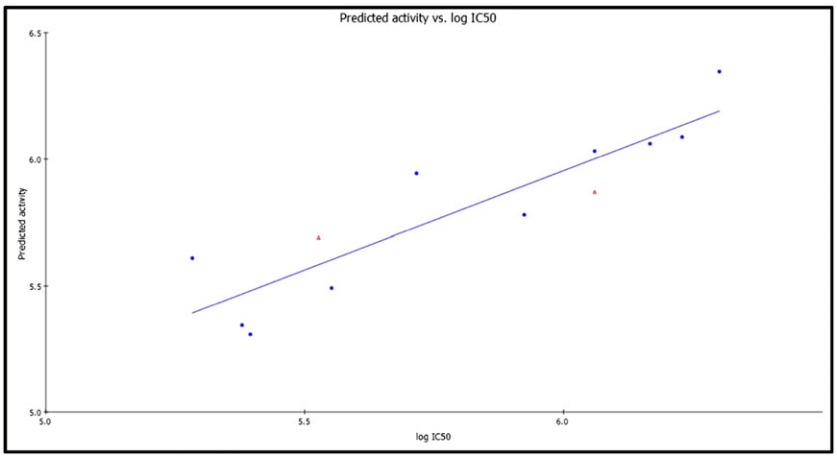


Figure 1. Predicted versus experimental $-\log IC_{50}$ values of the test set and training set according to Equation (1). (r^2 = 0.830). [Color figure can be viewed at wileyonlinelibrary.com]

QSAR model was validated employing leave one-out cross-validation, r^2 (squared correlation coefficient value), and external validation using compounds (erlotinib, **6c**), as well as residuals between the predicted and experimental activity of the training and test set and the results are displayed in Table 2.

QSAR study results.

The following equation represents our best performing QSAR models.

$$-\log IC_{50} = 5.7158 + 0.10457*\text{VSA Atomic Areas} - 3.2728*\text{Molecular Fractional Polar Surface Area} \quad [2]$$

$-\log IC_{50}$: (the negative logarithmic value of the concentration required to produce 50% inhibition of HepG2).

Table 2

Experimental activity of the synthesized compounds against the predicted activity according to the model equation.

Compd.	Experimental activity ($-\log IC_{50}$)	Predicted activity ($-\log IC_{50}$)	Residual
1	5.28	5.60	−0.32
2a	5.92	5.78	0.14
2d	5.37	5.34	0.03
3	5.55	5.49	0.06
4	5.39	5.31	0.08
5	6.16	6.06	0.10
6a	6.30	6.34	−0.04
6d	6.06	6.03	0.03
7a	5.72	5.94	−0.22
7b	6.22	6.09	0.13
6c[a]	6.06	5.87	0.19
Erlotinib[a]	5.53	5.69	−0.16

[a](**6c**, **erlotinib**) were used for external validation through calculating its predicted activity from the QSAR model constructed using the training set.

Abbreviations used: VSA_Atomic Areas is a molecular property that calculates the atomic surface area for each atom in the molecule.

Molecular Fractional Polar Surface Area is the ratio of the polar surface area divided by the total surface area [23–25].

Validation of QSAR. QSAR model was validated employing leave one-out cross-validation, and calculating the predicted activity for test set through running as an external test compounds on the constructed QSAR model using "Calculate Molecular Properties" protocol and selecting the model from the "Other" set, as well as the residuals between the experimental activities and those predicted by the QSAR study, are presented in Table 1.

The regression values were as follows: r^2 = 0.830, q^2 = 0.646, and least-squared error = 0.1795.

It should be noted that the predicated IC_{50} by our QSAR model were very close to those experimentally observed, indicating that this model can be safely applied for predication of more effective hits having the same skeletal framework.

EXPERIMENTAL

All chemicals and solvents, purchased from Sigma-Aldrich (Egyptian branch, Egyptian International Center for Import, Cairo, Egypt), were used without further purification. All melting points are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analyses were carried out at the Micro analytical Center, National Research Center, Cairo, Egypt By Elementar Viro El Microanalysis; IR spectra (KBr) were recorded on infrared spectrometer FT-IR 400D using OMNIC program and are reported frequency of absorption in terms of cm^{-1} and ^1H NMR spectra recorded on a Bruker spectrophotometer at 400 MHz using

tetramethylsilane as internal standard and with residual signals of the deuterated solvent δ = 7.26 ppm for $CDCl_3$ and δ 2.51 ppm for DMSO-d6. ^{13}C NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals δ = 77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. Referenced to solvent signals δ = 77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 e.v using the electron ionization technique. Homogeneity of all compounds synthesized was checked by thin-layer chromatography.

General procedure for the preparation of compound 1 in literature [2]. General procedure for the preparation of the compounds 2. An equimolar mixture of compound **1a–d** (2.26–3.14 g 0.01 mol) and methyl hydrazine, thiourea, thiosemicarbazide, and methylglycinate (0.01 mol) in 50-mL boiling ethanol. The reaction mixture was refluxed for 6 h. The solid that separated after cool was filtered off, washed by petroleum ether (bp 40–60°C), dried, and then crystallized from the proper solvent to afford compounds **2a–d**.

3-Amino-5,5-diphenyl-2-methyl-4-oxo-4,5-dihydropyrazole (2a). Yield 73%. Mp 230–232. IR ν_{max} cm^{-1}: 3379, 3214 (NH), 3052 (CH_{Ar}), 1711 (CO). ^1H NMR (DMSO): δ ppm s (3.45, 3H, CH_3), m (7.38–7.56 10H, ArH), bs (11.2, 2H, NH exchangeable). ^{13}C NMR δ 55.6 (CH_3), 112 (2C), 120.4 (2CH), 129.6 (2CH), 130.5 (CH), 131.5 (CH), 132.3 (2CH), 134.8 (CH), 137.4 (CH), 143.4 (C), 168.0 (C), 190.2 (C) and *Anal*. Calcd for $C_{16}H_{15}N_3O$ (265): %C, 72.45; H, 5.66; N, 15.84; found, %C, 72.38; H, 5.58; N, 15.80. MS: *m/z* 265 [M^+.], 158 [3-amino-5-phenylpyrazole moiety] $^+$, 103, 85, 71, 42.

3-Amino-5,5-bis(2-chlorophenyl)-2-methyl-4-oxo-4,5-dihydro-pyrazole (2b). Yield 77%. Mp 246–248. IR υ_{max} cm^{-1}: 3320, 3276 (NH), 3049 (CH_{Ar}), 1718 (CO). ^1H NMR (DMSO): δ pp 3.45 (s, 3H, CH_3), 7.43–7.82 (m, 8ArH), 12.1 (s, 2H, NH, exchangeable). ^{13}C NMR δ 56.8 (CH_3), 114 (2C), 121.6 (2CH), 128.4 (2CH), 130.8 (CH), 131.9 (CH), 133.6 (2CH), 134.6 (CH), 136.9 (CH), 143.5 (C), 168.4 (C), 190.1 (C) and *Anal*. Calcd for $C_{16}H_{13}N_3OCl_2$ (334): %C 57.48, H 3.89, N 12.50, Cl 21.25; found, %C 57.35, H 3.65, N 12.07, Cl 21.02. MS: *m/z* 306 [M^+. −CO], 283.5 [M^+. −Cl], 262 [diaryl ketene ion entity], 234, 193.5 [3-amino-5-(2-chlorophenyl) pyrazole]$^+$, 137.5, 70, 56.

3-Amino-5,5-bis(4-chlorophenyl)-2-methyl-4-oxo-4,5dihydropyrazole (2c). Yield 74%. Mp 238–240. IR υ_{max} cm^{-1}: 3307, 3264 (NH), 3049 (CH_{Ar}), 1719 (CO). ^1H NMR (DMSO): δ ppm s (3.65, 3H, CH_3), m (7.2–7.7, 8H, ArH), s (12.3, 2H, NH exchangeable), and *Anal*. Calcd for $C_{16}H_{13}N_3OCl_2$ (334): %C 57.48, H 3.89; N, 12; 50, Cl, 21.25. Found: %C 57.37; H, 3.79; N 12.12; Cl 21.08. MS: *m/z* 334 [M^+.], 298.5 [M—Cl], 234 [diarylmethine]$^+$, 193 [3-amino-5(4-chlorophenyl)pyrazole]$^+$, 137.5, 70.

3-Amino-5,5-bis(furan-2-yl)-2-methyl-4-oxo-4,5-dihydropyrazole (2d). Yield 65%. Mp 182–184. IR υ_{max} cm^{-1}: 3320, 3276 (NH), 3080 (CH_{Ar}), 1718 (CO). ^1H NMR (DMSO): δ ppm s (3H, CH_3), m (6.82–7.12, 6H, ArH), s (11.8, 12.9, 3H, NH exchangeable). ^{13}C NMR δ 119.4 (2C), 131.6 (CH), 132.2 (CH), 137.2 (CH), 137.9 (CH), 141.6 (CH), 141.9 (CH), 143.5 (C), 168.4 (C), 190.1 (C) and *Anal*. Calcd for $C_{12}H_{11}N_3O_3$ (245): %C 58.77; H 4.48; N 17.14; found, %C, 58.40; H 4.15; N 16.95. MS: *m/z* 245 [M^+.], 203 [M^+. −CO], 176, 160, 93, 70.

General procedure for 2-amino-5-hydroxy-6-imino-4,5-diphenyl-5,6-dihydro-4*H*-1,3-thiazine-4-carbonitrile (3). A grinding mixture of **1a** (2.26 g; 0.01 mol) with thiourea (1 g; 0.015 mol) and small amount of boiling ethanol (5 mL), after 15 min, a white precipitate was formed, filtered off, dried, and recrystallized from dioxane to give compound **3**.

Yield 65%. Mp 284–286. IR υ_{max} cm^{-1}: 3278 (NH), 3050 (CH_{Ar}), 1674 (CO). ^1H NMR (DMSO-d_6): δ ppm 7.41–7.68 (m, 10H, ArH), 8.8 (s, 4H, NH exchangeable). ^{13}C NMR δ 56.3 (CH_3), 113.6 (2C), 122.1 (2CH), 128.0 (2CH), 129.9 (CH), 131.3 (CH), 132.6 (2CH), 135.6 (CH), 139.6 (CH), 141.5 (C), 167.4 (C), 190.2 (C) and *Anal*. Calcd for $C_{16}H_{14}N_4O_4S$ (358): %C, 53.63; H, 3.91; N, 15.64; S, 8.93; found, %C, 53.50; H, 3.85; N, 15.56; S, 8.87. MS: *m/z* 358 [M^+.], 330, 284, 204.

General procedure for the preparation of pyrrolo[2,3-*e*] triazine derivative 4. An equimolar mixture of compound **1** (2.26 g; 0.01 mol) and thiosemicarbazide (0.01 mol) in 50-mL boiling ethanol. The reaction mixture was refluxed for 4 h. The solid that separated after cool was filtered off, dried, and then recrystallized from ethanol to give the following.

6-Amino-3-mercapto-7,7a-diphenyl-7,7a-dihydro-1H-pyrrolo[2,3-e][1,2,4]triazin-7-ol (4). Yield 70%. Mp 192–194. IR υ_{max} cm^{-1}: 3543 (OH), 3287 (NH), 3052 (CH_{Ar}), 2860 (SH), 1629 (C═N). ^1H NMR (DMSO-d_6): δ ppm 7.16–7.72 (m, 10H, ArH), 5.6, 8.6, 13.2 (s, 1H exchangeable). ^{13}C NMR δ 66.3 (C), 98.6 (C), 125.8 (2CH), 126.0 (CH), 126.9 (2CH), 127.8 (CH), 128.4 (2CH), 128.6 (2CH), 144.4 (C), 147.5 (C), 165.2 (C), 166.5 (C), 180.2 (C). *Anal*. Calcd for $C_{17}H_{15}N_5OS$ (337): %C, 60.53; H, 4.45; N, 20.77; S 9.49. Found: %C, 60.48; H, 4.40; N, 20.71;S, 9.45. MS: *m/z* 337 [M^+.] 309, 264, 182, 155.

General procedure for the preparation of 3,3-diphenyl-2-methyl-6-oxo-1,2,7-trihydro-pyrazolo[3,4-*b*] *pyrazine 5*. A mixture of **2a** (2.5 g; 0.01 mol) and methylglycinate (1.1 mL, 0.01 mol) in 50-ml boiling ethanol. The reaction mixture was refluxed for 4 h; the solid that separated after cool was filtered off, dried, and then recrystallized from dioxane to give compound **5a**:

Yield 70%. Mp 164–166. IR υ_{max} cm^{-1}: 3317, 3256 (NH), 3050 (CH_{Ar}), 1668 (C═O). ^1H NMR (DMSO-d_6): δ ppm 3.65 (s, 3H, CH_3), 6.8 (s,1H, CH_{py}), 7.21–7.70 (m, 10H, ArH), 6.4, 9.7 (s, 2H, NH exchangeable). ^{13}C NMR δ 44.6 (CH_3), 91.6 (C), 96.1 (C), 126.1 (2CH),

128.3 (4C), 129.3 (5CH), 134.4 (2C), 139.9 (2C), 145.4 (CH), 150.4 (C). *Anal*. Calcd for $C_{18}H_{16}N_4O$ (304): %C, 71.05; H, 5.26; N, 18.42; found, %C, b70.80; H, 5.08; N, 18.28. MS: *m/z* 304 [M^+.], 167, 123, 136 [pyrazolopyrazine moiety].

General procedure for the preparation of the compounds 6. An equimolar amount of compounds **1a**–**d** (2.26–3.14 g, 0.01 mol) and active methylene precursor, for example, ethylacetoacetate, ethylmethylketone (MEK), cyclopentanone and/or cyclohexanone (0.01 mol), sodium ethoxide (8 mL), and ethanol (50 mL), was refluxed for 3 h and leave overnight 3 days. The reaction mixture was poured into ice/HCl, filtered the crude product, and washed by petroleum ether (bp 40–60°C) and then crystallized to give compounds (**6a**–**d**).

Ethyl 2-acetyl-3,4-dicyano-4-hydroxy-3,4-diphenylbutanoate (6a). Yield 65%. Mp 146–178. IR υ_{max} cm^{-1}: 1670, 1745 (CO), 2222 (CN), 3364 (OH). ^{1}H NMR (DMSO): δ ppm 1.12 (t, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.92 (q, 2H, CH_2), 4.50 (s, 1H, CH $(CO)_2$)] 5.5 (s, 1H, OH exchangeable). 7.44–7.73 (m, 10H, ArH). ^{13}C NMR δ 15.1 (CH_3), 27.6 (CH_3), 36.6 (C), 54.7 (CH), 60.3 (C), 77.5 (C), 118.1 (C), 121.2 (C), 125.9 (3CH), 126.0 (CH), 126.2 (2CH), 128.3 (2CH), 128.8 (2CH), 145.3 (C), 148.5 (C), 169.8 (C), 203.2 (C). *Anal*. Calcd for $C_{22}H_{20}N_2O_4$: (376) %C, 70.02; H, 5.31; N, 7.44. Found: %C, 69.90; H, 5.25; N, 7.45. MS: *m/z* 376 [M^+].

2-Hydroxy-3-(2-oxobutyl)-2,3-diphenylsuccinonitrile (6b). Yield 63%. Mp 130–132. IR υ_{max} cm^{-1}: 1691 (CO), 2220 (CN), 3545 (OH). ^{1}H NMR (DMSO): δ ppm 1.2 (t, 3H, CH_3), 2.47 (s, 2H, CH_2), 3.51 (q, 2H, CH_2), 5.2 (s, 1H, OH exchangeable), 7.44–7.83 (m, 10H, ArH). ^{13}C NMR δ 7.9 (CH_3), 12.6 (C), 35.7 (C), 36.6 (2C), 80.3 (C), 118.1 (C), 125.9 (3CH), 126.1 (3CH), 128.4 (2CH), 128.8 (2CH), 145.5 (C), 148.5 (C), 210.7 (C). *Anal*. Calcd for $C_{20}H_{18}N_2O_2$ (318): %C, 75.47; H, 5.66; N, 8.80. Found: %C, 75.42; H, 5.60; N, 8.73. MS: *m/z* 318 [M^+].

2-Hydroxy-3-(2-oxocyclopentyl)-2,3-diphenylsuccinonitrile (6c). Yield 67%. Mp 122–124. IR υ_{max} cm^{-1}: 1700 (CO), 2220 (CN), 2950 (CH_{Ali}), 3477 (OH). ^{1}H NMR (DMSO-d_6): δ ppm 1.81–2.01 (m, 6H, $CH_{cyclopent}$), 2.3 (s, 1H, $CH_{cyclopent}$), 6.30 (br. s, 1H exchangeable), 7.09–7.78 (m, 10H, ArH). ^{13}C NMR δ 14.3 (C), 20.8 (C), 37.7 (C), 53.1 (C), 41.2 (C), 78.1 (C), 118.1 (C), 121.6 (C), 125.5 (CH), 125.9 (4CH), 128.1 (CH), 128.5 (4CH), 139.2 (C), 146.1 (C), 218.5 (C). *Anal*. Calcd for $C_{21}H_{18}N_2O_2$ (330): %C, 76.36; H, 5.45;N, 8.4. Found: %C, 76.29; H, 5.39; N, 8.42; MS: *m/z* 330[M^+.].

1,2-Dicyano-1,2-diphenyl-3-(camphor-2-yl)propanol (6d). Yield 68%. Mp 152–154. IR υ_{max} cm^{-1}: 1795 (CO), 2217 (CN), 3050 (CH_{Ar}), 3370 (OH). ^{1}H NMR (DMSO): δ 1.10 (s, 3H, CH_3a), 1.21 (s, 3H, CH_3b), 1.80 (m, 5H, $CHCH_2CH_2$, camphormoiety), 1.91 (s, 3H, CH_3), 2.71 (dd, 1H, CHcamph), 5.6 (s, 1H, OH exchangeable), 7.11–7.75 (m, 10H, ArH). ^{13}C NMR δ 10.1 (CH_3), 19.4 ($2CH_3$), 29.3 (C), 30.2 (C), 33.8 (CH), 39.9 (C), 46.5 (C), 47.5 (CH), 59.2 (C), 78.5 (C), 118.0 (C), 121.7 (C), 125.9 (4CH), 128.1 (2CH), 128.5 (4CH), 139.2 (C), 146.1 (C), 222.6 (C). *Anal*. Calcd for $C_{26}H_{26}N_2O_2$ (398): %C, 78.39; H, 6.53; N, 7.03; found, %C, 78.30; H, 6.54; N, 7.00. MS: *m/z* 398 [M^+.].

General procedure for the preparation of the compounds 7. A mixture of **6a**,**b** (0.01 mol), ammonium acetate (2.31 g, 0.03 mol) was heated in an oil bath at 150°C for 2 h; the mixture was poured onto water after cooling. The solid that separated after cool was filtered off, dried, and then crystallized from the proper solvent to give compounds (**7a**,**b**).

Ethyl-6-amino-2-methyl-5-oxo-4,4-diphenyl-4,5-dihydropyridine-3-carboxylate (7a). Yield 65%. Mp 176–178. IR υ_{max} cm^{-1}: 1613 (C═N), 1685 (CO), 3272 (NH). ^{1}H NMR (DMSO-d_6): δ ppm 2.02 (m, 6H, H-cyclopent), 7.44–7.73 (m, 10H, ArH), 9.2 (s, 1H, NH exchangeable). ^{13}C NMR δ 14.2 (CH_3), 22.0 (CH_3), 52.7 (C), 61.7 (C), 121.0 (C), 126.2 (2CH), 128.5 (4CH), 129.5 (4CH), 133.8 (C), 139.5 (C), 155.0 (C), 158.0 (C), 167.2 (C), 199.6 (C). *Anal*. Calcd for $C_{20}H_{18}N_2O$ (302): %C, 79.47; %H 5.96, %N 9.27; found, %C 79.42, %H 5.93, %N; 9.25. MS: *m/z* 302 [M^+], 197.

2-Amino-6-ethyl-4,4-diphenylpyridin-3(4*H*)-one (7b). Yield 74%. Mp 210–212. IR υ_{max} cm^{-1}: 1630 (C═N), 1691 (CO), 3185 (NH). ^{1}H NMR (DMSO-d_6): δ ppm 2.2 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.44–7.83 (m, 10H, ArH), 9.4 (s, 1H, NH exchangeable). ^{13}C NMR δ 12.9 (CH_3), 36.3 (C), 52.7 (C), 115.7 (CH), 126.2 (2CH), 128.2 (4CH), 129.2 (4CH), 133.8 (2C), 144.6 (C), 158.0 (C), 199.6 (C). *Anal*. Calcd for $C_{20}H_{18}N_2O_2$ (318): %C, 75.47; H, 5.66; N, 8.80.l found: %C, 75.43; H, 5.60; N, 8.73. MS: *m/z* 318 [M^+], 275, 213.

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