Synthesis of Novel Pyrazole Derivatives as Antineoplastic Agent

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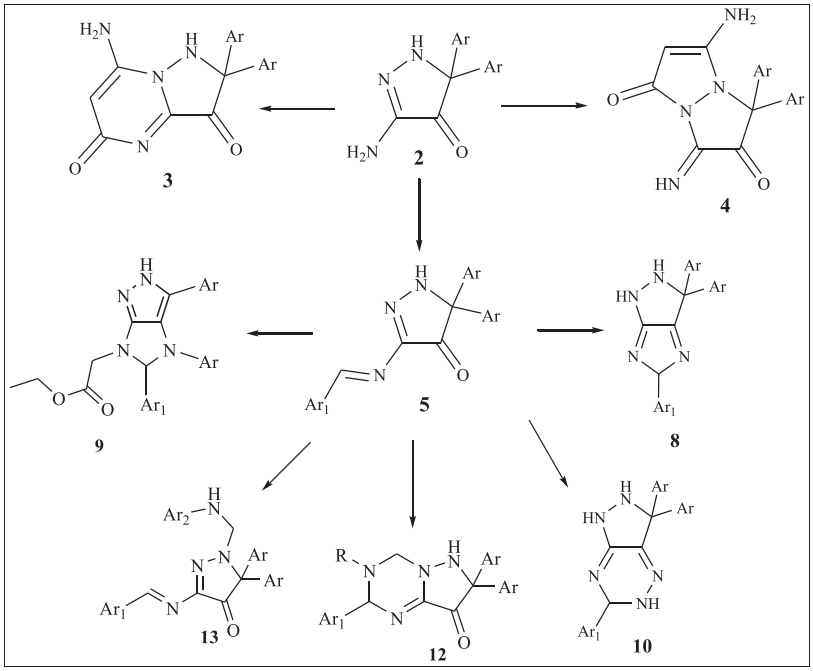

Anticancer evaluation of pyrazole **2** and Schiff base **5** is reported. Synthesis of some important heterocyclic compounds via 2,3-diaryloxirane-2,3-dicarbonitrile **1**, pyrazole **2**, and Schiff base **5** with different nitrogen nucleophiles afforded new routes for synthesized fused heterocyclic derivatives. These compounds can be used as a key starting materials to synthesize some important imidazolo-[4,5-*c*]pyrazole, pyrazolo[3,4-*e*]1,2,4-triaging, imidazolo[3,2-*b*]pyrazole, and pyrazolo-pyrazine, as anticancer reagents showed good results at optimum conditions (400–500 ppm), particularly the bridge head nitrogen compounds, and could be used to improve them. Electromeric effect of the halogen atom in the aryl moieties can be controlled upon the rate of reaction and the yield of the product. The structure of the synthesized new compounds would be characterized by elemental and spectral data.

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INTRODUCTION

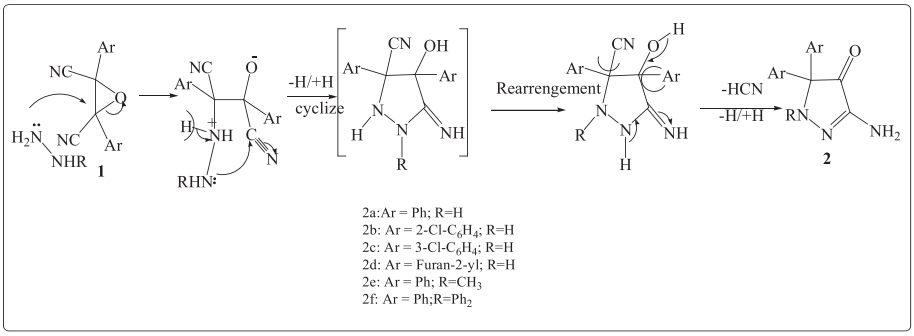
Pyrazole is considered as significant tender of heterocyclic nitrogen compound [1–3], in which derivatives show a widespread of biological activities such as anticancer [4,5], anti-inflammatory [6], antifungal [7,8], antiproliferative [9], insecticidal [10], plant growth regulation [11], anti-biofilm [12], and herbicidal activities [13–15]. Numerous pyrazole derivatives, for example, tebufenpyrad as pesticides and penthiopyrad as fungicides, have been successfully established. They characterize an important class of natural and synthetic products and are extremely useful for the creation of bioactive materials in medicinal chemistry and therapeutic drug industry.

RESULTS AND DISCUSSION

Chemistry. The different kinds of electrophilic center in 2,3-diaryloxirane-2,3-dicarbonitrile **1** are allowed to react with simply bi-nucleophiles [16,17] to afford the new heterocyclic compounds; they are dependent upon the type of nucleophile. 2,3-Diaryloxirane-2,3-dicarbonitrile **1** is allowed to react with hydrazine precursors, such as hydrazine hydrate, methylhydrazine, and phenylhydrazine to afford the corresponding pyrazole derivative **2** that proposed the mechanism of pyrazole product **2** as shown in Scheme 1.

The spectral analysis confirmed the existence of carbonyl groups and absence of the cyano groups. ^{1}H NMR spectrum revealed three signals for acidic protons exchangeable by D_2O; these explained the presence of

Scheme 1. Outline the mechanism for the formation of compound **2**.



amino pyrazole **2** in imine form (cisoid structure) (Fig. 1). The product's yields reflected the stability of compounds **2a–f** and how the aryl substituents have saved theirs. In case of derivatives **2e** and **2f**, intramolecular 1,2[H] shift occurs to afford the more stable products. The substituted aryl groups are expected to enhance the reaction rate that can be affected by the migratory aptitude phenomena.

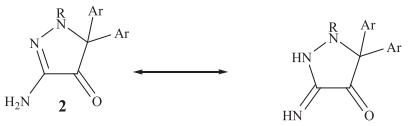
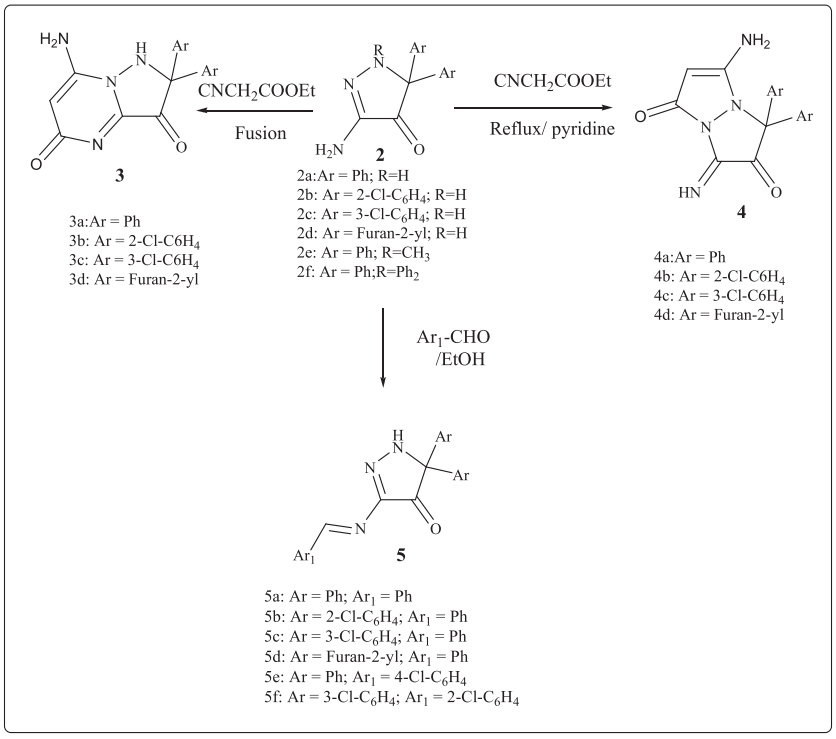


Figure 1. Outline the isomerization of the compound **2** to the cisoid structure.

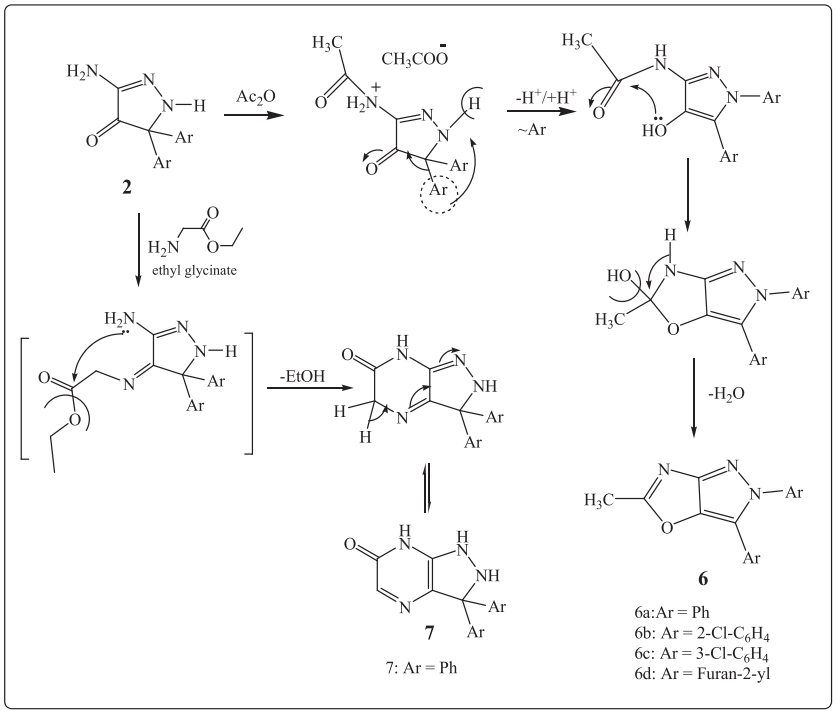
Synthesized pyrazole derivatives **2a–f** can be supported chemically and has confirmed the two stable resonating structures (Fig. 1), when they allowed the reaction with ethyl cyanoacetate. Reaction of pyrazoles **2a–f** with ethyl cyanoacetate at different conditions afforded isomers **3** and **4**. Grinding followed by fusion of compounds **2a–f** with ethyl cyanoacetate afforded pyrazolopyrimidone derivative **3**, but when allowed to reflux at normal condition, these afforded pyrazolopyrazolone derivative **4** (Scheme 2).

Compound **4a** $\Delta E = E_{LUMO} - E_{HOMO} = -3.477 - (-4.128) = 0.592$ is more stable than compound **3a** $\Delta E = E_{LUMO}\text{-}E_{HOMO} = -2.421 - (-7.961) = 5.490$. So the thermochemical reaction afforded the more stable product **4**. But the grinding and fusion reaction

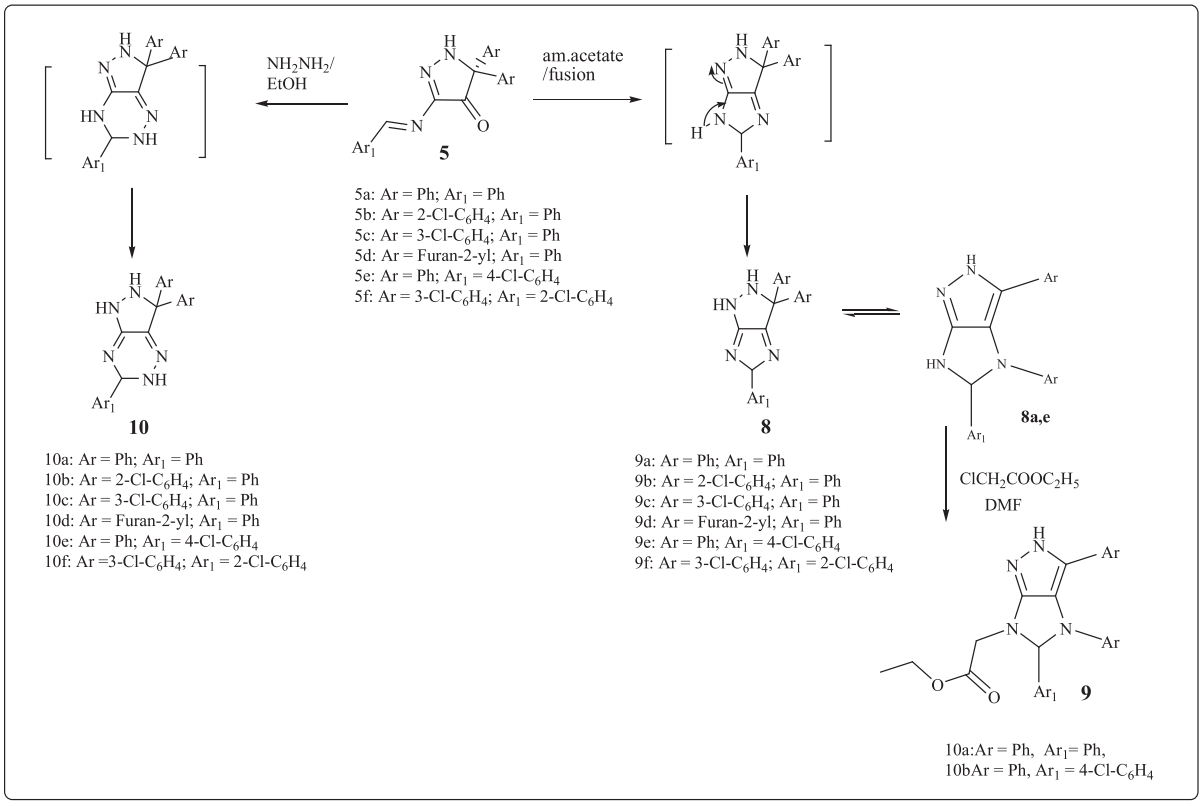
Scheme 2. Synthetic routes for compounds **3**, **4** and **5** *via* reaction of compounds **2** with ethylcyanoacetate and aromatic aldehydes respectively.



Scheme 3. Synthetic routes for compounds **6** and **7** *via* reaction of compounds **2** with acetic anhydride and ethylglycinate respectively.



Scheme 4. Synthetic routes for compounds **8**, **9** and **10** *via* reaction of compounds **5**.

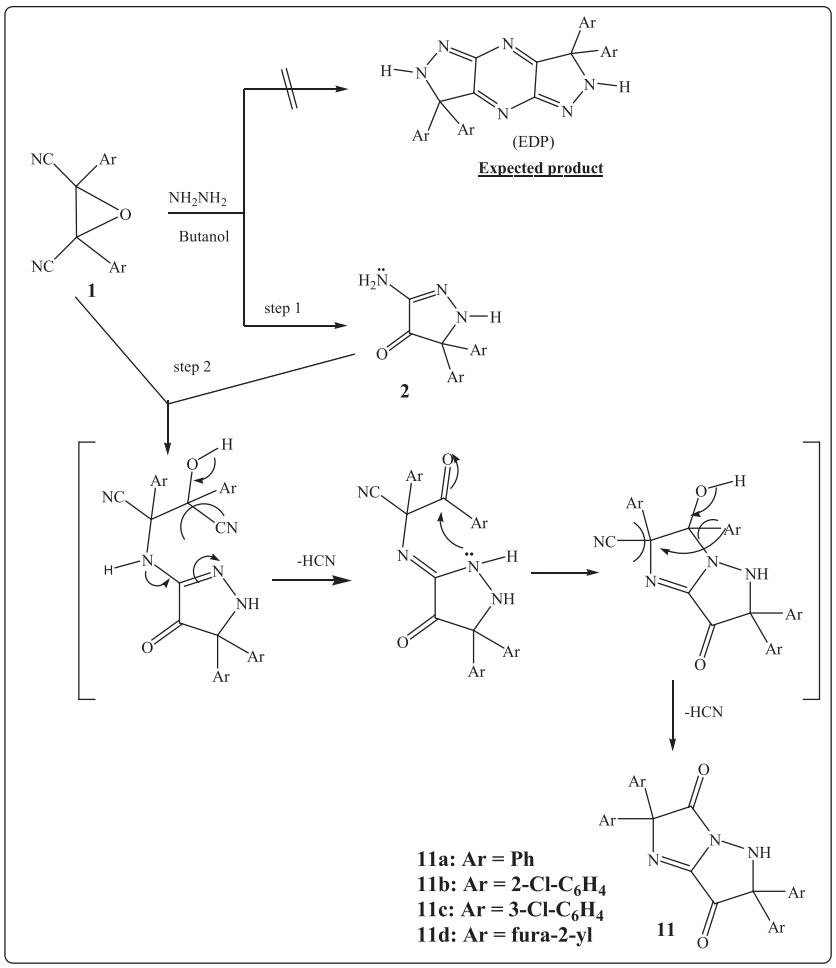


approached photochemical reaction that has $\Delta E = E_{LUMO(1)} - E_{LUMO} = -1.502 - (-2.421) = 0.919$ in compound **3a**. The spectral analysis of the chemical structures of compounds **3** and **4** was outlined and approved by ^1H NMR. When pyrazole derivatives **2a–f** were allowed to react with aromatic aldehydes, the presence of boiling ethanol afforded Schiff base **5**. The stability of Schiff base **5** can be controlled upon the migration of the aryl groups in position *5* in pyrazole moiety, whenever the attacking nucleophiles approached (see later in the reaction of Schiff base **5**). The presence of halogen atom in the aryl group of Schiff bases can be affected by their reactivity. It can be forced upon the rate of reaction and increased the yield of products (see more in the Experimental part).

Reaction of pyrazoles **2a–d** with acetic anhydride afforded oxazolopyrazole **6a–d** via acetylation and migration and followed by the ring closure (Scheme 3). The driving force of the migration of the aryl group is due to the more thermodynamic stability (aromaticity) of the pyrazole ring. The ^1H and ^{13}C NMR confirmed the existence of two aryl groups that were in different positions and not in the same site, which can help us to form the suggested mechanism that affords imidazolo-pyrazolone derivatives **6a–d** as outlined in Scheme 3. On the other hand, pyrazole **2a** is allowed to react with ethylglycinate in boiling ethanol to afford pyrazolo[3,4-*b*] pyrazine derivative **7**.

Reaction of arylidenes **5a–f** with ammonium acetate afforded tetrahydroimidazo[4,5-*c*]pyrazoles **8a–f,** and products **8a**, **e** treated with ethyl chloroacetate in the presence of potassium carbonate afforded ester products **9a**, **b**. Treatment of **5a–f** with hydrazine hydrate in ethanol gave pyrazolo[3,4-*e*]1,2,4-triazines **10a–f** in good yield (Scheme 4) via spontaneous [1,3]-hydrogen shift to afford more thermodynamic stability. The [1,3]H migration shift is energetically more favored than the aryl group is, which transfers to nitrogen, although the authors think that the electron-rich aryl groups are a good migrating group, and so they can enhance the rate of

Scheme 5. Synthetic routes for compounds **11** *via* reaction of compounds **1** with hydrazine hydrate in boiling butanol.



reaction. However, we found experimentally that the time allowed for the complete reaction of all derivatives **8a–f** was isolated at the same time.

When diaryloxirane dicarbonitrile **1**, allowed to react with hydrazine hydrate in boiling butanol afforded products **11a–d**, we suggested the following mechanism that afforded imidazolo-pyrazolone derivatives **11a–d** as outlined in Scheme 5.

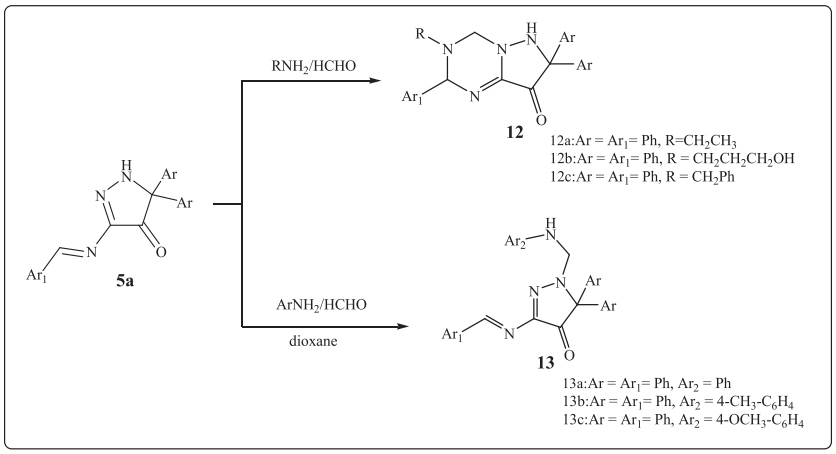
In the runaway of Schiff bases, the authors reported that the behavior of 3-(arylidenimino)-5,5-diphenyl-4-oxo-4,5-dihydropyrazole **5a** with aliphatic amine (e.g., ethylamine, 3-aminopropanol, or benzylamine, in the presence of formaldehyde) via [4 + 2] cycloaddition afforded pyrazolo[2,3-*a*]1,3,5-triazine derivatives **12a–c**. In the same manner, reaction of 3-(benzylideneamino)-5,5-diphenyl-4-oxo-4,5-dihydropyrazole **5a** with aromatic amine, formaldehyde, in boiling dioxane afforded N-substituted pyrazolone derivatives **13a–c** via the Mannich reaction (Scheme 6).

The homoannular diene tautomer can be equilibrated and shifted to more stable pyrazolo[3,4-*b*]pyrazinone **7**, which can be evident by cyclization via the treatment of **7** with chloroacetic acid in the presence of phosphorous oxychloride that afforded fused tricyclic heterocycle **14**. New chalcone **16** could be synthesized via reaction of tricyclic derivative **15** with benzaldehyde (Scheme 7), which garnered great attention because of its pharmaceutical and biocidal activities [18].

Anticancer moiety. Eleven compounds were assayed over three different human tumor cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as illustrated in Table 1 and Figure 2.

From Table 1, **10a** possessed the highest cytotoxicity on breast human tumor cell line (MCF-7). Therefore, it is subjected to further assay at lower concentrations (50, 25, and 12.5 ppm) to calculate their LC50, which is 8.4 ± 0.02 on MCF-7. On the one hand, **2d**, **8a**, **12a**, and **13a** showed moderate activity over MCF-7. Meanwhile,

Scheme 6. Synthetic routes for compounds **12** and **13** *via* reaction of compound **5a** with different mannish reagents.



Scheme 7. Synthetic routes for compounds **14**, **15** and **16** *via* reaction of compounds **7** with different carbon electrophiles.

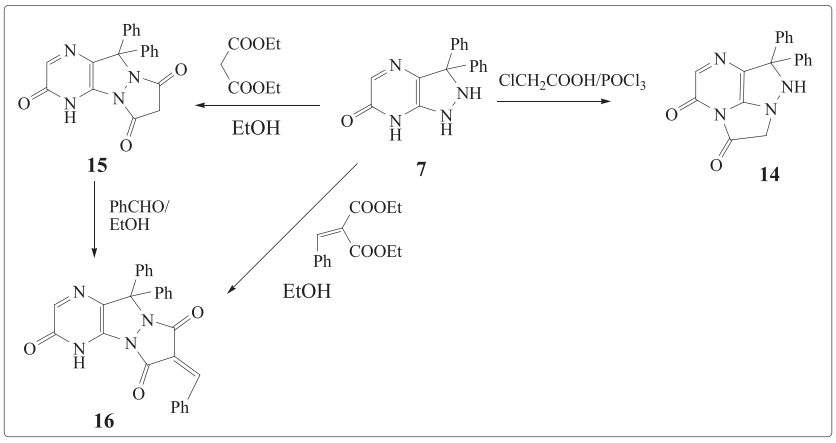


Table 1

Screening the cytotoxicity of sample, *in vitro*, against three human tumor cell lines: breast carcinoma (MCF-7), colon carcinoma (HCT-116), and hepatocellular carcinoma (HepG2).

	Cytotoxicity (%)		
Sample	MCF-7	HCT-116	HepG-2
2a	18.9	10.4	8.5
2d	63.7	6.8	0
5a	2.1	10.5	9.8
5d	5.5	11.1	5.7
6b	13.1	7.5	14.5
7	10.1	12.6	6.8
8a	38.2	27.4	18.2
10a	96.6	40	48.1
11a	13.4	1.1	6
12a	46.4	22.6	21
13a	39.9	17.2	7.8
Doxorubicin	99	98	99.5

Each result is a mean of three replicate samples.

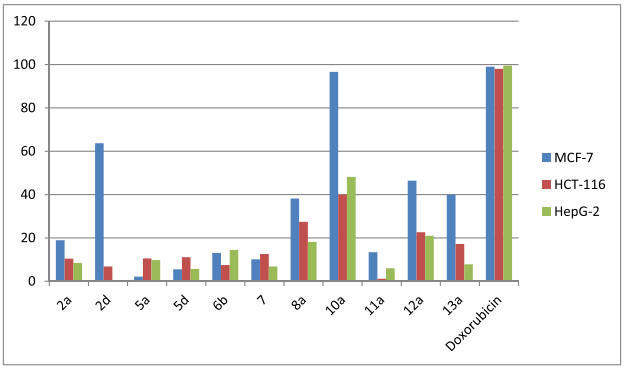


Figure 2. The results of screening the cytotoxicity of 11 compounds, *in vitro*, against three human tumor cell lines: breast carcinoma (MCF-7), colon carcinoma (HCT-116), and hepatocellular carcinoma (HepG2). [Color figure can be viewed at wileyonlinelibrary.com]

Table 2

LC50 (the concentration required to kill 50% of the cell population) of active compound exhibiting more than 60% cytotoxicity on cell lines of breast carcinoma (MCF-7).

	LC50
Compound	MCF-7
10a	8.4 ± 0.02
Doxorubicin	26.1 (±1.3)

Values of LC50 (± standard errors) are calculated using SPSS statistical program.

2a, **5a**, **5d**, **6b**, **7**, and **11a** have weak cytotoxic effect on MCF-7. On the other hand, **10a** showed moderate activity on both HCT-116 and HepG-2, while **2a**, **2d**, **5a**, **5d**, **6b**, **7**, **11**a, and **12a** have weak cytotoxicity on HCT-116 and HepG-2.

Compound **10**, which possessed high activity over each carcinoma cell line, was further assayed at lower concentrations to calculate their LC50 (Table 2).

CONCLUSION

I- In the present work, the authors successfully synthesized a series of some important Schiff bases and novel fused heterocycle derivatives, which are expected to enhance the biological profile manyfold than do their parent nuclei. Migration of the aryl groups in derivatives of **2**, **5**, **11**, and **7** is confirmed by ^{1}H and ^{13}C NMR. The authors also successfully synthesized a series of some important derivatives, for example, amino triazinone **10**, pyrrolotriazine **12**, pyrazolopyrazinone **13**, tricyclic **15**, and chalcone **16.** Matching mono- or bi-heterocyclic structure to the pyrazole moiety will be enhanced the biological activity and become as bio-isosterstructures.

II- Eleven compounds were preliminarily screened at 100 ppm for their cytotoxicity using three human tumor cell lines [human breast carcinoma (MCF-7), human colon carcinoma (HCT-116), and hepatocellular carcinoma (HepG2).

EXPERIMENTAL

General. All the chemicals and solvents, purchased from Sigma-Aldrich (Egyptian branch, Egyptian International Center for Import, Cairo, Egypt), were used without further purification. Thin-layer chromatography analyses of compounds were performed on silica gel G-coated aluminum foils. The solutions of compounds were applied as a spot on the aluminum foils about 2 cm above the lower edge. The mobile phases were selected according to the polarity of compounds (ethyl acetate: hexane). All melting points were determined by using open capillary melting point apparatus. Fourier transform infrared FT-IR spectra (KBr) were recorded on a Thermo-Scientific (Nicole 6700) spectrophotometer (Thermo Electron Corporation, Waltham, MA). The ^{1}H NMR spectra were recorded on Bruker 800 (^{13}C) (Bruker, Middle East Branch Dubai) and Joel 400 (^{1}H) MHz (Jeol Service Bureau, Egypt), respectively, with high-resolution NMR spectrometer using trimethylsily as an internal standard. Chemical shifts were reported in ppm (δ), and signals were described as singlet (s), doublet (d), triplet (t), and multiple (m). The mass spectra were recorded via direct infusion on a Waters Micro-Mass ZQ 2000 mass spectrophotometer (Edwards / Waters Alliance, Milford, MA), and data were acquired from electrospray ionization

source. Later, the microanalysis was performed by atomic absorption spectrophotometer. All compounds were analyzed for C, H, N, and Cl using Elementar (Vario Micro Cube) (Elementar India Pvt Ltd, India), where combustion tube was ignited at 1150°C, reduction tube temperature was 850°C, and pressure was maintained at 1200 mbar using helium and oxygen gas. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) at 70 eV using the electron ionization technique.

General procedure for the preparation of compound 1 is described in the literature [1]. A mixture of $K_4[Fe(CN)_6]$ (0.2 mmol) and aroyl chloride (1 mmol) was refluxed at 170°C for 1 h. After cooling the reaction mixture, triphenyl-phosphine (0.5 mmol), and triethylamine (0.02 mmol) in CH_2Cl_2 (20 mL) were added slowly, and the reaction mixture was refluxed for 3 h. The reaction was monitored by thin-layer chromatography. After completion of the reaction, it was neutralized with concentrated hydrochloric acid solution, and the precipitate was filtered and recrystallized with proper solvent.

General procedure for the preparation of compound 2. Reflux an equimolar mixture of compound **1** (0.01 mol) and hydrazine derivatives (0.01 mol) in ethanol (30 mL) for 5–6 h. The solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from the proper solvents.

3-Amino-5,5-diphenyl-4-oxo-4,5-dihydropyrazole (2a). Yield 73%, mp 230–232°C, EtOH. IR (KBr): ν [3310, 3270] (NH, NH_2), 3052 (CH_{Ar}), 1720 (CO). ^{1}H NMR (DMSO): δ 7.38–7.56 (m, 10H, ArH), 11.8 and 13.2 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 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 $C_{15}H_{13}N_3O$ (251): C, 71.70; H, 5.21; N, 16.70. Found: C, 71.60; H, 5.15; N, 16.50. MS: *m*/*z*: 251 [$M^{+\cdot}$], 194, 180, 158, 121, 103.

3-Amino-5,5-bis(2-chlorophenyl)-4-oxo-4,5-dihydropyrazole (2b). Yield 74%, mp 246–248°C, EtOH. IR (KBr): ν [3436, 3276] (NH, NH_2), 3063 (CH_{Ar}), 1712 (CO). ^{1}H NMR (DMSO): δ 7.43–7.82 (m, 8H, ArH), 6.5, 8.4, and 13.2 (s, 3NH, acidic protons exchanged in D_2O), ^{13}C NMR: δ 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 $C_{15}H_{11}Cl_2N_3O$ (320): C, 56.27; H, 3.46; N, 13.12; Cl, 22.15. Found: C, 56.55; H, 3.35; N, 13.07; Cl, 21.82. MS: *m*/*z* 292 [$M^{+\cdot}$ − CO], 284.5 [$M^{+\cdot}$ − Cl], 262, 234, 193.5, 137.5, 70, 56.

3-Amino-5,5-bis(3-chlorophenyl)-4-oxo-4,5-dihydropyrazole (2c). Yield 77%, mp 238–240°C, EtOH. IR (KBr): ν [3390, 3255] (NH, NH_2), 3055 (CH_{Ar}), 1706 (CO). ^{1}H NMR (DMSO): δ 7.45–7.7 (m, 8H, ArH), 6.7, 8.3, and 13.2 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 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 $C_{15}H_{11}Cl_2N_3O$ (320): C, 56.25; H, 3.44; N, 13.16; Cl, 22.15. Found: C, 56.47; H, 3.39; N, 13.12; Cl, 21.88. MS: *m*/*z* 320 [$M^{+\cdot}$], 284.5 [M^+ − Cl], 234, 193, 137.5.

3-Amino-5,5-bis(furan-2-yl)-4-oxo-4,5-dihydropyrazole (2d). Yield 65%, mp 182–184°C, EtOH. IR (KBr): ν [3457, 3338] (NH, NH_2), 3065 (CHAr), 1718 (CO). ^{1}H NMR (DMSO): δ 6.82–7.12 (m, 6H, ArH), 6.2, 8.5, and 12.9 (s, 3NH, acidic protons exchanged in D_2O); ^{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 $C_{11}H_9N_3O_3$ (231): C, 57.14; H, 3.89; N, 18.18. Found: C, 57.10; H, 3.75; N, 18.15. MS: *m*/*z* 231 [$M^{+\cdot}$], 203 [$M^{+\cdot}$ − CO], 176, 160, 93, 70.

3-Amino-5,5-diphenyl-1-methyl-4-oxo-4,5-dihydropyrazole (2e). Yield 64%, mp 204–206°C, EtOH. IR (KBr): ν [3324] (NH), 3056 (CH_{Ar}), 1722 (CO). ^{1}H NMR (DMSO): δ 3.36 (s, 3H, CH_3), 7.21–7.66 (m, 10H, ArH), 6.3, 8.6 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 35.2 (CH_3), 113.2 (2C), 122.4 (2CH), 128.6 (2CH), 130.8 (CH), 131.7 (CH), 133.1 (2CH), 135.2 (CH), 137.7 (CH), 145.2 (C), 168.4 (C), 190.0 (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 [$M^{+\cdot}$], 253, 209, 158, 103, 85.

3-Amino-1,5,5-triphenyl-4-oxo-4,5-dihydropyrazole (2f). Yield 60%, mp 218–220°C, EtOH. IR (KBr): ν 3321 (NH), 3060 (CH_{Ar}), 1720 (CO). ^{1}H NMR (DMSO): δ 7.28–7.80 (m, 15H, ArH), 5.9, 8.5 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 109.2 (2C), 121.8 (2CH), 122.6 (2CH), 126.8 (CH), 128.6 (2CH), 130.8 (CH), 131.7 (CH), 132.1 (2CH), 133.1 (2CH), 134.2 (CH), 135.2 (CH), 137.7 (CH), 145.2 (C), 168.4 (C), 190.0 (C) and *Anal*. Calcd. for $C_{21}H_{17}N_3O$ (327): C, 72.45; H, 5.66; N, 15.84. Found: C, 72.38; H, 5.58; N, 15.80. MS: *m*/*z* 327 [$M^{+\cdot}$], 236, 193, 179, 147, 132, 103.

General procedure for the preparation of compound 3. A mixture of **2** (0.01 mol) and ethyl cyanoacetate (0.05 mol) was grinded together using a mortar and pestle for 25–30 min. And fusion of the reaction mixture was for 1 h. The color of the reaction mixture turned light yellow from colorless starting reactants. The progress of the reaction was monitored by thin-layer chromatography using $CHCl_3$:EtOAC 50:50 as solvent system. Then the reaction mixture was left overnight whereby a yellow solid crude product was obtained, which was recrystallized.

7-Amino-2,2-diphenyl-1,2-dihydropyrazolo[1,5-a]pyrimidine-3,5-dione (3a). Yield 82%, mp 140–142°C, crystallized from EtOH. IR (KBr): ν 3357, 3245 (NH, NH_2), 3056 (CH_{Ar}), 1695, 1666 (CO). ^{1}H NMR (DMSO): δ 6.11 (s, 1H, ═CH), 7.15–7.70 (m, 10H, ArH), 5.21, 6.50 (s, 3NH,

acidic protons exchanged in D_2O); ^{13}C NMR: δ 73.2 (CH), 92.8 (C), 126.7 (2CH), 127.9 (2CH), 129.4 (4CH), 130.9 (2CH), 137.4 (2C), 150.9 (C═N), 161.4 (C═O), 171.2 (═C–NH_2), 203.1 (C) and *Anal*. Calcd. for $C_{18}H_{14}N_4O_2$ (318): C, 67.92; H, 4.43; N, 17.60. Found: C, 67.63; H, 4.29; N, 17.29. MS: *m*/*z* 318 [$M^{+\cdot}$], 241, 159, 105.

7-Amino-5,5-bis(2-chlorophenyl)-1,2-dihydropyrazolo[1,5-a]pyrimidine-3,5-dione (3b). Yield 85%, mp 162–164°C, crystallized from EtOH. IR (KBr): ν 3299, 3233 (NH, NH_2), 3054 (CH_{Ar}), 1702, 1668 (CO). ^1H NMR (DMSO): δ 6.02 (s, 1H, ═CH), 7.23–7.80 (m, 8H, ArH), 5.7, 6.4 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 73.6 (CH), 92.3 (C), 127.6 (2CH), 129.1 (2CH), 130.6 (2CH), 131.3 (2CH), 137.2 (2C), 149.3 (2C), 153.2 (C═N), 170.2 (═C–NH_2), 171.1 (C═O), 203.1 (C) and *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_4O_2$ (386): C, 55.83; H, 3.12; Cl, 18.31; N, 14.47. Found: C, 55.41; H, 3.00; Cl, 18.00; N, 14.05. MS: *m*/*z* 386 [$M^{+\cdot}$], 350.5 [$M^{+\cdot}$ − Cl], 194, 140, 70.

7-Amino-5,5-bis(3-chlorophenyl)-1,2-dihydropyrazolo[1,5-a]pyrimidine-3,5-dione (3c). Yield 80%, mp 184–186°C, crystallized from EtOH. IR (KBr): ν 3336, 3267 (NH, NH_2), 3062 (CH_{Ar}), 1701, 1676 (CO). ^1H NMR (DMSO): δ 6.02 (s, 1H, ═CH), 7.5–7.8 (m, 8H, ArH), 5.3, 6.1 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 73.6 (CH), 94.1 (C), 128.0 (2CH), 129.9 (2CH), 130.3 (2CH), 132.6 (2CH), 138.6 (2CH), 149.6 (2CH), 151.5 (C═N), 153.2 (C═O), 169.4 (═C–NH_2), 204.2 (C═O) and *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_4O_2$ (386): C, 55.83; H, 3.12; Cl, 18.31; N, 14.47. Found: C, 55.40; H, 2.97; Cl, 17.95; N, 13.93. MS: *m*/*z* 386 [$M^{+\cdot}$], 350.5 [$M^{+\cdot}$ − Cl], 194, 140, 70.

7-Amino-5,5-bis(furan-2-yl)-1,2-dihydropyrazolo[1,5-a]pyrimidine-3,5-dione (3d). Yield 75%, mp 128–130°C, crystallized from EtOH. IR (KBr): ν 3448, 3327 (NH, NH_2), 3058 (CH_{Ar}), 1700, 1667 (CO). ^1H NMR (DMSO): δ 6.02 (s, 1H, ═CH), 6.96–7.74 (m, 6H, ArH), 5.6, 6.5 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 72.8 (CH), 92.9 (C), 111.2 (2CH), 115.2 (2CH), 136.9 (2CH), 151.2 (2C), 151.6 (C═N), 153.5 (C═O), 169.4 (═C–NH_2), 202.1 (C═O) and *Anal*. Calcd. for $C_{14}H_{10}N_4O_4$ (298): C, 56.38; H, 3.38; N, 18.79. Found: C, 56.00; H, 3.00; N, 18.00. MS: *m*/*z* 298 [$M^{+\cdot}$], 270 [$M^{+\cdot}$ − CO], 194, 175.

General procedure for the preparation of compound 4.

A mixture of **2** (0.01 mol) and ethyl cyanoacetate (0.015 mol) in pyridine (10 mL) was heated under reflux for 6 h. The reaction mixture was allowed to cool and poured into ice/conc. HCl, and the product was filtered, dried, and crystallized from suitable solvent.

3-Amino-5,5-diphenyl-7-imino-7-hydro-1H,5H-pyrazolo[1,2-a]pyrazole-1,6-dione (4a). Yield 73%, mp 222–224°C, crystallized from EtOH. IR (KBr): ν 3276, 3214 (NH), 3062 (CH_{Ar}), 1702, 1672 (CO). ^1H NMR (DMSO): δ 4.21 (s, 1H, ═CH), 7.2–7.7 (m, 8H, ArH), 6.1, 9.2 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 75.4 (CH), 94.3 (C), 127.4 (2CH), 129.2 (2CH), 130.2 (4CH), 130.9 (2CH), 137.4 (2C), 151.7 (C═N), 169.2 (═C–NH_2), 170.4 (C═O), 200.4 (C) and *Anal*. Calcd. for $C_{18}H_{14}N_4O_2$ (318): C, 67.92; H, 4.43; N, 17.60. Found: C, 67.40; H, 4.25; N, 17.10. MS: *m*/*z* 318 [$M^{+\cdot}$], 241, 159, 105.

3-Amino-5,5-bis(2-chlorophenyl)-7-imino-7-hydro-1H,5H-pyrazolo[1,2-a]pyrazole-1,6-dione (4b). Yield 77%, mp 216–218°C, crystallized from dioxane. IR (KBr): ν 3336, 3226 (NH), 3062 (CH_{Ar}), 1705, 1670 (CO). ^1H NMR (DMSO): δ 4.32 (s, 1H, ═CH), 7.5–7.8 (m, 8H, ArH), 6.3, 9.1 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 76.8 (CH), 94.5 (C), 128.4 (2CH), 129.6 (2CH), 130.6 (2CH), 131.3 (2CH), 139.2 (2C), 151.6 (2C), 153.2 (C═N), 170.2 (═C–NH_2), 171.1 (C═O), 203.1 (C) and *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_4O_2$ (386): C, 55.83; H, 3.12; Cl, 18.31; N, 14.47. Found: C, 55.45; H, 3.08; Cl, 18.11; N, 14.00. MS: *m*/*z* 386 [$M^{+\cdot}$], 315 [$M^{+\cdot}$ − 2Cl], 194, 140, 70.

3-Amino-5,5-bis(3-chlorophenyl)-7-imino-7-hydro-1H,5H-pyrazolo[1,2-a]pyrazole-1,6-dione (4c). Yield 72%, mp 238–240°C, crystallized from DMF. IR (KBr): ν 3336, 3226 (NH), 3062 (CH_{Ar}), 1705, 1670 (CO). ^1H NMR (DMSO): δ 4.32 (s, 1H, ═CH), 7.5–7.8 (m, 10H, Ar-H), 6.3, 9.1 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 79.6 (CH), 95.1 (C), 128.0 (2CH), 129.9 (2CH), 131.3 (2CH), 132.6 (2CH), 139.6 (2C), 147.6 (2C), 152.1 (C═N), 168.5 (═C–NH_2), 169.4 (C═O), 201.2 (C) and *Anal*. Calcd. for $C_{18}H_{12}Cl_2N_4O_2$ (386): C, 55.83; H, 3.12; Cl, 18.31; N, 14.47. Found: C, 55.25; H, 3.03; Cl, 18.02; N, 13.87. MS: *m*/*z* 386 [$M^{+\cdot}$], 350.5 [$M^{+\cdot}$ − Cl], 194, 140, 70.

3-Amino-5,5-di(furan-2-yl)-7-imino-7-hydro-1H,5H-pyrazolo[1,2-a]pyrazole-1,6-dione (4d). Yield 68%, mp 204–206°C, crystallized from dioxane. IR (KBr): ν 3402, 3321 (NH), 3058 (CH_{Ar}), 1703, 1672 (CO). ^1H NMR (DMSO): δ 4.11 (s, 1H, ═CH), 6.62–7.54 (m, 6H, furH), 5.6, 9.3 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 75.8 (CH), 92.9 (C), 109.5 (2CH), 111.2 (2CH), 141.2 (2CH), 151.5 (C═N), 151.9 (2C), 167.4 (═C–NH_2), 169.9 (C═O), 200.1 (C═O) and *Anal*. Calcd. for $C_{14}H_{10}N_4O_4$ (298): C, 56.38; H, 3.38; N, 18.79. Found: C, 56.09; H, 3.06; N, 18.05. MS: *m*/*z* 298 [$M^{+\cdot}$], 270 [$M^{+\cdot}$ − CO], 194, 175.

General procedure for the preparation of compound 5.

Reflux an equimolar mixture of compound **2** (0.01 mol) and aromatic aldehydes, namely, benzaldehyde, 4-chlorobenzaldehyde, and 2-chlorobenzaldehyde (0.01 mol), in ethanol (30 mL) for 2–6 h. The solid that separated after cooling was filtered off, dried, and crystallized from the proper solvents.

3-(Benzylideneamino)-5,5-diphenyl-1H-pyrazol-4(5H)-one (5a). Yield 70%, mp 212–214°C, EtOH. IR (KBr): ν 3421 (NH), 3056 (CH_{Ar}), 1706 (CO). ^1H NMR (DMSO):

δ 6.2 (s, 1H, CH═), 7.16–7.72 (m, 15 ArH), 13.2 (s, 1H, acidic NH protons exchanged in D_2O); ^{13}C NMR: δ 112 (2C), 114.8 (CH), 117.4 (CH), 120.4 (2CH), 128.2 (2CH), 129.1 (2CH), 130.5 (CH), 131.5 (CH), 132.2 (2CH), 133.8 (2CH), 134.8 (CH), 137.4 (C), 138.2 (CH), 143.4 (C), 167.0 (C), 189.7 (C) and *Anal*. Calcd. for $C_{22}H_{17}N_3O$ (339): C, 77.87; H, 5.01; N, 12.38. Found: C, 77.81; H, 5.05; N, 12.32. MS: *m*/*z* 339 [$M^{+\cdot}$], 246, 194, 178, 166, 145.

3-(Benzylideneamino)-5,5-bis(2-chlorophenyl)-1H-pyrazol-4(5H)-one (5b). Yield 74%, mp 226–228°C, EtOH. IR (KBr): ν 3322 (NH), 3058 (CH_{Ar}), 1670 (CO). ^1H NMR (DMSO): δ 6.2 (s, 1H, CH═), 7.16–7.72 (m, 13ArH), 13.0 (s, 1H, acidic NH protons exchanged in D_2O); ^{13}C NMR: δ 109.5 (2C), 113.7 (CH), 115.4 (CH), 119.8 (2CH), 124.2 (2CH), 129.1 (2CH), 131.3 (CH), 131.7 (CH), 132.6 (2CH), 133.4 (2CH), 135.3 (C), 137.6 (CH), 139.2 (CH), 143.4 (C), 168.3 (C), 191.2 (C) and *Anal*. Calcd. for $C_{22}H_{15}Cl_2N_3O$ (408): C, 64.72, H, 3.68; N, 10.31; Cl, 17.37. Found: C, 64.83, H, 3.65, N, 10.35, Cl, 17.00. MS: *m*/*z* 391 [$M^{+\cdot}$ − OH], 295, 280, 264, 236, 193, 145.

3-(Benzylideneamino)-5,5-bis(3-chlorophenyl)-1H-pyrazol-4(5H)-one (5c). Yield 76%, mp 252–254°C, EtOH. IR (KBr): ν 3264 (NH), 3058 (CH_{Ar}), 1729 (CO). ^1H NMR (DMSO): δ 6.2 (s, 1H, CH═), 7.12–7.89 (m, 13ArH), 12.9 (s, 1H acidic NH proton exchanged in D_2O); ^{13}C NMR: δ 110.7 (2C), 112.9 (CH), 114.4 (CH), 120.8 (2CH), 123.2 (2CH), 128.1 (2CH), 130.8 (CH), 131.2 (CH), 132.1 (2CH), 132.8 (2CH), 134.3 (C), 136.8 (CH), 138.1 (CH), 141.1 (C), 168.4 (C), 190.0 (C) and *Anal*. Calcd. for $C_{22}H_{15}Cl_2N_3O$ (408): C, 64.72; H, 3.67; N, 10.31; Cl, 17.37. Found: C, 64.80; H, 3.63; N, 10.33; Cl, 17.12. MS: *m*/*z* 408 [$M^{+\cdot}$], 354, 236, 260, 235, 145.

3-(Benzylideneamino)-5,5-di(furan-2-yl)-1H-pyrazol-4(5H)-one (5d). Yield 64%, mp 210–212°C, EtOH. IR (KBr): ν 3278 (NH), 3080 (CH_{Ar}), 1719 (CO). ^1H NMR (DMSO): δ 7.12–7.91 (m, 12ArH and olefinic proton), 12.7 (s, 1H, acidic NH proton exchanged in D_2O); ^{13}C NMR: δ 120.4 (2C), 125.6 (2CH), 129.2 (CH), 131.6 (2CH), 132.2 (CH), 133.2 (CH), 134.9 (C), 136.2 (CH), 137.5 (CH), 138.2 (CH), 140.8 (CH), 141.9 (CH), 143.5 (C), 168.4 (C), 190.1 (C) and *Anal*. Calcd. for $C_{18}H_{13}N_3O_3$ (319): C, 67.71; H, 4.07; N, 13.16. Found: C, 67.70; H, 4.02; N, 13.15. MS: *m*/*z* 319 [$M^{+\cdot}$], 224, 172, 148, 145.

3-(4-Chlorobenzylideneamino)-5,5-diphenyl-1H-pyrazol-4(5H)-one (5e). Yield 72%, mp 226–228°C, EtOH. IR (KBr): ν 3290 (NH), 3052 (CHAr), 1722 (CO). 1H NMR (DMSO): δ 6.57 (s, 1H, CH═), 7.31–7.95 (m, 14ArH), 12.5 (s, 1H, acidic NH proton exchanged in D_2O); ^{13}C NMR: δ 113.2 (CH), 113.8 (2C), 119.4 (2CH), 122.6 (2CH), 125.8 (CH), 126.7 (2CH), 128.6 (2CH), 130.8 (C), 131.7 (CH), 133.1 (2CH), 135.2 (CH), 137.7 (CH), 138.1 (C), 145.2 (C), 168.4 (C), 190.0 (C) and *Anal*. Calcd. for $C_{22}H_{16}ClN_3O$ (373.5): C, 70.68; H, 4.28; N, 11.24; Cl, 9.48. Found: C, 70.65; H, 4.26; N, 11.21; Cl, 9.38. MS: *m*/*z* 373.5 [$M^{+\cdot}$], 219.5 [$M^{+\cdot}$ − biphenyl], 194, 179, 166.

3-(2-Chlorobenzylideneamino)-5,5-bis(3-chlorophenyl)-1H-pyrazol-4(5H)-one (5f). Yield 80%, mp 244–246°C, EtOH. IR (KBr): ν 3289 (NH), 3050 (CH_{Ar}), 1721 (CO). ^1H NMR (DMSO): δ 6.42 (s, 1H, CH═), 7.28–7.94 (m, 12ArH), 12.6 (s, 1H acidic NH proton exchanged in D_2O); ^{13}C NMR: δ 109.2 (2C), 115.4 (CH), 118.9 (2C), 119.4 (2CH), 122.6 (2CH), 125.8 (CH), 126.7 (2CH), 130.8 (C), 131.7 (CH), 133.1 (2CH), 135.2 (CH), 137.7 (CH), 138.1 (C), 145.2 (C), 168.4 (C), 190.0 (C) and *Anal*. Calcd. for $C_{22}H_{14}Cl_3N_3O$ (442.5): C, 59.66; H, 3.17; N, 9.51; Cl, 24.02. Found: C, 59.55; H, 3.05; N, 9.22; Cl, 24.14. MS: *m*/*z* 444.5 [$M^{+\cdot}$ + 2], 442.5 [$M^{+\cdot}$], 305, 260, 179.

General procedure for the preparation of compound 6. Reflux a mixture of **2a–d** (0.01 mol) and acetic anhydride (0.1 mol) on water bath for 2 h. The excess acetic anhydride was removed by distillation, and the separated product was washed by (pet 40–60), dried, and crystallized from toluene–ethanol mixture.

5-Methyl-2,3-diphenyl-2H-pyrazolo[3,4-d]oxazole (6a). Yield 75%, mp 140–142°C. IR (KBr): 3062 (CH_{Ar}), 2950 (CH_{Ali}), 1636 (C═N). ^1H NMR (DMSO): δ 3.43 (s, 3H, CH_3), 7.19–7.76 (m, 10ArH); ^{13}C NMR: δ 22.1 (CH_3), 112.1 (CH), 121.2 (CH), 128.8 (2CH), 133.2 (CH), 133.7 (CH), 134.2 (CH), 134.8 (CH), 137.6 (CH), 138.7 (CH), 140.2 (C), 142.1 (C), 143.4 (C), 144.5 (C), 155.2 (C), 190.4 (C) and *Anal*. Calcd. for $C_{17}H_{13}N_3O$ (275): C, 74.18; H, 4.72; N, 15.27. Found: C, 74.20; H, 4.75; N, 15.24. MS: *m*/*z* 275 [M^+], 260, 246, 232 [M^+ − CH_3CO], 198.

2,3-Bis(2-chlorophenyl)-5-methyl-2H-pyrazolo[3,4-d]oxazole (6b). Yield 77%, mp 152–154°C. IR (KBr): 3049 (CH_{Ar}), 2980 (CH_{Ali}), 1630 (C═N). ^1H NMR (DMSO): δ 3.68 (s, 3H, CH_3), 7.10–7.38 (m, 8H, ArH). ^{13}C NMR: δ 22.6 (CH_3), 110.1 (CH), 121.3 (CH), 128.9 (CH), 129.3 (CH), 132.5 (CH), 133.2 (CH), 133.6 (CH), 135.6 (2C), 137.6 (CH), 140.2 (C), 141.5 (C), 143.4 (C), 144.1 (C), 158.2 (C), 189.7 (C) and *Anal*. Calcd. for $C_{17}H_{11}Cl_2N_3O$ (344): C, 59.30; H, 3.20; N, 12.24; Cl, 20.60. Found: C, 59.44; H, 3.18; N, 12.23; Cl, 20.37. MS: *m*/*z* 344 [M^+], 328, 251, 232.

2,3-Bis(3-chlorophenyl)-5-methyl-2H-pyrazolo[3,4-d]oxazole (6c). Yield 74%, mp 146–148°C. IR (KBr): 3050 (CH_{Ar}), 2952 (CH_{Ali}), 1613 (C═N). ^1H NMR (DMSO): δ 3.59 (s, 3H, CH_3), 7.22–7.75 (m, 8H, ArH). ^{13}C NMR: δ 22.4 (CH_3), 109.6 (CH), 121.7 (CH), 129.7 (2CH), 132.5 (CH), 133.2 (CH), 133.6 (CH), 134.6 (CH), 138.6 (2C), 140.2 (C), 141.5 (C), 143.4 (C), 144.1 (C), 152.6 (C), 190.2 (C) and *Anal*. Calcd. for $C_{17}H_{11}Cl_2N_3O$: C, 59.30; H, 3.20; N, 12.24; Cl, 20.60. Found: C, 59.46; H, 3.19; N, 12.22; Cl, 20.39. MS: *m*/*z* 344 [M^+], 328, 285, 121.

2,3-Bis(furan-2-yl)-5-methyl-2H-pyrazolo[3,4-d]oxazole (6d). Yield 70%, mp 136–138°C. IR (KBr): 3061 (CH_{Ar}), 2922 (CH_{Ali}), 1630 (C═N), ^{1}H NMR (DMSO): δ 4.14 (s, 3H, CH_3), 6.96–7.55 (m, 6H, ArH). ^{13}C NMR: δ 23.2 (CH_3), 129.7 (CH), 132.5 (CH), 133.6 (CH), 134.6 (CH), 138.6 (CH), 138.9 (CH), 141.5 (C), 143.4 (C), 144.1 (C), 189.6 (2C), 192.2 (C) and *Anal*. Calcd. for $C_{13}H_9N_3O_3$ (255): C, 61.17; H, 3.52; N, 16.47. Found: C, 61.15; H, 3.50; N, 16.43. MS: *m*/*z* 255 [M^+], 240, 197, 188.

3,3-Diphenyl-6-oxo-1,2,7-trihydro-pyrazolo[3,4-b]pyrazine (7). Reflux a mixture of **2**a (0.01 mol) and ethylglycinate (0.01 mol) in ethanol (30 mL) for 4 h. The solid that separated after cooling was filtered off, dried, and crystallized from dioxane. Yield 70%, mp 164–166°C. IR (KBr): ν 3317, 3256 (NH), 3050 (CH_{Ar}), 1668 (C═O). ^{1}H NMR: (DMSO): δ 6.8 (s, 1H, CHpy), 7.21–7.70 (m, 10ArH), 6.4, 9.7, and 12.4 (s, 3NH, acidic protons exchanged in D_2O), and *Anal*. Calcd. for $C_{17}H_{14}N_4O$ (290): % C, 70.34; H, 4.82; N, 19.31. Found: % C, 70.30; H, 4.78; N, 19.28. MS: *m*/*z* 290 [$M^{+\cdot}$], 167, 123, 136.

General procedure for the preparation of compound 8.

Heat a mixture of **5** (0.01 mol) and ammonium acetate (0.03 mol) in an oil bath at 190°C for 1–4 h. After cooling, the mixture was poured onto water; the solid that separated was filtered off, dried, and crystallized from DMF.

3,3,5-Triphenyl-1,2,3,5-tetrahydroimidazo[4,5-c]pyrazole (8a). Yield 69%, mp 164–166°C. IR (KBr): ν 3333, 3196 (NH), 3066 (CH_{Ar}), 1604 (C═N). ^{1}H NMR: (DMSO): δ 5.1 (s, 1H, CH-Ar), 7.21–7.70 (m, 15ArH), 9.7 and 12.4 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 111.4 (2C), 113.9 (CH), 115.4 (2CH), 121.7 (CH), 126.2 (2CH), 128.3 (CH), 131.1 (2CH), 131.4 (CH), 132.0 (2CH), 133.0 (CH), 134.8 (2CH), 137.4 (C), 138.2 (CH), 142.6 (C), 167.6 (C), 169.2 (C) and *Anal*. Calcd. for $C_{22}H_{18}N_4$ (338): C, 78.08; H, 5.36; N, 16.56. Found: C, 78.06; H, 5.27; N, 16.67. MS: *m*/*z* 338 [$M^{+\cdot}$], 292, 247, 194, 159, 91.

3,3-Bis(2-chlorophenyl)-5-phenyl-1,2,3,5-tetrahydroimidazo[4,5-c]pyrazole (8b). Yield 68%, mp 180–182°C. IR (KBr): ν 3380, 3276 (NH), 3050 (CH_{Ar}), 1614 (C═N). ^{1}H NMR: (DMSO): δ 5.8 (s, 1H, CH-Ar), 7.02–7.92 (m, 13ArH), 9.9 and 12.5 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 112.5 (2C), 114.4 (CH), 115.8 (2CH), 118.4 (CH), 122.2 (CH), 128.1 (2CH), 130.6 (2CH), 131.3 (CH), 133.6 (2CH), 134.4 (2CH), 135.1 (C), 137.6 (CH), 139.7 (CH), 142.4 (C), 168.3 (C), 169.2 (C) and *Anal*. Calcd. for $C_{22}H_{16}Cl_2N_4$ (407): C, 64.88; H, 3.96; N, 17.41; Cl, 13.76. Found: C, 64.98; H, 3.95; N, 17.31; Cl, 13.76. MS: *m*/*z* 409 [$M^{+\cdot}$ + 2], 407 [M^+], 354, 280.5, 213, 193, 125.5.

3,3-Bis(3-chlorophenyl)-5-phenyl-1,2,3,5-tetrahydroimidazo[4,5-c]pyrazole (8c). Yield 80%, mp 122–124°C. IR (KBr): ν 3364, 3280 (NH), 3050 (CH_{Ar}), 1619 (C═N). ^{1}H NMR: (DMSO): δ 5.3 (s, 1H, CHAr), 7.22–7.89 (m, 13ArH), 10.1 and 12.9 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 110.7 (2C), 112.9 (CH), 114.4 (CH), 120.8 (2CH), 123.2 (2CH), 128.1 (2CH), 130.8 (CH), 131.2 (CH), 132.1 (2CH), 132.8 (2CH), 134.3 (C), 136.8 (CH), 138.1 (CH), 141.1 (C), 167.4 (C), 168.0 (C) and *Anal*. Calcd. for $C_{22}H_{16}Cl_2N_4$ (407): C, 64.88; H, 3.96; N, 17.41; Cl, 13.76. Found: C, 65.01; H, 3.94; N, 17.27; Cl, 13.78. MS: *m*/*z* 371.5 [$M^{+\cdot}$ − Cl], 295, 281.

3,3-Di(furan-2-yl)-5-phenyl-1,2,3,5-tetrahydroimidazo[4,5-c]pyrazole (8d). Yield 76%, mp 224–228°C. IR (KBr): ν 3278, 3232 (NH), 3080 (CH_{Ar}), 1617 (C═N). ^{1}H NMR: (DMSO): δ 4.8 (s, 1H, CHAr), 6.64–7.23 (m, 11ArH), 10.2 and 12.7 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 121.1 (2C), 124.6 (CH), 128.2 (2CH), 130.6 (CH), 131.2 (2CH), 133.2 (CH), 135.2 (C), 136.2 (CH), 137.5 (CH), 138.2 (CH), 140.8 (CH), 143.2 (CH), 144.5 (C), 167.4 (C), 168.1 (C) and *Anal*. Calcd. for $C_{18}H_{14}N_4O_2$ (318): C, 67.91; H, 4.43; N, 17.60. Found: C, 67.89; H, 4.37; N, 17.58. MS: *m*/*z* 318 [$M^{+\cdot}$], 147, 170, 148, 82.

5-(4-Chlorophenyl)-3,3-diphenyl-1,2,3,5-tetrahydroimidazo[4,5-c]pyrazole (8e). Yield 72%, mp 226–228°C. IR (KBr): ν 3323, 3190 (NH), 3052 (CH_{Ar}), 1620 (C═N). ^{1}H NMR (DMSO): δ 5.0 (s, 1H, CH-Ar), 7.11–7.75 (m, 14ArH), 10.3 and 12.5 (s, 2NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 113.2 (CH), 111.4 (2C), 117.4 (2CH), 123.6 (2CH), 126.8 (2CH), 127.2 (CH), 129.3 (2CH), 130.5 (C), 131.8 (CH), 132.7 (2CH), 136.2 (CH), 137.7 (CH), 138.1 (C), 144.2 (C), 167.4 (C), 168.3 (C) and *Anal*. Calcd. for $C_{22}H_{17}ClN_4$ (372.5): C, 70.87; H, 4.60; N, 15.03; Cl, 9.50. Found: C, 70.82; H, 4.54; N, 15.01; Cl, 9.63. MS: *m*/*z* 372.5 [$M^{+\cdot}$], 218, 214, 159, 91.

5-(2-Cholorophenyl)-3,3-bis(3-chlorophenyl)-1,2,3,5-tetrahydroimidazo[4,5-c]pyrazole (8f). Yield 80%, mp 244–246°C. IR (KBr): ν 3328, 3200 (NH), 3050 (CH_{Ar}), 1619 (C═N). ^{1}H NMR (DMSO): δ 5.2 (s, 1H, CHAr), 7.28–7.94 (m, 12ArH), 9.5 and 12.6 (s, 2NH, acidic protons exchanged in D_2O).^{13}C NMR: δ 111.2 (2C), 113.4 (CH), 117.9 (2C), 118.8 (2CH), 122.6 (CH), 124.8 (2CH), 126.7 (2CH), 129.8 (C), 131.7 (CH), 132.4 (CH), 134.2 (2CH), 136.7 (CH), 137.7 (C), 145.2 (C), 167.2 (C), 168.0 (C) and *Anal*. Calcd. for $C_{22}H_{15}Cl_3N_4$ (441.5): C, 59.82; H, 3.42; N, 12.68; Cl, 24.08. Found: C, 59.96; H, 3.38; N, 12.70; Cl, 23.96. MS: *m*/*z* 443.5 [$M^{+\cdot}$ + 2], 441.5 [$M^{+\cdot}$], 305, 314.5, 251, 249, 191, 126.

General procedure for the preparation of compound 9.

Reflux an equimolar mixture of compound **5a** (0.01 mol) with ethyl chloroacetate (0.015 mol) in the presence of fresh potassium carbonate (0.03 mol) and dioxane (30 mL) for 24 h. The solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from DMF.

Ethyl 2-(3,4,5-triphenyl-4,5-dihydroimidazo[4,5-c]pyrazol-6(2H)-yl) acetate (9a). Yield 76%, mp 154–158°C. IR (KBr): ν 3260 (NH), 3080 (CH_{Ar}), 1765 (C═O), 1629 (C═N). ^{1}H NMR (DMSO): δ 1.32 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 4.8 (s, 2H, CH_2), 5.2 (s, 1H, CHN_2), 6.64–7.23 (m, 15ArH), 12.7 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 34.2 (CH_3), 61.3 (CH_2), 70.2 (CH_2), 121.1 (2C), 124.6 (CH), 128.2 (2CH), 130.6 (CH), 131.2 (2CH), 133.2 (CH), 135.2 (C), 136.2 (CH), 137.5 (2CH), 138.2 (2CH), 140.8 (CH), 143.2 (CH), 144.5 (2C), 167.4 (2C), 168.1 (C), 178.2 (C) and *Anal*. Calcd. for $C_{26}H_{24}N_4O_2$ (424): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.49; H, 5.57; N, 13.08.

Ethyl-2-(5-(4-chlorophenyl)-3,4-diphenyl-4,5-dihydroimidazo [4,5-c]pyrazol-6(2H)-yl)acetate (9b). Yield 76%, mp 138–140°C. IR (KBr): ν 3278 (NH), 3084 (CH_{Ar}), 1762 (C═O), 1630 (C═N). ^{1}H NMR (DMSO): δ 1.31 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 4.9 (s, 2H, CH_2), 5.3 (s, 1H, CHN_2), 7.04–7.63 (m, 14ArH), 12.3 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 33.2 (CH_3), 61.1 (CH_2), 71.2 (CH_2), 122.1 (2C), 124.4 (CH), 128.2 (2CH), 130.6 (CH), 131.5 (2CH), 133.4 (CH), 135.2 (C), 136.5 (CH), 137.1 (2CH), 138.3 (2CH), 140.9 (CH), 143.5 (CH), 144.9 (2C), 167.5 (2C), 168.8 (C), 179.2 (C) and *Anal*. Calcd. for $C_{26}H_{23}ClN_4O_2$ (458.5): C, 68.04; H, 5.05; Cl, 7.72; N, 12.21. Found: C, 68.00; H, 5.00; Cl, 7.67; N, 12.10.

General procedure for the preparation of compound 10. Reflux an equimolar mixture of compound **4** (0.01 mol) and hydrazine derivatives (0.01 mol) in ethanol (30 mL) for 3–6 h. The solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from DMF.

3,7-Triphenyl-3,5,6,7-tetrahydro-2H-pyrazolo[3,4-e][1,2,4] triazine (10a). Yield 70%, mp 190–192°C. IR (KBr): ν 3421, 3260 (NH), 3063 (CH_{Ar}), 1630 (C═N). ^{1}H NMR (DMSO): δ 5.3 (s, 1H, CHAr), 7.13–7.68 (m, 15ArH), 6.3, 10.2, and 12.8 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 110.6 (2C), 112.4 (CH), 113.8 (2CH), 120.1 (CH), 124.4 (2CH), 127.4 (CH), 128.5 (2CH), 130.3 (CH), 131.3 (2CH), 133.6 (CH), 135.6 (2CH), 137.2 (C), 139.7 (CH), 144.6 (C), 167.6 (C), 168.7 (C) and *Anal*. Calcd. for $C_{22}H_{19}N_5$ (353): C, 74.77; H, 5.42; N, 19.81. Found: C, 74.75; H, 5.36; N, 19.89. MS: *m*/*z* 353 [$M^{+\cdot}$], 248 [$M^+ - PhNHNH_2$], 105, 91.

7,7-Bis(2-chlorophenyl)-3-phenyl-3,5,6,7-tetrahydro-2H-pyrazolo[3,4-e][1,2,4]triazine (10b). Yield 72%, mp 180–182°C. IR (KBr): ν 3424, 3252 (NH), 3056 (CH_{Ar}), 1642 (C═N). ^{1}H NMR (DMSO): δ 5.2 (s, 1H, CHAr), 7.30–7.78 (m, 13ArH), 6.5, 9.8, and 12.4 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 111.2 (2C), 114.7 (CH), 115.9 (2CH), 117.4 (CH), 120.2 (CH), 126.1 (2CH), 128.6 (2CH), 130.3 (CH), 132.6 (2CH), 133.4 (2CH), 134.1 (C), 136.6 (CH), 138.7 (CH), 142.4 (C), 167.3 (C), 168.2 (C) and *Anal*. Calcd. for $C_{22}H_{17}Cl_2N_5$ (422): C, 62.57; H, 4.06; N, 16.58; Cl, 16.79. Found: C, 62.71; H, 4.01; N, 16.60; Cl, 16.68. MS: *m*/*z* 424 [$M^{+\cdot}$ + 2], 422 [M^+], 295, 282, 236, 139.5, 111.5, 91.

7,7-Bis(3-chlorophenyl)-3-phenyl-3,5,6,7-tetrahydro-2H-pyrazolo[3,4-e][1,2,4]triazine (10c). Yield 77%, mp 122–124°C. IR (KBr): ν 3430, 3260 (NH), 3058 (CH_{Ar}), 1645 (C═N). ^{1}H NMR (DMSO): δ 5.3 (s, 1H, CHAr), 7.09–7.98 (m, 13ArH), 6.7, 9.55, and 12.9 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 110.9 (2C), 113.9 (CH), 115.4 (CH), 117.8 (2CH), 120.2 (2CH), 126.7 (2CH), 128.8 (CH), 130.2 (CH), 132.1 (2CH), 132.9 (2CH), 134.3 (C), 136.8 (CH), 138.1 (CH), 141.1 (C), 167.4 (C), 168.0 (C) and *Anal*. Calcd. for $C_{22}H_{17}Cl_2N_5$ (422): C, 62.57; H, 4.06; N, 16.58; Cl, 16.79. Found: C, 62.69; H, 3.99; N, 16.58; Cl, 16.74. MS: *m*/*z* 422 [$M^{+\cdot}$], 386.5 [$M^{+\cdot} - Cl$], 281, 139.5, 111.5.

7,7-Di(furan-2-yl)-3-phenyl-3,5,6,7-tetrahydro-2H-pyrazolo [3,4-e][1,2,4]triazine (10d). Yield 68%, mp 220–222°C. IR (KBr): ν 3420, 3268 (NH), 3080 (CH_{Ar}), 1632 (C═N). ^{1}H NMR (DMSO): δ 4.9 (s, 1H, CHAr), 6.64–7.23 (m, 11ArH), 6.4, 10.2, and 12.7 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 119.1 (2C), 122.6 (CH), 126.2 (2CH), 129.6 (CH), 131.1 (2CH), 132.2 (CH), 134.2 (C), 135.2 (CH), 136.5 (CH), 138.2 (CH), 140.8 (CH), 143.2 (CH), 145.5 (C), 167.7 (C), 168.6 (C) and *Anal*. Calcd. for $C_{18}H_{15}N_5O_2$ (333): C, 64.86; H, 4.54; N, 21.01. Found: C, 64.85; H, 4.47; N, 21.00. MS: *m*/*z* 333 [$M^{+\cdot}$], 237, 96.

3-(4-Chlorophenyl)-7,7-diphenyl-3,5,6,7-tetrahydro-2H-pyrazolo[3,4-e][1,2,4]triazine (10e). Yield 70%, mp 232–234°C. IR (KBr): ν 3429, 3259 (NH), 3050 (CH_{Ar}), 1633 (C═N). ^{1}H NMR (DMSO): δ 5.0 (s, 1H, CHAr), 7.11–7.75 (m, 14H, ArH), 6.6, 10.3, and 12.5 (bs, 3H, acidic 3NH protons exchanged in D_2O); ^{13}C NMR: δ 112.2 (CH), 112.6 (2C), 115.4 (2CH), 120.6 (2CH), 122.8 (2CH), 125.2 (CH), 128.3 (2CH), 130.5 (C), 131.8 (CH), 132.7 (2CH), 134.2 (CH), 136.7 (CH), 138.1 (C), 142.2 (C), 166.8 (C), 168.3 (C) and *Anal*. Calcd. for $C_{22}H_{18}ClN_5$ (387.5): C, 68.13; H, 4.68; N, 18.06; Cl, 9.14. Found: C, 68.10; H, 4.64; N, 18.03; Cl, 9.23. MS: *m*/*z* 387.5 [$M^{+\cdot}$], 280.

3-(2-Chlorophenyl)-7,7-bis(3-chlorophenyl)-3,5,6,7-tetrahydro-2H-pyrazolo[3,4-e][1,2,4]triazine (10f). Yield 75%, mp 260–262°C. IR (KBr): ν 3430, 3279 (NH), 3050 (CH_{Ar}), 1631 (C═N). ^{1}H NMR (DMSO): δ 5.2 (s, 1H, CHAr), 7.08–7.70 (m, 12ArH), 6.4, 10.7, and 12.6 (s, 3NH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 112.7 (2C), 115.4 (CH), 119.5 (2C), 120.8 (2CH), 122.6 (CH), 124.8 (2CH), 126.7 (2CH), 128.8 (C), 130.7 (CH), 133.4 (CH), 135.2 (2CH), 137.5 (CH), 139.7 (C), 145.2 (C), 166.2 (C), 168.2 (C) and *Anal*. Calcd. for $C_{22}H_{16}Cl_3N_5$ (456.5): C, 57.85; H, 3.53; N, 15.33; Cl 23.29. Found: C, 57.96; H, 3.49; N, 15.32; Cl, 23.20. MS: *m*/*z* 459.5

[$M^{+\cdot}$ + 3], 458.5 [$M^{+\cdot}$ + 2], 456.5 [$M^{+\cdot}$], 316, 278, 263, 234, 177, 139.5, 105.

General procedure for the preparation of compound 11. Reflux an equimolar mixture of compound **1** (0.01 mol) and hydrazine hydrate (0.01 mol) in butanol (15 mL) for 8 h. The solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from the proper solvents.

3,6-Dioxo-2,2,5,5-tetraphenyl-[1H]imidazolo[3,2-b]pyrazole (11a). Yield 30%, mp 296–298°C, DMF. IR (KBr): ν 3119 (NH), 3074 (CH_{Ar}), 1663 (C═O). ^{1}H NMR (DMSO): δ 7.04–7.582 (m, 20ArH), 13.00 (s, 1H, acidic NH proton exchanged in D_2O); ^{13}C NMR: δ 112 (2C), 120.4 (2CH), 124.6 (2CH), 126.5 (2CH), 129.5 (2CH), 130.3 (2CH), 132.4 (2CH), 133.6 (2CH), 134.5 (2CH), 136.5 (2CH), 137.3 (2CH), 139.8 (C), 140.4 (C), 166.8 (2C), 168.0 (C), 190.1 (2C) and *Anal*. Calcd. for $C_{29}H_{21}N_3O_2$ (443): C, 78.55; H, 4.74; N, 9.48. Found: C, 78.52; H, 4.73; N, 9.45. MS: *m*/*z* 443 [$M^{+\cdot}$], 415, 384, 347, 314, 262, 158.

3,6-Dioxo-2,2,5,5-tetra(2-chlorophenyl)-[1H]imidazolo[3,2-b]pyrazole (11b). Yield 27%, mp 282–284°C, DMF. IR (KBr): ν 3331 (NH), 3050 (CH_{Ar}), 1690 (C═O). ^{1}H NMR (DMSO): δ 7.54–8.20 (m, 16ArH), 12.51 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ ^{13}C NMR: δ 111.3 (2C), 121.4 (2CH), 123.7 (2CH), 125.8 (2CH), 128.6 (2CH), 131.8 (2C), 132.0 (2C), 133.2 (2CH), 134.0 (2CH), 137.1 (2C), 137.3 (2C), 139.8 (2CH), 142.4 (2CH), 168.6 (C), 190.2 (2C) and *Anal*. Calcd. for $C_{29}H_{17}Cl_4N_3O_2$ (581): C, 59.89; H, 2.92; N, 7.22; Cl, 24.44. Found: C, 59.88; H, 2.93; N, 7.10; Cl, 24.03. MS: *m*/*z* 583 [$M^{+\cdot}$ + 2], 581 [$M^{+\cdot}$], 550, 338, 262, 235, 193.5.

3,6-Dioxo-2,2,5,5-tetra(3-chlorophenyl)-[1H]imidazolo[3,2-b]pyrazole (11c). Yield 26%, mp 302–304°C, DMF. IR (KBr): ν 3336 (NH), 3100 (CH_{Ar}), 1678 (CO). ^{1}H NMR (DMSO): δ 7.50–8.11 (m, 16ArH), 13.2 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 111.4 (2C), 121.3 (2CH), 123.9 (2CH), 126.0 (2CH), 129.0 (2CH), 131.7 (2C), 132.0 (2C), 133.3 (2CH), 133.8 (2CH), 137.0 (2C), 137.5 (2C), 139.4 (2CH), 142.1 (2CH), 167.4 (2C), 192.1 (2C) and *Anal*. Calcd. for $C_{29}H_{17}Cl_4N_3O_2$ (581): C, 59.89; H, 2.92; N, 7.22; Cl, 24.44. Found: C, 59.87; H, 2.72; N, 7.24; Cl, 24.45. MS: *m*/*z* 583 [$M^{+\cdot}$ + 2], 581 [$M^{+\cdot}$], 263.5, 235, 193.

2,6-Dihydro-3,3,7,7-tetrafuran-2-yl-bispyrazolo[3,4-b,e]pyrazine (11d). Yield 25%, mp 260–262°C, DMF. IR (KBr): ν 3376 (NH), 3073 (CH_{Ar}), 1685 (C═O). ^{1}H NMR (DMSO): δ 6.98–7.34 (m, 12ArH), 12.9 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 129.6 (2CH), 130.2 (2CH), 134.2 (2CH), 135.4 (2CH), 141.6 (2CH), 141.9 (2CH), 166.5 (C), 160.8 (2C), 188.5 (2C), 191.8 (2C), 191.1 (2C) and *Anal*. Calcd. for $C_{21}H_{13}N_3O_6$ (403): C, 62.53; H, 3.22; N, 10.42. Found: C, 62.54; H, 3.23; N, 10.39. MS: *m*/*z* 403 [$M^{+\cdot}$], 269, 175, 158, 145.

General procedure for the preparation of compound 12. In a one-pot reaction of arylidine **5a** (0.01 mol), alkyl amine (0.01 mol), for example, ethylamine, 3-aminopropanol, and benzylamine, in the presence of formaldehyde (0.01 mol) was heated in an oil bath at 190°C for 2–3 h. The mixture was poured onto water after cooling. The solid that separated was filtered off, dried, and crystallized from EtOH.

3-Ethyl-2,7,7-triphenyl-3,4,6,7-tetrahydropyrazolo[1,5-a][1,3,5]triazin-8(2H)-one (12a). Yield 78%, mp 260–262°C. IR (KBr): ν 3279 (NH), 3050 (CH_{Ar}), 1687 (CO), 1631 (C═N). ^{1}H NMR: (DMSO): δ 1.23 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.31 (s, 2H, CH_2N_2), 5.2 (s, 1H, CH), 7.08–7.70 (m, 15ArH), 11.6 (s, 1NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 38.3 (CH_3), 57.2 (CH_2), 74.5 (CH_2), 112.7 (CH), 115.4 (CH), 119.5 (2C), 120.8 (2CH), 122.6 (CH), 124.8 (2CH), 126.7 (2CH), 128.8 (2C), 130.7 (CH), 133.4 (CH), 135.2 (2CH), 137.5 (CH), 139.7 (C), 145.2 (C), 166.2 (C), 178.2 (C) and *Anal*. Calcd. for $C_{25}H_{24}N_4O$ (396): C, 75.73; H, 6.10; N, 14.13. Found: C, 75.66; H, 5.99; N, 14.02.

3-(3-Hydroxypropyl)-2,7,7-triphenyl-3,4,6,7-tetrahydropyrazolo[1,5-a][1,3,5]triazin-8(2H)-one (12b). Yield 85%, mp 284–286°C. IR (KBr): ν 3430 (OH), 3229 (NH), 3050 (CH_{Ar}), 1683 (CO), 1629 (C═N). ^{1}H NMR (DMSO): δ 2.23 (m, 6H, $(CH_2)_3$), 4.2 (s, 2H, CH_2N_2), 5.2 (s, 1H, CH), 7.08–7.70 (m, 15ArH), 10.7 and 12.6 (s, 1NH and 1OH, acidic protons exchanged in D_2O); ^{13}C NMR: δ 39.4 (CH_2), 61.4 ($2CH_2$), 76.4 (CH_2), 112.7 (CH), 115.4 (2C), 119.5 (2C), 120.8 (2CH), 122.6 (CH), 124.8 (2CH), 126.7 (2CH), 128.8 (C), 130.7 (CH), 132.4 (CH), 136.2 (2CH), 137.5 (CH), 140.7 (C), 147.2 (C), 165.2 (C), 168.2 (C) and *Anal*. Calcd. for $C_{26}H_{26}N_4O_2$ (426): C, 73.22; H, 6.14; N, 13.14. Found: C, 73.16; H, 6.09; N, 13.12.

3-Benzyl-2,7,7-triphenyl-3,4,6,7-tetrahydropyrazolo[1,5-a][1,3,5]triazin-8(2H)-one (12c). Yield 74%, mp 222–224°C. IR (KBr): ν 3250 (NH), 3040 (CH_{Ar}), 1682 (CO), 1629 (C═N). ^{1}H NMR (DMSO): δ 5.2 (s, 2H, CH_2Ph), 4.5 (s, 2H, CH_2), 5.1 (s, 1H, CH), 7.08–7.70 (m, 20ArH), 11.4 (s, 1NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 53.4 (CH_2), 77.2 (CH_2), 112.7 (CH), 115.4 (2CH), 119.5 (2C), 120.8 (2CH), 122.6 (2CH), 124.8 (2CH), 126.7 (2CH), 128.8 (C), 130.7 (2C), 133.4 (2CH), 135.2 (2CH), 137.5 (2CH), 139.7 (2C), 145.2 (2C), 166.2 (C), 168.2 (C) and *Anal*. Calcd. for $C_{30}H_{26}N_4O$ (458): C, 78.58; H, 5.72; N, 12.22. Found: C, 78.36; H, 5.59; N, 12.12.

General procedure for the preparation of compound 13. Reflux an equimolar mixture of compound **5a** (0.01 mol) with aromatic amine, for example, aniline, *p*-toluidine and *p*-anisidine, formaldehyde (0.01 mol), and dioxane (30 mL) for 6 h. The solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from DMF.

3-(Benzylideneamino)-5,5-diphenyl-1-((phenylamino)methyl)-1H-pyrazol-4(5H)-one (13a). Yield 77%, mp 194–196°C. IR (KBr): ν 3321 (NH), 3063 (CH_{Ar}), 1685 (CO), 1635 (C═N). ^{1}H NMR (DMSO): δ 5.1 (s, 2H, CH_2), 8.1 (s, 1H, CH), 7.13–7.68 (m, 20ArH), 11.8 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 67.3 (CH_2), 110.6 (2C), 112.4 (CH), 113.8 (2CH), 120.1 (CH), 124.4 (2CH), 127.4 (2CH), 128.5 (2CH), 130.3 (2CH), 131.3 (2CH), 133.6 (CH), 135.6 (2CH), 137.2 (2C), 139.7 (2CH), 144.6 (2C), 167.6 (2C), 188.7 (C) and *Anal*. Calcd. for $C_{29}H_{24}N_4O$ (444): C, 78.36; H, 5.44; N, 12.60. Found: C, 78.25; H, 5.36; N, 12.42.

1-((p-Toluidino)methyl)-3-(benzylideneamino)-5,5-diphenyl-1H-pyrazol-4(5H)-one (13b). Yield 77%, mp 184–186°C. IR (KBr): ν 3319 (NH), 3060 (CH_{Ar}), 1680 (CO), 1628 (C═N). ^{1}H NMR (DMSO): δ 2.21 (s, 3H, CH_3), 5.1 (s, 2H, CH_2), 7.9 (s, 1H, CH), 7.13–7.68 (m, 19ArH), 11.6 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 45.2 (CH_3), 67.3 (CH_2), 110.6 (2C), 112.4 (CH), 113.8 (2CH), 120.1 (CH), 124.4 (2CH), 127.4 (2CH), 128.5 (2CH), 130.3 (2CH), 131.3 (2CH), 133.6 (CH), 135.6 (2CH), 137.2 (2C), 139.7 (2CH), 144.6 (2C), 167.6 (2C), 188.7 (C) and *Anal*. Calcd. for $C_{30}H_{26}N_4O$ (458): C, 78.58; H, 5.72; N, 12.22. Found: C, 78.45; H, 5.56; N, 12.10.

3-(Benzylideneamino)-1-((4-methoxyphenylamino)methyl)-5,5-diphenyl-1H-pyrazol-4(5H)-one (13c). Yield 77%, mp 194–196°C. IR (KBr): ν 3325 (NH), 3055 (CH_{Ar}), 1681 (CO), 1630 (C═N). ^{1}H NMR (DMSO): δ 4.2 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 8.0 (s, 1H, CH), 7.13–7.78 (m, 19ArH), 11.4 (s, NH, acidic proton exchanged in D_2O); ^{13}C NMR: δ 58.2 (CH_3), 67.3 (CH_2), 110.6 (2C), 112.4 (CH), 113.8 (2CH), 120.1 (CH), 124.4 (2CH), 127.4 (2CH), 128.5 (2CH), 130.3 (2CH), 131.3 (2CH), 133.6 (CH), 135.6 (2CH), 137.2 (2C), 139.7 (2CH), 144.6 (2C), 167.6 (2C), 188.7 (C) and *Anal*. Calcd. for $C_{30}H_{26}N_4O_2$ (474): C, 75.93; H, 5.52; N, 11.81. Found: C, 75.75; H, 5.46; N, 11.52.

1,7-Acetyl-3,3-diphenyl-6-oxo-1,2,7-trihydro-pyrazolo[3,4-b]pyrazine (14). Reflux an equimolar mixture of compound **7** (0.01 mol) and chloroacetic acid (0.01 mol) in (20 mL) phosphorous oxychloride for 2 h. The reaction mixture was poured onto ice/H_2O, and the solid that separated was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from toluene. Yield 55%, mp 110–112°C. IR (KBr): ν 3222 (NH), 1670, 1685 (CO), 1613 (C═N). ^{1}H NMR (DMSO): δ 4.50 (s, 2H, CH_2), 6.2 (s, 1H, PyH), 7.44–7.73 (m, 10ArH), 6.2 (s, 1H, acidic NH proton exchanged in D_2O) and *Anal*. Calcd. for $C_{19}H_{14}N_4O_2$ (330): % C, 69.08; H, 4.27; N, 16.96. Found: % C, 69.00; H, 4.19; N, 16.95. MS: *m*/*z* 330 [M^+], 288, 134.

3,3-Diphenyl-1,2-(methylenedicarbonyl)-6-oxo-1,2,7-trihydro-pyrazolo[3,4-b]pyrazine (15). Reflux an equimolar mixture of compound **7** (0.01 mol) and diethylmalonate (0.015 mol) in ethanol (30 mL) for 4 h. The solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and recrystallized from ethanol. Yield 57%, mp 124–126°C. IR (KBr): ν 3245 (NH), 1650, 1672, 1691 (CO), 1630 (C═N), ^{1}H NMR (DMSO): δ 4.41 (s, 2H, $CH_2(CO)_2$), 6.7 (s, 1H, PyH), 7.44–7.83 (s, 10H, ArH), 12.7 (s, acidic NH proton exchanged in D_2O), and *Anal*. Calcd. for $C_{20}H_{14}N_4O_3$ (358): % C, 67.03; H, 3.94; N, 15.63. Found: % C, 67.05; H, 3.88; N, 15.61. MS: *m*/*z* 358 [M^+], 290, 281, 239.

1,2-(Benzylidinemethdicarbonyl)-3,3-diphenyl-6-oxo-1,2,7-trihydro-pyrazolo[3,4-b]pyrazine (16). Method A. Reflux an equimolar mixture of compound **15** (0.01 mol) and benzaldehyde (0.015 mol) in ethanol (30 mL) for 3 h; the solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from butanol with yield of 25%.

Method B. Reflux an equimolar mixture of compound **7** (0.01 mol) and diethyl benzylidene malonate (0.01 mol) in ethanol (30 mL) for 6 h; the solid that separated after cooling was filtered off, washed by petroleum ether (bp 40–60°C), dried, and crystallized from butanol with yield of 24%. mp 180–182°C. IR (KBr): ν 3240 (NH), 1655, 1676, 1685 (CO), 1625 (C═N). ^{1}H NMR (DMSO): δ 6.8 (bs, 2H, PyH and H arylidine), 7.12–7.53 (m, 15ArH), 12.9 (s, acidic NH proton exchanged in D_2O) and *Anal*. Calcd. for $C_{27}H_{18}N_4O_3$ (446): % C, 72.64; H, 4.06; N, 12.55. Found: % C, 72.85; H, 4.15; N, 12.83. MS: *m*/*z* 446 [M^+], 316, 267, 239.

ANTICANCER MOIETY

Materials and methods. ***Cell lines.*** Human breast carcinoma (MCF-7 cell line), colon carcinoma (HCT-116 cell line), and liver carcinoma (HepG 2 cell line) were obtained from Vacsera (Giza, Egypt).

Cell culture. The procedure was performed in a sterile area using a laminar air flow cabinet biosafety class II level.

Culture was maintained in RPMI 1640 medium with 1% antibiotic–antimycotic mixture (10,000 U/mL potassium penicillin, 10,000 μg/mL streptomycin sulfate, and 25 μg/mL amphotericin B) and 1% L-glutamine and supplemented with 10% heat-inactivated fetal bovine serum. Culturing and subculturing were carried out according to Thabrew et al. [19]. Doxorubicin was used as a positive control. A negative control composed of DMSO was also used.

Cell viability assay. This was performed according to Moustafa et al. [20] as described by Mosmann [21]. Following culturing for 10 days, the cells were seeded at concentration of 10 × 103 cells/well in case of MCF-7 and HepG 2, and 20 × 103 cells/well in a fresh complete growth medium in case of HCT-116 cell lines

using 96-well microtiter plastic plates at 37°C for 24 h under 5% CO_2, in a water jacketed carbon dioxide incubator. Fresh medium (without serum) was added, and cells were incubated either alone (negative control) or with samples to give a final concentration of 100 μg/mL. After 24-h incubation, the medium was aspirated, and then 40 μL MTT salt (2.5 mg/mL) was added to each well and incubated for further 4 h at 37°C under 5% CO_2. To stop the reaction and dissolve the formed crystals, 200 μL 10% sodium dodecyl sulfate in deionized water was added to each well and incubated overnight at 37°C. The absorbance was measured using a microplate multi-well reader at 595 nm and a reference wavelength of 690 nm. Cell viability was assessed according to the mitochondrial-dependent reduction of yellow MTT to purple formazan.

Determination of LC50 values. The LC50 values were calculated for the promising active extracts using probit analysis and utilizing the SPSS computer program (SPSS for Windows, statistical analysis software package/version 9/1989 SPSS Inc., Chicago, IL, USA).

REFERENCES AND NOTES

[1] Lim, J.; Altman, M. D.; Baker, J.; Brubaker, J. D.; Chen, H. M.; Chen, Y. P.; Kleinschek, M. A.; Li, C. M.; Liu, D.; Maclean, J. K. F. Bioorg Med Chem Lett 2015, 25, 5384.

[2] Liu, X. H.; Tan, C. X.; Weng, J. Q. Phosphorus Sulfur Silicon Relat Elem 2011, 186, 558.

[3] Bavetsias, V.; Perez-Fuertes, Y.; McIntyre, P. J.; Atrash, B.; Kosmopoulou, M.; O'Fee, L.; Burke, R.; Sun, C. B.; Faisal, A.; Bush, K. Bioorg Med Chem Lett 2015, 25, 4203.

[4] Ghadbeigi, S.; Ostad, S. N.; Shafiee, A.; Amini, M. Lett Drug Des Discov 2015, 12, 754.

[5] Antoszczak, M.; Maj, E.; Napiórkowska, A.; Stefańska, J.; Augustynowicz-Kopeć, E.; Wietrzyk, J.; Janczak, J.; Brzezinski, B.; Huczyński, A. Molecules 2014, 19, 19435.

[6] Chavan, H. V.; Bandgar, B. P.; Adsul, L. K.; Dhakane, V. D.; Bhale, P. S.; Thakare, V. N.; Masand, V. Bioorg Med Chem Lett 2013, 23, 1315.

[7] Du, S.; Tian, Z.; Yang, D.; Li, X.; Li, H.; Jia, C.; Che, C.; Wang, M.; Qin, Z. Molecules 2015, 20, 8395.

[8] Du, S.; Lu, H.; Yang, D.; Li, H.; Gu, X.; Wan, C.; Jia, C.; Wang, M.; Li, X.; Qin, Z. Molecules 2015, 20, 4071.

[9] Wang, Y. H.; Goto, M.; Wang, L. T.; Hsieh, K. Y.; Morris-Natschke, S. L.; Tang, G. H.; Long, C. L.; Lee, K. H. Bioorg Med Chem Lett 2014, 24, 4818.

[10] Fu, C. R.; Pei, J.; Ning, Y.; Liu, M.; Shan, P. C.; Liu, J.; Li, Y. Q.; Hu, F. Z.; Zhu, Y. Q.; Yang, H. Z. Pest Manag Sci 2014, 70, 1207.

[11] Yan, S. L.; Yang, M. Y.; Sun, Z. H.; Min, L. J.; Tan, C. X.; Weng, J. Q.; Wu, H. K.; Liu, X. H. Lett Drug Des Discov 2014, 11, 940.

[12] Reddy, K. R.; Poornachandra, Y.; Dev, G. J.; Mallareddy, G.; Nanubolu, J. B.; Kumar, C. G.; Narsaiah, B. Bioorg Med Chem Lett 2015, 25, 2943.

[13] Wu, H.; Feng, J.-T.; Lin, K.-C.; Zhang, X. Molecules 2012, 17, 12187.

[14] Liu, X. H.; Weng, J. Q.; Wang, B. L.; Li, Y. H.; Tan, C. X.; Li, Z. M. Res Chem Intermed 2014, 40, 2605.

[15] Weng, J. Q.; Liu, X. H.; Tong, G. T. T. Asian J Chem 2013, 25, 2149.

[16] Azab, M. E.; Rizk, S. A.; Amr, A. E. Molecules 2015, 20, 18201.

[17] El-Hashash, M. A.; Rizk, S. A.; Atta-Alla, S. R. Molecules 2015, 20, 22069.

[18] El-Hashash, M. A.; Rizk, S. A. J Heterocyclic Chem 2017, 54, 1776.

[19] Thabrew, M.; Hughes, R. D.; Mcfarlane, I. G. J Pharm Pharmacol 1997, 49, 1132.

[20] Moustafa, S. M.; Menshawi, B. M.; Wassel, G. M.; Mahmoud, K.; Mounier, M. M. Int J ChemTech Res 2014, 6, 1074.

[21] Mosmann, T. J immunol meth 1983, 65, 55.