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ARTICLE

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Synthesis of new pyrazoles, oxadiazoles, triazoles, pyrrolotriazines, and pyrrolotriazepines as potential cytotoxic agents

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Abstract

4-Oxo-4-phenylbutanehydrazide **(1)** reacted with many active methylene reagents such as acetylacetone, diethylmalonate, ethylacetoacetate, ethylcyanoacetate, benzoyl-acetonitrile, and malononitrile under neat conditions to afford the corresponding pyrazoles **(2–7)**, also, treatment of butanehydrazide **(1)** with electrophilic reagents as triethylorthoformate, dimethylformamide-dimethylacetal, acetic anhydride, and carbon disulfide to give 1,3,4-oxadiazoles **(8,10,11)** and *N*′-acetyl-butanehydrazide **(9)**. Reacted of butanehydrazide **(1)** with potassium thiocyanate gave 1,2,4-triazoles **(12)**. Similarly, treatment of **(1)** with chloroacetamide gave 1,2,4-triazinones **(13)**. The pyrrolotriazinones **(14)** was obtained by cyclization of **(13)**. Also, butanehydrazide (**1**) was utilized as a starting material for the synthesized of new Schiff bases as *N*′-(4-sub-benzylidene)-phenylbutane-hydrazide **(15a-c)**, which are used as an initiative to prepare new compounds such as 1,2,4-triazepinones **(16a-c)**, pyrrolotriazepinones **(17a-c)**, 1,2,4-triazines **(18a-c)**, and pyrrolotriazines **(19a-c)** by reacted of **(15a-c)** with each chloroacetamide or formamide. The chemical structure of the newly prepared compounds was determined through the spectrum data, including IR, NMR, and MS. The prepared compounds were tested for their in vitro antitumor activities. The compounds **17a-c**, **16a-c**, and **19a-c** displayed activity against several types of cancer cell lines.

1 | INTRODUCTION

Over the last 10 years, cancer is a disease with high mortality recognized via abnormal cell proliferation and spread. Hence, synthesizing and designing new anticancer drugs with high adequacy and selectivity have important up-to-date significance. In this work, we highlight some of the heterocyclic compounds that might have biological and medicinal relation greatly such as; pyrazole nucleus is considered of among the azole family involves a (five-member ring), pyrazole is a type found in a system of small molecules which display a wide spectrum of pharmaceutical and medicinal properties.[1] Further, pyrazole derivatives are well-known to exhibit a wide spectrum of biological properties as follows: anticancer, antitumor, antioxidant, antimicrobial, anti-inflammatory and analgesic, antidepressant, antipyretic, antiviral, anti-HIV, anticonvulsant, antifungal, and antibacterial.[2–15] In recent years, many pharmaceutical drugs discovered from pyrazole analogs have been commercialized,[16] such as Sildenafil,[17] Fomepizole inhibits alcohol dehydrogenase and inhibits phosphodiesterase; Rimonabant,[18] is used to treat obesity and act as a cannabinoid ligand; Celecoxib,[19] exhibit anti-inflammatory and display COX-2 effects (Figure 1).

Moreover, 1,3,4-oxadiazoles containing are well known for their different biological activities like antimicrobial,[20] anticonvulsant,[21] anti-spasmolytic and hypotensive,[22] anti-inflammatory and analgesic,[23] anti-proliferative,[24] anticancer,[25] hypoglycemic,[26] anti-allergic,[27] and ability to bind to DNA.[28] Furthermore, 1,2,4-Triazole derivatives are known for their pharmacological activity as an analgesic, anticonvulsant and anti-inflammatory,[29] antiviral,[30] anti-tumor,[31] and antimicrobial.[8,32–33] Also, 1,2,4-triazines are considered as 6-aza analogs of pyrimidine bases, it is known that pyrimidines have great biological importance, the 1,2,4-Triazine derivatives have been discovered to demonstrate the diversity of biological uses such as antimicrobial, antiprotozoal, antimalarial, antiparasitic, antiviral, anti-HIV, anticancer, antihypertensive, antihistaminic, tuberculostatic, cardiotonic, nootropic, neuroleptic, estrogen receptor modulators, cyclin-dependent kinase inhibitors, anti-inflammatory, and analgesic activities.[34] Furthermore, triazepine derivatives are known to possess antifungal, antibacterial, antiviral, and psychotropic activities.[35,36] Triazepine derivatives have the ability to inhibit the dipeptidyl peptidase IV (DPP-IV) and treatment of diabetes.[37] In addition, 1,2,4-triazepines have many biological activities like renal vasodilator, salidiuretic, analgesic, antioxidant, and immunomodulating activities.[35,38] The fusion of triazepine to the pyrimidine moiety increases the improvement of the biological activity. Also, Benzodiazepines are psychoactive drugs with sedative, anxiolytic, amnestic properties, and skeletal muscle relaxant. Newly, benzodiazepines and benzotriazepines have been substantiated as potent and highly eclectic protein interaction inhibitors of bromodomain and extra-terminal (BET) proteins [39]. In continuation of our past work in the synthesis of heterocyclic compounds that have different biological and pharmaceutical activities.[2–11,28,32–33,40–45] So, in this manuscript, we prepared new heterocyclic compounds via new procedures such as pyrazoles, 1,3,4-oxadiazoles, 1,2,4-triazoles, 1,2,4-triazines, pyrrolotriazines, 1,2,4-triazepinones and pyrrolotriazepinones and these new compounds are very important class because they afford a wide range of pharmacological activities as, antitumor activity through present study in the manuscript.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The reaction of 4-oxo-4-phenylbutanehydrazide (**1**),[44,45] with many active methylene reagents such as acetylacetone, diethylmalonate, ethylacetoacetate, ethyl cyanoacetate, benzoyl-acetonitrile, and malononitrile under neat conditions to afford the corresponding 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (**2**), 1-(4-oxo-4-phenylbutanoyl) pyrazolidine-3,5-dione (**3**), 1-(5-methyl-3-oxo-2, 3-dihydro-1*H*-pyrazol-1-yl)-4-pheny lbutane-1,4-dione (**4**), 1-(5-amino-3-oxo-2, 3-dihydro-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (**5**), 1-(5-amino-3-phenyl-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (**6**), 3-amino-5-(3-oxo-3-phenylpropyl)-4*H*-pyrazole-4-carbonitrile (**7**), respectively via the intermediate shown in Scheme 1. The ^{1}H-NMR spectrum of **2** showed one singlet signal at δ 6.41 ppm to the one proton of the (CH-pyrazole). The IR spectrum of **3** revealed the absorption bands at ν 3250 cm^{-1} due to the (NH) group and 1725, 1690, 1685, 1681 cm^{-1} to four carbonyl groups. The ^{1}H-NMR spectrum of **4** displayed one singlet signal at δ 12.12 ppm corresponding to the one proton of the (NH) group (with D_2O exchangeable). Also, The ^{1}H-NMR spectrum of **5** exhibited two singlet signals at δ 6.55, 12.01 ppm corresponding to the two and one protons of the (NH_2) and (NH) groups (with D_2O exchangeable), respectively. Furthermore, IR spectrum of **6** showed absorption bands at ν 3420 cm^{-1} for (NH_2) group and 1715, 1676 cm^{-1} for two carbonyl groups. Moreover, the

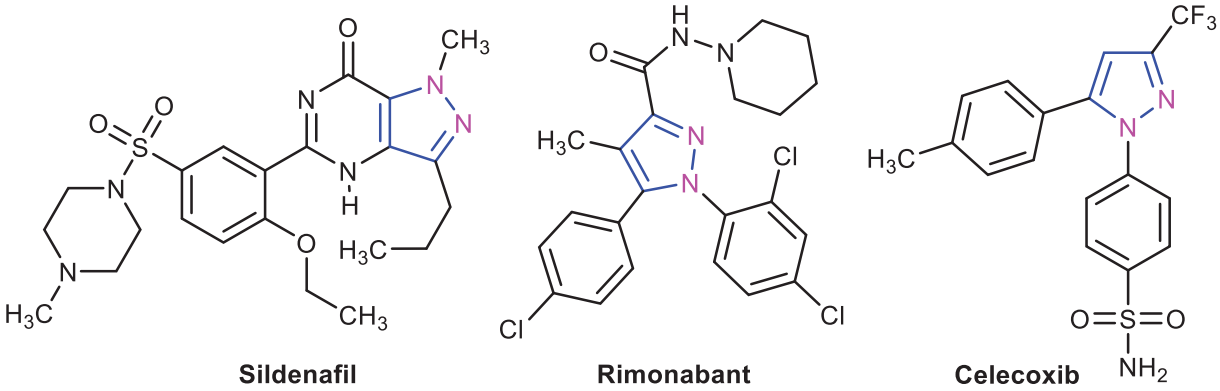
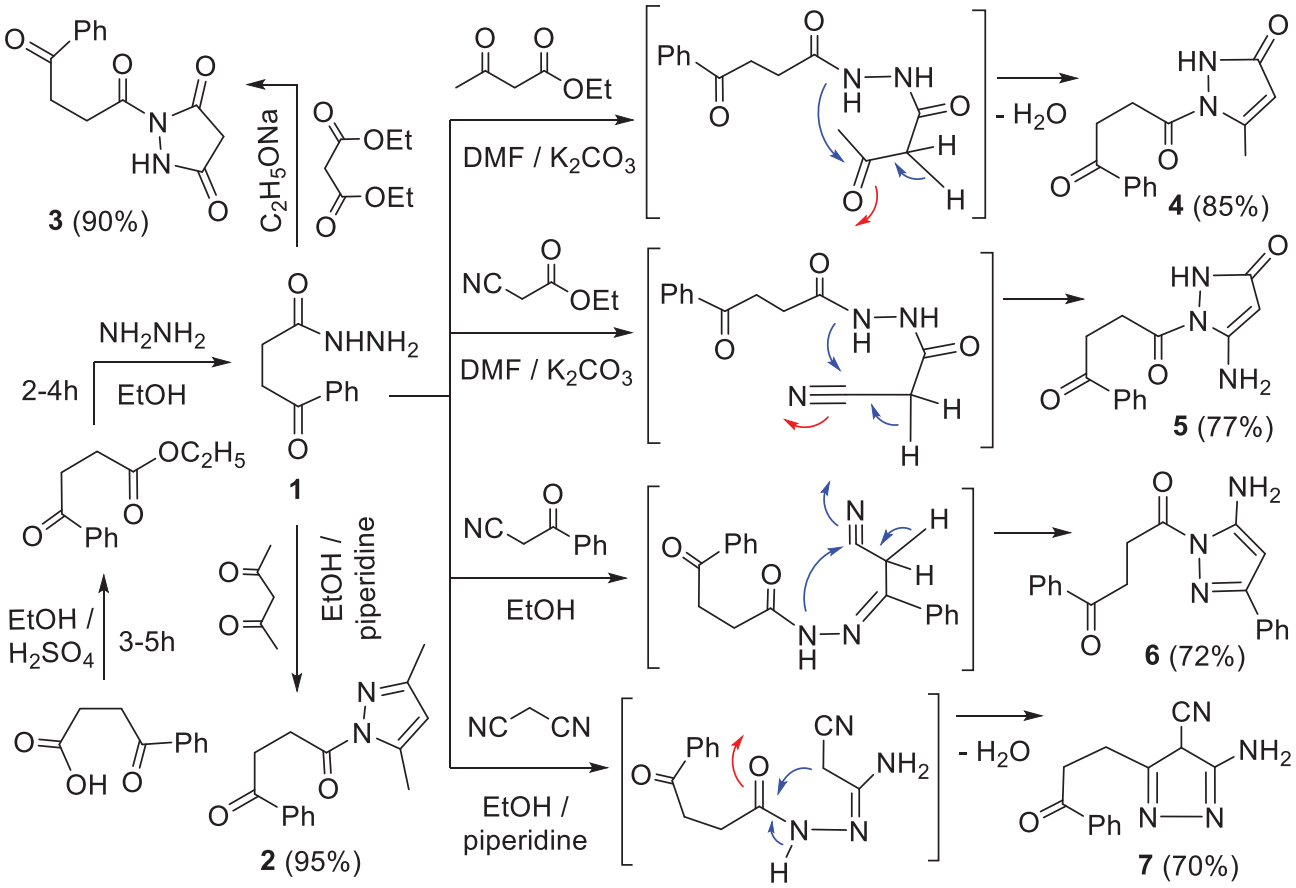


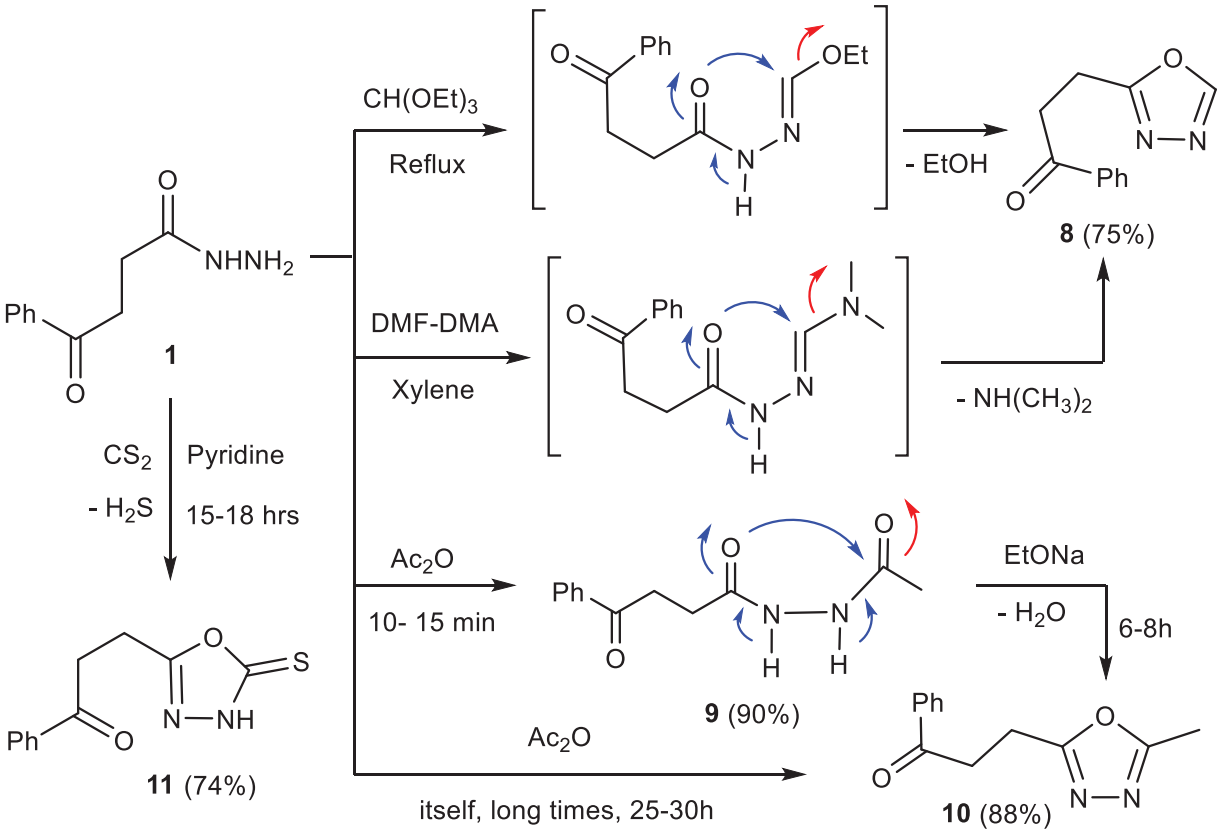
FIGURE 1 The pyrazole derivatives drugs with bioactive molecules [Colour figure can be viewed at wileyonlinelibrary.com]



SCHEME 1 Synthesis of pyrazole derivatives from butanehydrazide [Colour figure can be viewed at wileyonlinelibrary.com]

IR spectrum of **7** displayed the absorption bands at ν 3425 cm^{-1} due to the NH_2 group and 2210 and 1727 cm^{-1} for the one (CN) and one carbonyl group, respectively. Besides, The ^{1}H-NMR spectrum of **7** exposed one singlet signal at δ 6.25 ppm to the two protons of the (NH_2) groups (with D_2O exchangeable). The MS of **2**, **3**, **4**, **5**, **6**, and **7** demonstrated molecular ion peaks at m/z = 256 (M^+, 67%), 260 (M^+, 100%), 258 (M^+, 92%), 259 (M^+, 85%), 319 (M^+, 84%), 240 (M^+, 100%), respectively. All spectral data IR, NMR, MS, and elemental analysis of new compounds were elucidated in the experimental part (Scheme 1).

Similarly, when 4-oxo-4-phenylbutanehydrazide (**1**) was treated with triethylorthoformate or dimethylform amidedimethylacetal in xylene afforded 3-(1,3,4-oxadiazol-2-yl)-1-phenylpropan- 1-one (**8**) via the intermediate shown in Scheme 2. The IR spectrum of compound **8** showed the existence absorption bands at ν 3080, 2970 cm^{-1} of one CH-aryl and CH-alkyl group's and 1730 cm^{-1} of one carbonyl group and the ^{13}C-NMR spectrum of **8** presented absorption signals at δ 26.5 and 37.1 ppm, conforming to two carbon atom of the ($2CH_2$) groups and 115.4 ppm to one carbon atom of the (CH-oxadiazole), and 191.8 ppm to one carbon atom of the one carbonyl group. Condensation of carbohydrazides (**1**) with acetic anhydride for 10–15 min gave ***N′***-acetyl-4-oxo-4-phenylbutanehydrazide (**9**) which underwent intermolecular cyclization in ethanolic sodium ethoxide solution for 6–8 h to give 3-(5-methyl-1, 3, 4-oxadiazol-2-yl)-1-phenylpropan-1-one (**10**). Also, we obtained the latter compound (**10**) by refluxing of carbohydrazides (**1**) in acetic anhydride for a long time about 25–30 h. IR spectrum of (**9**) showed absorption bands at ν 3250 cm^{-1} for (2NH) and 1720, 1681 cm^{-1} for two carbonyl groups. In addition, the ^{1}H-NMR spectrum of (**9**) exhibited two singlet signals at δ 10.05 and 10.47 ppm to the two protons of the (2NH) groups (with D_2O exchangeable). Likewise, its ^{1}H-NMR spectrum of (**10**) revealed the following signals at δ 1.86 ppm to singlet of three protons (CH_3) and 2.39–-2.43 ppm to triplet of the two protons (CH_2) and 3.76–-3.90 ppm to triplet of two protons (CH_2) groups. In addition, the 1-phenyl-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) propan-1-one (**11**) was synthesized by the reaction of carbo-hydrazides (**1**) with carbondisulfide in pyridine solution. The ^{1}H-NMR spectrum of **11** showing one singlet signals at δ 11.20 ppm for the one proton of one (NH) group (D_2O exchangeable). Also, the mass spectrum of **8**, **9**, **10** and **11** showed the molecular ion peak at $m/$

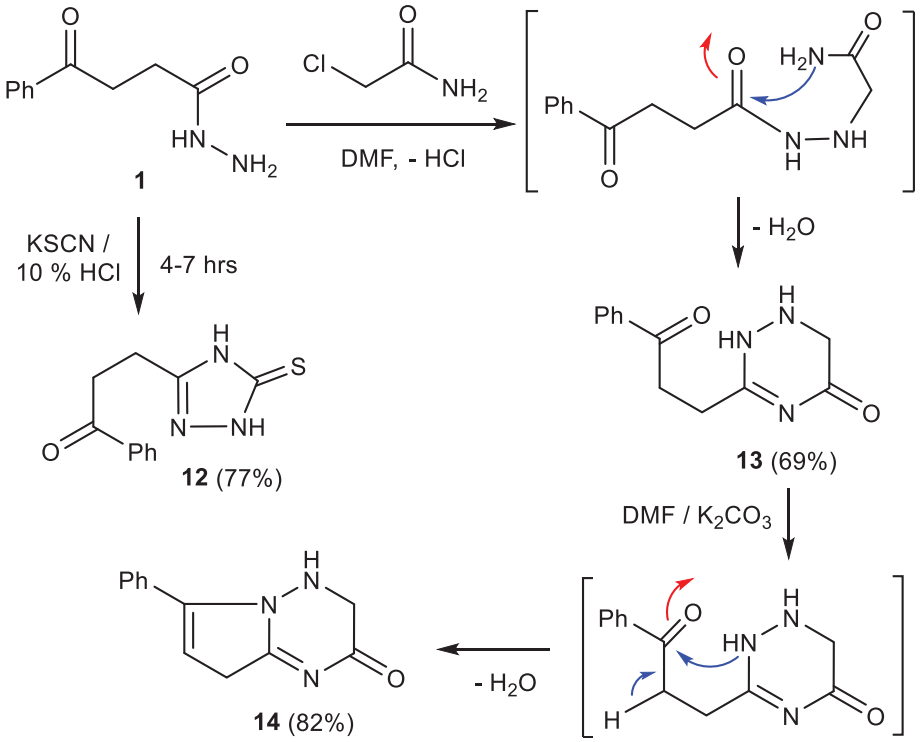


SCHEME 2 Synthesis of substituted 1,3,4-oxadiazoles from butanehydrazide [Colour figure can be viewed at wileyonlinelibrary.com]

z = 202 (M^+, 90%), 234 (M^+, 100%), 216 (M^+, 95%), 234 (M^+, 98%), respectively. The chemical structures of final products were fully confirmed via IR, NMR, and Mass spectra as shown in (Scheme 2).

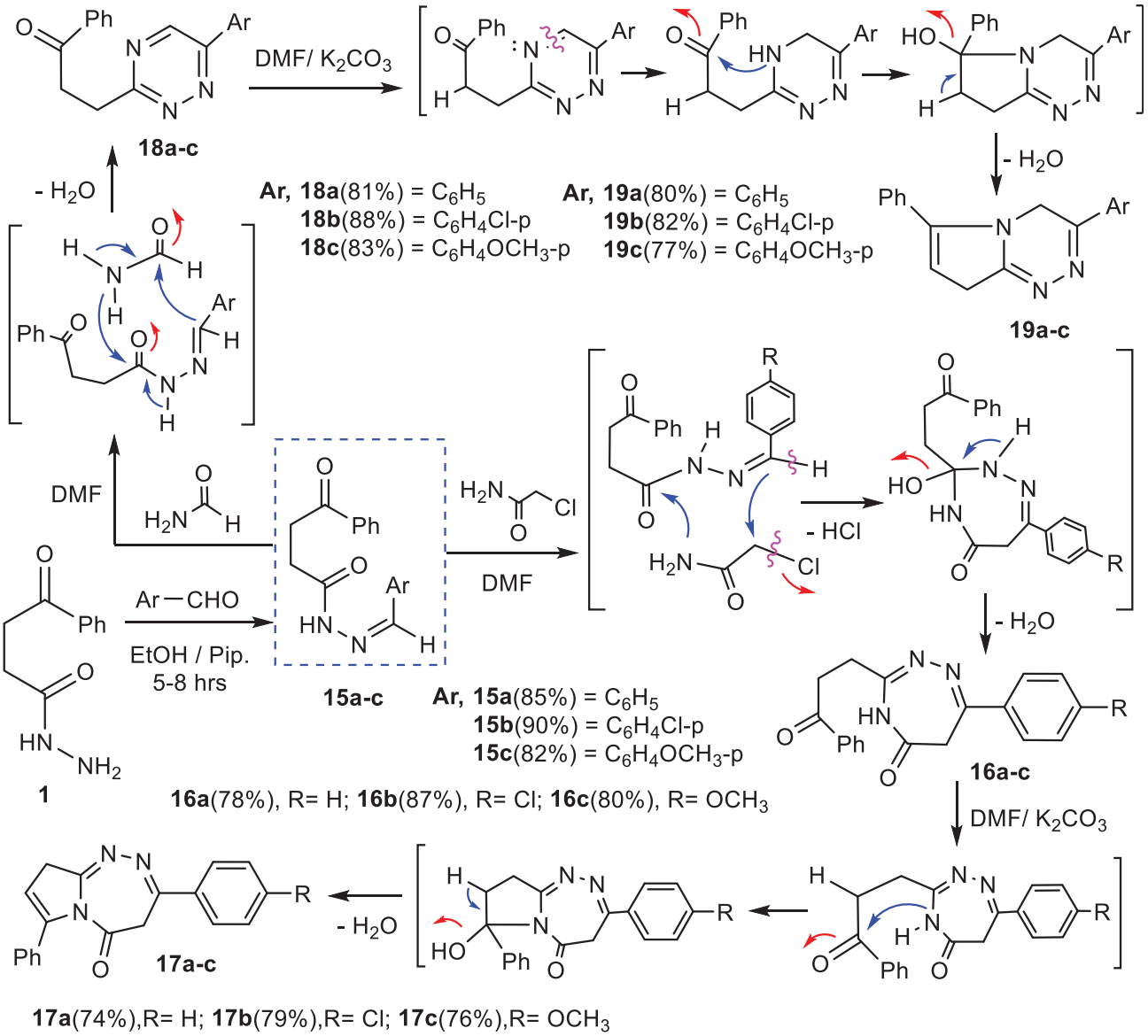
Our study was prolonged to the reaction of 4-oxo-4-phenylbutanehydrazide (**1**) with potassium thiocyanate in the presence of aqueous hydrochloric acid for 4–7 h gave 1-phenyl-3-(5-thioxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl) propan-1-one (**12**). Also, reacted of carbo-hydrazides (**1**) with chloroacetamide in dimethylformamide to give 3-(3-oxo-3-phenylpropyl)-1,6-dihydro-1,2,4-triazin-5(2*H*)-one (**13**) via the intermediate shown in Scheme 3. Thus, the same acyclic compound (**13)** underwent intramolecular cyclization in boiling dimethylformamide in the presence of anhydrous potassium carbonate afforded 6-phenyl-3,4-dihydropyrrolo [1,2-b] [1,2,4] triazin-2(8*H*)-one (**14**). The IR spectrum of **12** showed absorption bands at ν 3338–3131 cm^{-1} for the two (2NH) and 1673 cm^{-1} for the one carbonyl groups. Likewise, the ^{1}H-NMR spectrum of **12** showed two singlet signals at δ 10.85 and 12.91 ppm for the two protons of one (2NH) groups (D_2O exchangeable). Also, the IR spectrum of **13** indicated absorption bands at ν 3270–3200 cm^{-1} for the two (2NH) and 1735, 1672 cm^{-1} for the two carbonyl groups and the ^{1}H-NMR spectrum of **13** exhibited two singlet signals at δ 11.60 and 12.20 ppm for the two protons of one (2NH) groups (D_2O exchangeable). Similarly, the IR spectrum of **14** revealed absorption bands at ν 3255 cm^{-1} for the one (NH) and 1685 cm^{-1} for the one carbonyl group and the ^{1}H-NMR spectrum of **14** demonstrated one singlet signal at δ 11.59 ppm for the one proton of (NH) group (D_2O exchangeable). Moreover, the mass spectrum of **12**, **13**, and **14** displayed the molecular ion peak at m/z = 233 (M^+, 94%), 231 (M^+, 100%), 213 (M^+, 97%), respectively. The chemical structures of the final products were fully confirmed through IR, ^{1}H-NMR, and MS as shown in (Scheme 3).

The reaction of 4-oxo-4-phenylbutanehydrazide (**1**) with appropriate aryl aldehydes namely; (benzaldehyde, 4-chlorobenzaldehyde, or 4-methoxybenzaldehyde) in ethanol with the presence of piperidine as a base gave *N*′-(4-substituted-benzylidene)-4-oxo-4-phenylbutanehydrazide (**15a-c**). The IR spectrum of **15a** exposed absorption bands at ν 3230 cm^{-1} for the one (NH) and 1738, 1677 cm^{-1} for the two carbonyl groups and the ^{1}H-NMR spectrum of **15a** proved one singlet signal at δ 11.50 ppm for the one proton of (NH) group (D_2O exchangeable). Besides, the mass spectrum of **15a**, **15b**, and **15c** showed the molecular ion peak at m/z = 280 (M^+, 100%), 314 (M^+, 97%), 310 (M^+, 88%),



SCHEME 3 Synthesis of 1,2,4-triazoles; 1,2,4-triazinones and pyrrolotriazinones [Colour figure can be viewed at wileyonlinelibrary.com]

respectively. Furthermore, the reaction of arylidene carbohydrazones (**15a-c**) with chloroacetamide in dimethylformamide to yield 7-(4-substituted-phenyl)-3-(3-oxo-3-phenylpropyl)-4,6-dihydro-5*H*-1,2,4-triazepin-5-one (**16a-c**) via the intermediate, the IR spectrum of **16a** was characterized via disappearance of carbonyl group and displayed an absorption bands at 3305 cm^{-1} for the one (NH) and 1733, 1685 cm^{-1} for the two carbonyl groups and the ^{1}H-NMR spectrum of **16a** evidenced one singlet signal at δ 8.52 ppm for the one proton of (NH) group (D_2O exchangeable) and the ^{13}C-NMR spectrum of **16a** exposed absorption signals at δ 15.6, 21.5, and 31.2 ppm, corresponding to three carbon atoms of the ($3CH_2$) groups and 168.6, 168.9 ppm, conforming to two carbon atoms of two carbonyl groups. Moreover, condensation of (**16a-c**) in dimethylformamide and anhydrous potassium carbonate with refluxing for 17–20 h under control (TLC) to give 3-(4-substituted-phenyl)-7-phenyl-4,9-dihydro-5*H*-pyrrolo[2,1-c] [1,2,4] triazepin-5-one **(17a-c)** via the intermediate, the IR spectrum of **17a** was described by disappearance of (NH) and carbonyl group and exhibited an absorption bands at 1678 cm^{-1} for the one carbonyl groups. The ^{1}H-NMR spectrum of **17a** showed one doublet signal at δ 2.62 ppm for the two protons of (CH_2) and one singlet signal at δ 3.90 ppm for the two protons of (CH_2) and one triplet signal at δ 4.90–5.10 ppm for the one proton of (CH_pyrrole). The mass spectra of **17a**, **17b**, and **17c** indicated molecular ion peaks at *m*/*z* 301 (M^+, 90%), 335(M^+, 30%), and 331 (M^+, 84%), respectively. Also, when arylidene carbohydrazones (**15a-c**) was treated with formamide in boiling dimethylformamide afforded a cyclic structure 3-(6-(4-substituted-phenyl)-1,2,4-triazin-3-yl)-1-phenylpropan-1-one (**18a-c**) via the intermediate. The ^{1}H-NMR spectrum of **18a** revealed two triplet signals at δ 2.70 and 2.82 ppm for the four protons of ($2CH_2$) and one singlet signal at δ 8.10 ppm for the one proton of (CH-triazine). Moreover, a cyclic structure (**18a-c**) underwent intramolecular cyclization in refluxing dime thylformamide in the presence of anhydrous potassium carbonate for 15–18 h to give 3-(4-substituted-phenyl)-6-phenyl-4, 8-dihydropyrrolo[2,1-c] [1,2,4] triazine (**19a-c**) via the intermediate shown in Scheme 4. The ^{1}H-NMR spectrum of **19a** showed one doublet signal at δ 3.11–-3.27 ppm for the two protons of (CH_2-pyrrole) and one singlet signal at δ 4.17 ppm for the two protons of (CH_2-triazine) and one triplet signal at δ 6.70 ppm for the one proton of (CH-pyrrole) and the ^{13}C-NMR spectrum of **19a** displayed absorption signals at δ 21.6 and 58.5 ppm, agreeing to two carbon atoms of the ($2CH_2$) groups and 79.7 ppm, matching to one carbon atoms of one (CH-pyrrole). The MS of **19a**, **19b**, and **19c** exhibited molecular ion peaks at *m*/*z* 273 (M^+, 100%), 307 (M^+, 40%), and 303 (M^+, 90%), respectively. All spectral data of new compounds are described in the experimental section (Scheme 4).



SCHEME 4 Synthesis of pyrrolo [2,1-c] [1,2,4] triazepinones and pyrrolotriazines [Colour figure can be viewed at wileyonlinelibrary.com]

3 | BIOLOGICAL ACTIVITIES

3.1 | Antitumor screening (in vitro *cytotoxicity*)

The new compounds such as pyrazoles, 1,3,4-oxadiazoles, 1,2,4-triazoles, pyrrolotriazines, and pyrrolotriazepines were tested for their in vitro cytotoxicity using the standard MTT method,[46–48] versus the human gastric carcinoma cells (MGC-803), nasopharyngeal carcinoma cells (CNE2), oral carcinoma cells (KB) and breast adenocarcinoma cells (MCF-7).The MTT method is based on the reduction of soluble 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide. As displayed in (Table 1), the final results in products **17a-c**, **16a-c**, **19a-c**, **14**, and **12** exposed different degrees of antitumor activity, and the antitumor influence of most products on different cancer cell lines was superior to the 5-fluorouracil positive control. Several of the compounds exhibited moderate and good activity on all the tested cancer cell lines. Therefore, the compounds **17a-c**, **16a-c**, **19a-c**, **14**, and **12** showed the highest cytotoxicity versus all carcinoma cell lines as follows; the MGC-803 (IC_{50}: **17a-c**, 11.3, 11.1, 11.2: **16a-c**, 11.7, 11.5, 11.6: **19a-c**, 12.2, 11.9, 12.1: **14**, 12.5 and **12**, 12.8 μM), the CNE2 (IC_{50}: **17a-c**, 12.3, 12.1, 12.2: **16a-c**,12.6, 12.4, 12.5: **19a-c**, 13.1, 12.8, 12.9: **14**, 13.4 and **12**, 13.8 μM), the KB (IC_{50}: **17a-c**, 11.4, 11.2, 11.3: **16a-c**, 11.7, 11.5, 11.6: **19a-c**, 12.1, 11.8, 11.9: **14**, 12.6 and **12**, 12.9 μM), the MCF-7 (IC_{50}: **17a-c**, 11.9, 11.7, 11.8: **16a-c**, 12.3, 12.1, 12.2: **19a-c**, 12.7, 12.5, 12.6: **14**, 12.9 and **12**, 14.2 μM), respectively. Furthermore, some compounds as; **18a-c**, **13**, **15a-c**, **11**, **10**, and

TABLE 1 Cytotoxic activity of the new compounds versus diverse human cancer cell lines

Compounds	In vitro cytotoxicity IC_{50} (μM)			
	MGC-803[a]	CNE2[a]	KB[a]	MCF-7[a]
1	>50	>50	>50	>50
2	34.4 ± 1.8	35.6 ± 1.7	33.9 ± 1.3	34.7 ± 1.5
3	37.2 ± 1.6	38.4 ± 1.3	37.7 ± 1.6	37.5 ± 1.4
4	31.1 ± 1.3	32.3 ± 1.5	30.8 ± 1.1	31.8 ± 1.6
5	27.9 ± 1.7	29.1 ± 1.2	27.6 ± 1.4	28.7 ± 1.2
6	25.7 ± 1.2	26.9 ± 1.4	25.4 ± 1.5	26.5 ± 1.1
7	24.5 ± 1.4	25.7 ± 1.6	24.2 ± 1.3	25.3 ± 1.5
8	22.3 ± 1.5	23.6 ± 1.8	22.1 ± 1.2	23.2 ± 1.4
9	44.5 ± 2.1	45.7 ± 2.2	44.2 ± 2.4	44.8 ± 2.3
10	19.2 ± 1.2	20.5 ± 1.7	18.9 ± 1.3	20.1 ± 1.8
11	17.5 ± 1.8	18.7 ± 1.4	17.2 ± 1.1	18.4 ± 1.6
12	12.8 ± 1.7	13.8 ± 1.5	12.9 ± 1.4	14.2 ± 1.5
13	14.1 ± 2.2	15.1 ± 2.1	14.2 ± 1.5	15.3 ± 1.4
14	12.5 ± 1.5	13.4 ± 1.3	12.6 ± 1.1	12.9 ± 1.2
15a	15.3 ± 2.2	15.9 ± 1.7	15.1 ± 1.5	16.2 ± 1.4
15b	14.6 ± 1.8	15.5 ± 1.9	14.7 ± 1.4	15.8 ± 1.7
15c	14.9 ± 2.1	15.8 ± 1.8	14.9 ± 1.6	15.9 ± 1.3
16a	11.7 ± 1.6	12.6 ± 1.4	11.7 ± 1.2	12.3 ± 1.5
16b	11.5 ± 1.2	12.4 ± 1.3	11.5 ± 1.5	12.1 ± 1.7
16c	11.6 ± 1.5	12.5 ± 1.6	11.6 ± 1.7	12.2 ± 1.8
17a	11.3 ± 1.4	12.3 ± 1.5	11.4 ± 1.3	11.9 ± 1.4
17b	11.1 ± 1.1	12.1 ± 1.3	11.2 ± 1.2	11.7 ± 1.6
17c	11.2 ± 1.3	12.2 ± 1.4	11.3 ± 1.1	11.8 ± 1.5
18a	13.7 ± 2.3	14.8 ± 1.9	13.9 ± 1.7	14.9 ± 2.1
18b	13.1 ± 1.8	14.2 ± 1.7	13.2 ± 1.5	14.5 ± 1.3
18c	13.3 ± 2.1	14.5 ± 1.4	13.6 ± 1.8	14.7 ± 2.2
19a	12.2 ± 1.3	13.1 ± 1.6	12.1 ± 1.4	12.7 ± 1.1
19b	11.9 ± 1.4	12.8 ± 1.1	11.8 ± 1.3	12.5 ± 1.4
19c	12.1 ± 1.7	12.9 ± 1.2	11.9 ± 1.6	12.6 ± 1.5
5-Fluorouracil	11.4 ± 1.2	12.2 ± 1.5	11.1 ± 1.1	11.9 ± 1.7

[a]**MGC-803** cells are drug-sensitive human gastric carcinoma cells, **CNE2** cells are drug-sensitive human nasopharyngeal carcinoma cells, **KB** cells are drug-sensitive human oral carcinoma cells and **MCF-7** cells are drug-sensitive human breast adenocarcinoma cells.

8 exposed modest cytotoxicity versus the carcinoma cell lines. Also, the remainder of the compounds indicated low cytotoxicity activities.

3.2 | Structure–activity relationships

In this study, through contrasting the monitored cytotoxicity activities of the new compounds, we obtained chemical structures, the (SAR's) were presumed. (A) The existence of the pyrrolotriazepine; 1,2,4-triazepine; pyrrolotriazine; 1,2,4-triazole; 1,2,4-triazine; 1,3,4-oxadiazole and pyrazole moieties possibly requested for a broad spectrum of the cytotoxicity activity. (B) The 3-(4-substituted-phenyl)-7-phenyl-4,9-dihydro-5*H*-pyrrolo[2,1-c] [1,2,4] triazepin-5-one (**17a-c**), 7-(4-substituted-phenyl)-3-(3-oxo-3-phenylpropyl)-4,6-dihydro-5*H*-1,2,4-triazepin-5-one (**16a-c**), 3-(4-substituted-phenyl)-6-phenyl-4,8-dihydropyrrolo[2,1-c] [1,2,4] triazine (**19a-c**), 6-phenyl-3,4-dihydropyrrolo[1,2-b] [1,2,4] triazin-2(8*H*)-one (**14**) and 1-phenyl-3-(5-thioxo-4,-5-dihydro-1*H*-1,2,4-triazol-3-yl) propan-1-one (**12**) displayed high in vitro anti-tumor activity and this confirms

previous scientific studies as follows; many heterocyclic compounds possess biological activities such as triazepines, oxadiazepines, oxadiazoles, pyrazolidines and ben zohydrazides, revealed cytotoxic activity,[05] and benzofur anquinoxalines, piperazinbenzofurans, and pyrazolobenzofurans showed cytotoxic activity,[02] and Pyrazolopyrimidoquinoline, triazolotetrahydropyrimidoquinoline, triazolopyrimidoquinoline exhibited potent antitumor activity.[4,49] Similarly, thiophenecarbohydrazide, thienopyr azole, and thieno-pyrimidine as potential antioxidant and antitumor agents.[3] Also, 1,2,4-triazine and 1,2,3-triazine derivatives are the most studied ones having remarkable antitumor activity.[50–53] (C) Thus, the products **17a-c**, **16a-c**, **19a-c**, **14**, and **12** presented high cytotoxicity versus all carcinoma cell lines in comparison with 5-Fluorouracil as stander drug.

4 | EXPERIMENTAL SECTION

4.1 | Materials

All materials used were obtained from Sigma Aldrich (Saint Lewis).

4.2 | Equipment's

All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. TLC analysis was carried out on silica gel 60 F_{254} precoated aluminum sheets. The IR spectra were recorded (KBr) on a Perkin–Elmer 1430 spectrometer (λ, cm^{-1}) in National Research Centre, Egypt. ^1H and ^{13}C-NMR spectra were measured on JEOL-ECA 500 and JEOL JNM-LA-400 FT NMR Spectrometers at 500, 125 MHz, respectively, using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as the solvent at the Microanalytical Center in National Research Centre, Egypt. The mass spectra (EI) were recorded on GCMS-QP 1000 EX (Shimadzu) at National Research Centre, Egypt. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center in National Research Centre, Egypt. The elemental analyses were found to agree favorably with the calculated values. Biological evaluations were done by the antitumor unit, Department of Pharmacognosy, Faculty of pharmacy, Mansoura University, Egypt.

4.3 | Synthesis of 4-oxo-4-phenylbutanehydrazide (1)

A mixture of ethyl 4-oxo-4-phenylbutanoate (2.10 ml, 0.01 mol) and hydrazine monohydrate (0.01 mol; 80%–90%) in absolute ethanol (30 ml) was stirred under refluxed for 2–4 h.[45] The reaction mixture was then allowed to cool to room temperature. The solid was filtered, washed with methanol, dried, and crystallized from dioxane to give **1**, as yellow crystals, in 90% yield, m. p. 170–172°C. IR (KBr): ν_{max} = 3405–3325 (brs, NH, NH_2), 3045 (CH, aryl), 2952 (CH, alkyl), 1722, 1675 (2C═O), 1578 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.22–2.27 (*t*, 2H, *J* = 5.48 Hz, CH_2), 3.20–3.25 (*t*, 2H, *J* = 5.49 Hz, CH_2), 6.10 (br, 2H, NH_2, D_2O exchangeable), 7.55–7.92 (*m*, 5H, Ar-H), 9.08 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 30.1, 33.8 (2C, $2CH_2$), 128.4, 128.9, 131.5, 134.8 (6C, Ar-C), 174.7, 182.2 (2C, 2C═O); MS (70 eV): *m/z* = 192 (M^+, 100%); Anal. Calc. (Found) for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49 (62.40); H, 6.29 (6.21); N, 14.57 (14.68).

4.4 | Synthesis of 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (2)

A solution of compound **1** (1.92 g, 0.01 mol) and acetyl acetone (1.03 ml, 0.01 mol) in absolute ethanol (40 ml) with catalytic amount of (1 ml) piperidine was heated under reflux for 10–15 h. the reaction mixture was allowed to cool, and poured into crushed ice then acidified with hydrochloric acid. The separated solid was filtered off washed with water (H_2O), dried and recrystallized from methanol as yellowish crystals in 95% yield, m. p. 274–276°C. IR (KBr): ν_{max} = 3055 (CH, aryl), 2950 (CH, alkyl), 1730, 1680 (2C═O), 1625 (C═N), 1582 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.15, 1.16 (2s, 6H, $2CH_3$), 2.01–2.22 (*t*, 2H, *J* = 4.80 Hz, CH_2), 3.72–3.95 (*t*, 2H, *J* = 4.75 Hz, CH_2), 6.41 (*s*, 1H, CH-pyrazole), 7.06–7.60 (*m*, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 28.6, 30.5 (2C, $2CH_3$), 39.1, 39.4 (2C, $2CH_2$),112.1(1C, CH-pyrazole), 123.2, 124.2, 126.4, 126.5, 136.2, 149.4 (8C, Ar-C), 160.6, 166.9 (2C, 2C═O); MS (70 eV): *m/z* = 256 (M^+, 67%); Anal. Calc. (Found) for $C_{15}H_{16}N_2O_2$ (256.31): C, 70.29 (70.35); H, 6.29 (6.23); N, 10.93 (10.86).

4.5 | Synthesis of 1-(4-oxo-4-phenylbutanoyl) pyrazolidine-3,5-dione (3)

A mix of compound **1** (1.92 g, 0.01 mol) and diethylmalonate (1.52 ml, 0.01 mol) in ethanolic sodium ethoxide was heated under reflux for 14–17 h. The reaction mixture was allowed to cool and poured into water/ice then acidified with hydrochloric acid. The separated solid was filtered off washed with water, dried and recrystallized from dioxane as white crystals in 90% yield, m. p. 242–244°C. IR (KBr): ν_{max} = 3250 (br, NH), 3060

(CH, aryl), 2958 (CH, alkyl), 1725, 1690, 1685, 1681 (4C═O), 1580 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.21–2.42 (*t*, 2H, *J* = 4.84 Hz, CH_2), 3.12 (*s*, 2H, CH_2, pyrazole), 3.27–3.38 (*t*, 2H, *J* = 4.77 Hz, CH_2), 7.41–7.81 (*m*, 5H, Ar-H); 10.47 (br, 1H, NH, D_2O exchangeable);^{13}C NMR (DMSO-d_6) δ = 28.5, 32.2 (2C, $2CH_2$), 50.2(1C, CH_2-pyrazole), 128.4, 128.7, 132.8, 135.6 (6C, Ar-C), 165.3, 168.8, 170.7, 185.1 (4C, 4C═O); MS (70 eV): *m/z* = 260 (M^+, 100%); Anal. Calc. (Found) for $C_{13}H_{12}N_2O_4$ (260.25): C, 60.00 (60.10); H, 4.65 (4.58); N, 10.76 (10.82).

4.6 | Synthesis of 1-(5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (4)

A mix of compound **1** (1.92 g, 0.01 mol) and ethyl acetoacetate (1.27 ml, 0.01 mol) in DMF (40 ml)/K_2CO_3 was heated under reflux for 12–15 h. The reaction mixture was allowed to cool and poured into water/ice. The separated solid was filtered off washed with water, dried and recrystallized from methanol as yellowish crystals in 85% yield, m. p. 255–257°C. IR (KBr): ν_{max} = 3260 (br, NH), 3065 (CH, aryl), 2962 (CH, alkyl), 1727, 1682, 1675 (3C═O), 1578 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.30 (*s*, 3H, CH_3), 2.63–2.69 (*t*, 2H, *J* = 4.88 Hz, CH_2), 3.30–3.33 (*t*, 2H, *J* = 4.85 Hz, CH_2), 5.70 (*s*, 1H, CH, pyrazole), 7.44–7.96 (*m*, 5H, Ar-H); 12.12 (br, 1H, NH, D_2O exchangeable);^{13}C NMR (DMSO-d_6) δ = 21.8 (1C, CH_3), 25.9, 35.4 (2C, $2CH_2$), 100.6 (1C, CH-pyrazole), 125.5, 128.4, 129.2, 135.9, 149.3 (7C, Ar-C), 164.8, 166.6, 169.2 (3C, 3C═O); MS (70 eV): *m/z* = 258 (M^+, 92%); Anal. Calc. (Found) for $C_{14}H_{14}N_2O_3$ (258.28): C, 65.11 (65.18); H, 5.46 (5.40); N, 10.85 (10.92).

4.7 | Synthesis of 1-(5-amino-3-oxo-2,3-dihydro-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (5)

A mixture of compound **1** (1.92 g, 0.01 mol) and ethylcyanoacetate (1.06 ml, 0.01 mol) in DMF (45 ml)/K_2CO_3 was heated under reflux for 14–17 h (TLC). The reaction mixture was allowed to cool and poured into H_2O / ice. The product solid was filtered off washed with water, dried and recrystallized from methanol as yellow crystals in 77% yield, m. p. 208–210°C. IR (KBr): ν_{max} = 3430–3405 (br, NH_2, NH), 3070 (CH, aryl), 2966 (CH, alkyl), 1720, 1684, 1670 (3C═O), 1587 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.24–2.31 (*t*, 2H, *J* = 4.82 Hz, CH_2), 3.03–3.39 (*t*, 2H, *J* = 4.81 Hz, CH_2), 5.05 (*s*, 1H, CH, pyrazole), 6.61 (*s*, 2H, NH_2), 7.06–7.64 (*m*, 5H, Ar-H); 10.27 (br, 1H, NH, D_2O exchangeable);^{13}C NMR (DMSO-d_6) δ = 30.5, 35.1 (2C, $2CH_2$), 80.2 (1C, CH-pyrazole), 128.1, 128.5, 133.6, 135.4, 156.4 (7C, Ar-C), 165.4, 168.8, 182.7 (3C, 3C═O); MS (70 eV): *m/z* = 259 (M^+, 85%); Anal. Calc. (Found) for $C_{13}H_{13}N_3O_3$ (259.27): C, 60.23 (60.30); H, 5.05 (5.12); N, 16.21 (16.27).

4.8 | Synthesis of 1-(5-amino-3-phenyl-1*H*-pyrazol-1-yl)-4-phenylbutane-1,4-dione (6)

A mixture of, **1** (1.92 g, 0.01 mol) and benzoyl acetonitrile (1.45 g, 0.01 mol) in absolute ethanol (40 ml) was refluxed for 6–9 h (TLC). After cooling, the solvent was evaporated and the solid residue was recrystallized from dioxane as yellow crystals in 72% yield, m. p. 223–225°C. IR (KBr): ν_{max} = 3420 (br, NH_2), 3075 (CH, aryl), 2962 (CH, alkyl), 1715, 1676 (2C═O), 1620 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.70–2.75 (*t*, 2H, *J* = 4.90 Hz, CH_2), 3.38–3.41 (*t*, 2H, *J* = 4.87 Hz, CH_2), 6.40 (*s*, 2H, NH_2), 6.80 (*s*, 1H, CH, pyrazole), 7.24–7.95 (*m*, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 23.3, 32.9 (2C, $2CH_2$), 88.9 (1C, CH-pyrazole), 123.9, 126.4, 129.9, 131.9, 132.5, 132.9, 135.3, 141.9, 148.8, 155.1 (14C, Ar-C), 165.6, 167.6 (2C, 2C═O); MS (70 eV): *m/z* = 319 (M^+, 84%); Anal. Calc. (Found) for $C_{19}H_{17}N_3O_2$ (319.36): C, 71.46 (71.40); H, 5.37 (5.45); N, 13.16 (13.23).

4.9 | Synthesis of 3-amino-5-(3-oxo-3-phenylpropyl)-4*H*-pyrazole-4-carbonitrile (7)

A mixture of compound **1** (1.92 g, 0.01 mol) and malononitrile (0.6 ml, 0.01 mol) in ethanol (40 ml) containing (1 ml) catalytic amount of piperidine was heated under reflux for 20–25 h.The reaction mixture was allowed to cool and poured into crushed ice then acidified with hydrochloric acid. The separated solid was filtered off washed with water, dried and recrystallized from DMF as yellowish crystals in 70% yield, m. p. 193–195°C. IR (KBr): ν_{max} = 3425 (br, NH_2), 3070 (CH, aryl), 2960 (CH, alkyl), 2210 (CN), 1727 (C═O), 1625 (C═N), 1586 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.63–2.68 (*t*, 2H, *J* = 4.88 Hz, CH_2), 3.30–3.35 (*t*, 2H, *J* = 4.84 Hz, CH_2), 4.45 (*s*, 1H, CH, pyrazole), 6.25 (*s*, 2H, NH_2), 7.50–7.97 (*m*, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 31.1, 35.3 (2C, $2CH_2$), 52.5 (1C, CH-pyrazole), 112.9 (1C, CN), 128.4, 128.9, 133.5, 136.3, 160.1, 163.5 (8C, Ar-C), 191.3 (1C, C═O); MS (70 eV): *m/z* = 240 (M^+, 100%); Anal. Calc. (Found) for $C_{13}H_{12}N_4O$ (240.27): C, 64.99 (64.90); H, 5.03 (5.10); N, 23.32 (23.25).

4.10 | Synthesis of 3-(1, 3, 4-oxadiazol-2-yl)-1-phenylpropan-1-one (8)

Method A: A mix of compound **1** (1.92 g, 0.01 mol) in triethylorthoformate (10 ml) was heated under reflux for 15–18 h.The reaction mixture was allowed to cool. The separated solid was filtered off washed with ether, dried and recrystallized from toluene to give yellow crystals. *Method B*: A mixture of compound **1** (1.92 g, 0.01 mol) and (DMF-DMA), dimethyl-formamidedimethylacetal (1.35 ml, 0.01 mol) in *p*-xylene (35 ml) was heated under reflux for 12–16 h. after cooling, the separated solid was filtered off, dried and recrystallized from dioxane as yellow crystals in 75% yield, m. p. 265–267°C. IR (KBr): ν_{max} = 3080 (CH, aryl), 2970 (CH, alkyl), 1730 (C═O), 1622 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.70–2.81 (*t*, 2H, *J* = 4.90 Hz, CH_2), 2.91–3.20 (*t*, 2H, *J* = 4.92 Hz, CH_2), 6.10 (*s*, CH, oxadiazole), 7.30–7.55 (*m*, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 26.5, 37.1 (2C, $2CH_2$), 115.4 (1C, CH-oxadiazole),128.2, 128.7, 133.7, 140.6 (6C, Ar-C), 191.8 (1C, C═O); MS (70 eV): *m/z* = 202 (M^+, 90%); Anal. Calc. (Found) for $C_{11}H_{10}N_2O_2$ (202.21): C, 65.34 (65.40); H, 4.98 (4.91); N, 13.85 (13.92).

4.11 | Synthesis of *N′*-acetyl-4-oxo-4-phenylbutanehydrazide (9)

A solution of compound **1** (1.92 g, 0.01 mol) in acetic anhydride (15 ml) was heated under reflux for 15 min. The reaction mixture was allowed to cool and poured into ice/water. The separated solid was filtered off washed with water, dried and recrystallized from methanol as brownish crystals in 90% yield, m. p. 183–185°C. IR (KBr): ν_{max} = 3250 (br, 2NH), 3080 (CH, aryl), 2975 (CH, alkyl), 1720, 1681 (2C═O),1586 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.82 (*s*, 3H, CH_3), 2.22–2.41 (*t*, 2H, *J* = 4.95 Hz, CH_2), 3.10–3.38 (*t*, 2H, *J* = 4.92 Hz, CH_2), 7.09–7.37 (*m*, 5H, Ar-H), 10.05, 10.47 (br, 2H, 2NH, D_2O exchangeable);^{13}C NMR (DMSO-d_6) δ = 20.8 (1C, CH_3), 31.9, 36.1 (2C, $2CH_2$), 128.1, 128.5, 133.4, 136.3, (6C, Ar-C), 165.9, 170.1, 188.5 (3C, 3C═O); MS (70 eV): *m/z* = 234 (M^+, 100%); Anal. Calc. (Found) for $C_{12}H_{14}N_2O_3$ (234.26): C, 61.53 (61.62); H, 6.02 (6.10); N, 11.96 (11.90).

4.12 | Synthesis of 3-(5-methyl-1,3,4-oxadiazol-2-yl)-1-phenylpropan-1-one (10)

Method A: Refluxing of compound **1** (1.92 g, 0.01 mol) in acetic anhydride (20 mL) for 25–30 h. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered off washed with water, dried and recrystallized from methanol as yellowish crystals. *Method B*: Refluxing of compound **9** (2.34 g, 0.01 mol) in ethanolic sodium ethoxide solution (prepared via dissolving 0.23 g of sodium metal in 40 ml ethanol) for 6–8 h. The reaction mixture was allowed to cool and poured into water/ice then acidified with conc. HCl. The precipitate separated was filtered off washed with water, dried and recrystallized from ethanol as yellowish crystals in 88% yield, m. p. 283–285°C. IR (KBr): ν_{max} = 3085 (CH, aryl), 2978 (CH, alkyl), 1732 (C═O), 1624 (C═N), 1592 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.86 (*s*, 3H, CH_3), 2.39–2.43 (*t*, 2H, *J* = 4.97 Hz, CH_2), 3.76–3.90 (*t*, 2H, *J* = 4.95 Hz, CH_2), 7.48–7.69 (*m*, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 23.2 (1C, CH_3), 27.1, 38.4 (2C, $2CH_2$), 128.4, 128.9, 133.5, 140.8, 160.1, 162.3 (8C, Ar-C), 193.2 (1C, C═O); MS (70 eV): *m/z* = 216 (M^+, 95%); Anal. Calc. (Found) for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65 (66.73); H, 5.59 (5.66); N, 12.96 (12.88).

4.13 | Synthesis of 1-phenyl-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) propan-1-one (11)

Method A: A mixture of compound **1** (1.92 g, 0.01 mol) in pyridine (25 ml) and carbon disulfide (0.6 ml, 0.01 mol) was heated under reflux for 15–19 h. The reaction mixture was allowed to cool and poured into ice/water then acidified with HCl. The separated solid was filtered off washed with water, dried and recrystallized from dioxane as yellowish crystals. *Method B*: A mixture of compound **1** (1.92 g, 0.01 mol) and carbon disulfide (excess 10–15 ml) was heated under reflux on a water-bath (75–85°C) in 35 ml pyridine for 12–15 h, under (TLC control). The reaction mixture was allowed to cool to 0°C for 12–14 h; the final precipitate was filtered off, washed with ethanol (50 ml), dried, and crystallized from methanol as yellowish crystals. *Method C*: A solution of compound **1** (1.92 g, 0.01 mol) in ethanol (40 ml) and aqueous potassium hydroxide (0.56 g, 0.01 mol) was refluxed for 30 min. After cooling to room temperature, carbon disulfide (1 ml) was added, refluxed for 3–5 h and poured into ice-water. The final solid obtained was filtered off, dried and recrystallized from dimethylformamide as yellowish crystals in 74% yield, m. p. 233–235°C. IR (KBr): ν_{max} = 3116 (NH), 3064(CH, aryl), 2960 (CH, alkyl), 1731 (C═O), 1634 (C═N), 1600 (C═C), 1264 (C═S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.66–2.71 (*t*, 2H, *J* = 5.01 Hz, CH_2), 3.28–3.33 (*t*, 2H, *J* = 5.05 Hz, CH_2), 7.57–7.98 (*m*, 5H, Ar-H), 11.20 (br, 1H, NH, D_2O

exchangeable); ^{13}C NMR (DMSO-d_6) δ = 28.7, 37.1 (2C, 2CH_2), 128.5, 128.7, 133.3, 137.5, 159.4 (7C, Ar-C), 181.6 (1C, C═S), 188.1 (1C, C═O); MS (70 eV): m/z = 234 (M^+, 98%); Anal. Calc. (Found) for $C_{11}H_{10}N_2O_2S$ (234.27): C, 56.40 (56.49); H, 4.30 (4.22); N, 11.96 (11.90).

4.14 | Synthesis of 1-phenyl-3-(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl) propan-1-one (12)

A mix of compound **1** (1.92 g, 0.01 mol) and potassium thiocyanate (KSCN, 0.97 g, 0.01 mol) in 10% HCl (hydrochloric acid) was heated under reflux for 6–9 h. The reaction mixture was allowed to cool and poured into ice/water. The separated solid was filtered off washed with water, dried and recrystallized from dioxane as brownish crystals in 77% yield, m. p. 292–294°C. IR (KBr): ν_{max} = 3338–3131 (2NH), 3012 (CH, aryl), 2957 (CH, alkyl), 1673 (C═O), 1633 (C═N), 1605 (C═C), 1263(C═S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.26–2.35 (t, 2H, J = 5.07 Hz, CH_2), 3.64–3.80 (*t*, 2H, J = 5.09 Hz, CH_2), 7.20–7.88 (*m*, 5H, Ar-H), 10.85, 12.91 (br, 2H, 2NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 30.7, 36.8 (2C, 2CH_2), 123.2, 128.7, 130.7, 151.6, 162.2 (7C, Ar-C), 188.2 (1C, C═S), 192.5 (1C, C═O); MS (70 eV): m/z = 233 (M^+, 94%); Anal. Calc. (Found) for $C_{11}H_{11}N_3OS$ (233.29): C, 56.63 (56.75); H, 4.75 (4.70); N, 18.01 (18.10).

4.15 | Synthesis of 3-(3-oxo-3-phenylpropyl)-1,6-dihydro-1,2,4-triazin-5 (2H)-one (13)

A mix of compound **1** (1.92 g, 0.01 mol) and chlor oacetamide (0.93 g, 0.01 mol) in dimethyl-formamide (30 ml) was heated under reflux for 24–28 h. The solvent was evaporated under reduced pressure and the residue was triturated with water. The final solid obtained was filtered, dried and recrystallized from dioxane as yellowish crystals in 69% yield, m. p. 302–304°C. IR (KBr): ν_{max} = 3270–3200 (2NH), 3080(CH, aryl), 2960 (CH, alkyl), 1735, 1672 (2C═O), 1636 (C═N), 1588 (C═C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.85–2.90 (*t*, 2H, J = 5.02 Hz, CH_2), 3.37–3.42 (*t*, 2H, J = 5.04 Hz, CH_2), 3.80 (*s*, 2H, J = 5.12 Hz, CH_2), 7.54–7.95 (*m*, 5H, Ar-H), 11.60, 12.20 (br, 2H, 2NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 27.3, 31.4, 58.1 (3C, 3CH_2), 128.1, 128.5, 133.4, 137.6, 157.1 (7C, Ar-C), 170.1185.5 (2C, 2C═O); MS (70 eV): m/z = 231 (M^+, 100%); Anal. Calc. (Found) for $C_{12}H_{13}N_3O_2$ (231.26): C, 62.33 (62.40); H, 5.67 (5.74); N, 18.17 (18.12).

4.16 | Synthesis of 6-phenyl-3,4-dihydropyrrolo [1,2-b] [1,2,4] triazin-2 (8H)-one (14)

A solution of **13** (2.31 g, 0.01 mol) and anhydrous potassium carbonate (2 g, 0.015 mol) in dimethylformamide (DMF, 45 ml) was refluxed for 13–16 h under control (TLC). The final product precipitated was filtered off and washed with cold water (100 ml), dried, and crystallized from ethanol as yellow crystals in 82% yield, m. p. 312–314°C. IR (KBr): ν_{max} = 3255 (NH), 3074 (CH, aryl), 2950 (CH, alkyl), 1685 (C═O), 1631 (C═N), 1583(C═C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.03–2.13 (*d*, 2H, J = 5.14 Hz, CH_2), 3.38 (*s*, 2H, J = 5.16 Hz, CH_2), 6.09 (*t*, 1H, J = 5.09 Hz, CH, pyrrole), 7.07–7.51 (*m*, 5H, Ar-H), 11.59 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 32.1, 52.5 (2C, 2CH_2), 95.8 (1C, CH, pyrrole), 127.8, 128.2, 128.7, 135.1,150.3, 163.8 (8C, Ar-C), 168.6 (1C, C═O); MS (70 eV): m/z = 213 (M^+, 97%); Anal. Calc. (Found) for $C_{12}H_{11}N_3O$ (213.24): C, 67.59 (67.65); H, 5.20 (5.14); N, 19.71 (19.80).

4.17 | Synthesis of *N*′-(4-substituted-benzylidene)-4-oxo-4-phenylbutanehydrazide (15a-c)

General procedure: A mixture of compound **1** (1.92 g, 0.01 mol) and appropriate aryl aldehydes namely; benzaldehyde (1.06 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.36 g, 0.01 mol) in ethanol (40 ml) with catalytic amount of piperidine was heated under reflux for 5–8 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off washed with water, dried and recrystallized from the ideal solvent to give **15a-c**.

4.18 | Synthesis of *N*′-benzylidene-4-oxo-4-phenylbutanehydrazide (15a)

The compound was obtained from the reaction of (**1**) and benzaldehyde, crystallized from acetone as white crystals in 85% yield, m. p. 320–322°C. IR (KBr): ν_{max} = 3230 (NH), 3068 (CH, aryl), 2957 (CH, alkyl), 1738, 1677 (2C═O), 1629 (C═N), 1585 (C═C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.72–2.77 (*t*, 2H, J = 5.06 Hz, CH_2), 3.34–3.39 (*t*, 2H, J = 5.08 Hz, CH_2), 7.25–7.97 (*m*, 10H, Ar-H), 8.05 (*s*, 1H, CH, proton), 11.50 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 22.2, 35.4 (2C, 2CH_2), 127.9, 128.2, 128.4, 131.2, 132.7, 133.4, 155.7, 156.8 (12C, Ar-C), 157.9 (1C, CH), 170.5, 181.4 (2C, 2C═O); MS (70 eV): m/z = 280

(M^+, 100%); Anal. Calc. (Found) for $C_{17}H_{16}N_2O_2$ (280.33): C, 72.84 (72.92); H, 5.75 (5.70); N, 9.99 (9.91).

4.19 | Synthesis of *N′*-(4-chlorobenzylidene)-4-oxo-4-phenylbutanehydrazide (15b)

The compound was obtained from the reaction of (**1**) and 4-chlorobenzaldehyde, crystallized from benzene as yellow crystals in 90% yield, m. p. 343–345°C. IR (KBr): ν_{max} = 3235 (NH), 3069 (CH, aryl), 2958 (CH, alkyl), 1740, 1680 (2C═O), 1635 (C═N), 1587 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.65–2.70 (*t*, 2H, *J* = 5.11 Hz, CH_2), 3.25–3.30 (*t*, 2H, *J* = 5.14 Hz, CH_2), 7.20–7.26 (dd, 2H, *J* = 7.55 Hz, 4-chlorophenyl), 7.45–7.82 (*m*, 5H, Ar-H), 7.88–7.95 (dd, 2H, *J* = 7.50 Hz, 4-chlorophenyl), 8.03 (*s*, 1H, CH, proton), 11.42 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 29.5, 34.1 (2C, $2CH_2$), 128.1, 128.4, 128.9, 129.8, 131.5, 132.7, 135.9, 136.2 (12C, Ar-C), 145.3(1C, CH), 172.6, 185.1 (2C, 2C═O); MS (70 eV): *m/z* = 314 (M^+, 97%); Anal. Calc. (Found) for $C_{17}H_{15}ClN_2O_2$ (314.77): C, 64.87 (64.95); H, 4.80 (4.88); N, 8.90 (8.84).

4.20 | Synthesis of *N′*-(4-methoxybenzylidene)-4-oxo-4-phenylbutanehydrazide (15c)

The compound was obtained from the reaction of (**1**) and 4-methoxyphenyl, crystallized from methanol as yellow crystals in 82% yield, m. p. 331–333°C. IR (KBr): ν_{max} = 3238 (NH), 3073 (CH, aryl), 2961 (CH, alkyl), 1745, 1684 (2C═O), 1637 (C═N), 1589 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.61–2.67 (*t*, 2H, *J* = 5.15 Hz, CH_2), 3.22–3.28 (*t*, 2H, *J* = 5.17 Hz, CH_2), 3.75 (*s*, 3H, OCH_3), 7.10–7.15 (dd, 2H, *J* = 7.57 Hz, 4-methoxyphenyl), 7.55–7.60 (dd, 2H, *J* = 7.59 Hz, 4-methoxyphenyl), 7.63–7.98 (*m*, 5H, Ar-H), 8.09 (*s*, 1H, CH, proton), 11.35 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 30.2, 34.7 (2C, $2CH_2$), 52.8 (1C, CH_3), 120.4, 127.1, 128.5, 128.7, 130.5, 133.6, 136.2, 143.9 (12C, Ar-C), 146.1 (1C, CH), 172.9, 185.8 (2C, 2C═O); MS (70 eV): *m/z* = 310 (M^+, 88%); Anal. Calc. (Found) for $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66 (69.74); H, 5.85 (5.80); N, 9.03 (9.13).

4.21 | Synthesis of 7-(4-substituted-phenyl)-3-(3-oxo-3-phenylpropyl)-4,6-dihydro-5*H*-1,2,4-triazepin-5-one (16a-c)

General procedure: A mixture of compound **15a-c** (0.01 mol) and chloroacetamide (0.93 g, 0.01 mol) in dimethylformamide (40 ml) was heated under reflux for 30–35 h, with control (TLC). The solvent was evaporated under reduced pressure and the residue was triturated with water. The solid precipitate obtained was filtered, dried and recrystallized from the suitable solvent to give **16a-c**.

4.22 | Synthesis of 3-(3-oxo-3-phenylpropyl)-7-phenyl-4,6-dihydro-5H-1,2,4-triazepin-5-one (16a)

The compound was obtained from the reaction of **15a** (2.80 g, 0.01 mol) and chloroacetamide, crystallized from methanol as yellowish crystals in 78% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3305 (NH), 3078 (CH, aryl), 2972 (CH, alkyl), 1733, 1685 (2C═O), 1631 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.23 (*s*, 2H, CH_2), 2.90–3.10 (*t*, 2H, *J* = 5.16 Hz, CH_2), 3.70–3.86 (*t*, 2H, *J* = 5.18 Hz, CH_2), 7.33–7.83 (*m*, 10H, Ar-H), 8.52 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 15.6, 21.5, 31.2 (3C, $3CH_2$), 121.5, 124.8, 130.2, 130.8, 130.9, 131.5, 136.1, 147.7, 158.3, 165.6 (14C, Ar-C), 168.6, 168.9 (2C, 2C═O); MS (70 eV): *m/z* = 319 (M^+, 6%); Anal. Calc. (Found) for $C_{19}H_{17}N_3O_2$ (319.36): C, 71.46 (71.52); H, 5.37 (5.31); N, 13.16 (13.24).

4.23 | Synthesis of 7-(4-chlorophenyl)-3-(3-oxo-3-phenylpropyl)-4,6-dihydro-5H-1,2,4-triazepin-5-one (16b)

The compound was obtained from the reaction of **15b** (3.14 g, 0.01 mol) and chloroacetamide, crystallized from ethanol as brownish crystals in 87% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3310 (NH), 3081 (CH, aryl), 2976 (CH, alkyl), 1735, 1689 (2C═O), 1634 (C═N), 1593 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.86 (*s*, 2H, CH_2), 3.01–3.07 (*t*, 2H, *J* = 5.20 Hz, CH_2), 3.33–3.39 (*t*, 2H, *J* = 5.19 Hz, CH_2), 7.35–7.66 (*m*, 5H, Ar-H), 7.70–7.77 (dd, 2H, *J* = 7.60 Hz, 4-chlorophenyl), 7.90–7.97 (dd, 2H, *J* = 7.57 Hz, 4-chlorophenyl), 9.25 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 25.8, 30.9, 39.1 (3C, $3CH_2$), 123.4, 127.9, 128.1, 128.5, 128.7, 133.6, 135.7, 136.2, 147.5, 153.9 (14C, Ar-C), 169.1, 184.8 (2C, 2C═O); MS (70 eV): *m/z* = 353 (M^+, 95%); Anal. Calc. (Found) for $C_{19}H_{16}ClN_3O_2$ (353.81): C, 64.50 (64.61); H, 4.56 (4.50); N, 11.88 (11.82).

4.24 | Synthesis of 7-(4-methoxyphenyl)-3-(3-oxo-3-phenylpropyl)-4,6-dihydro-5H-1,2,4-triazepin-5-one (16c)

The compound was obtained from the reaction of **15c** (3.10 g, 0.01 mol) and chloroacetamide, crystallized from

dioxane as brownish crystals in 80% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3315 (NH), 3085 (CH, aryl), 2982 (CH, alkyl), 1731, 1682 (2C═O), 1630 (C═N), 1582 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.90 (*s*, 2H, CH_2), 3.05–3.11 (*t*, 2H, *J* = 5.22 Hz, CH_2), 3.36–3.42 (*t*, 2H, *J* = 5.17 Hz, CH_2), 3.85 (*s*, 3H, OCH_3), 7.10–7.16 (dd, 2H, *J* = 7.65 Hz, 4-methoxyphenyl), 7.44–7.85 (*m*, 5H, Ar-H), 7.92–7.98 (dd, 2H, *J* = 7.62 Hz, 4-methoxyphenyl), 9.34 (br, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 26.1, 31.3, 39.7 (3C, $3CH_2$), 52.6 (1C, OCH_3), 121.8, 122.6, 128.2, 128.5, 128.9, 133.3, 136.4, 147.8, 154.2, 158.5 (14C, Ar-C), 170.6, 186.2 (2C, 2C═O); MS (70 eV): *m/z* = 349 (M^+, 92%); Anal. Calc. (Found) for $C_{20}H_{19}N_3O_3$ (349.39): C, 68.75 (68.67); H, 5.48 (5.55); N, 12.03 (12.10).

4.25 | Synthesis of 3-(4-substituted-phenyl)-7-phenyl-4,9-dihydro-5H-pyrrolo [2,1-c] [1,2,4] triazepin-5-one (17a-c)

General procedure: A mixture of **16a-c** (0.01 mol) and (K_2CO_3) anhydrous potassium carbonate (2 g, 0.015 mol) in dimethylformamide (DMF, 40 ml) was refluxed for 17–20 h under control (TLC). The product precipitated was filtered off and washed with cold water (100 ml), dried, and crystallized from the proper solvent to give **17a-c**.

4.26 | Synthesis of 3,7-diphenyl-4,9-dihydro-5H-pyrrolo [2,1-c] [1,2,4] triazepin-5-one (17a)

The compound was obtained from the reaction of **16a** (3.19 g, 0.01 mol) and DMF, crystallized from dioxane as yellow crystals in 74% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3072(CH, aryl), 2968 (CH, alkyl), 1678 (C═O), 1638 (C═N), 1580 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.62 (*d*, 2H, *J* = 5.13 Hz, CH_2), 3.90 (*s*, 2H, CH_2), 4.90–5.10 (*t*, 1H, *J* = 5.14 Hz, CH), 7.48–7.70 (*m*, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 33.5, 37.1(2C, $2CH_2$), 79.1(1C,CH), 120.5, 123.2, 128.7, 130.7, 130.8, 140.7, 150.6, 151.6, 160.7, 162.2, 165.3 (15C, Ar-C), 167.6 (1C, C═O); MS (70 eV): *m/z* = 301 (M^+, 90%); Anal. Calc. (Found) for $C_{19}H_{15}N_3O$ (301.35): C, 75.73 (75.66); H, 5.02 (5.10); N, 13.94 (13.88).

4.27 | Synthesis of 3-(4-chlorophenyl)-7-phenyl-4,9-dihydro-5H-pyrrolo [2,1-c] [1,2,4] triazepin-5-one (17b)

The compound was obtained from the reaction of **16b** (3.53 g, 0.01 mol) and DMF, crystallized from benzene as yellowish crystals in 79% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3075(CH, aryl), 2971 (CH, alkyl), 1680 (C═O), 1641 (C═N), 1583 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.93(*d*, 2H, *J* = 5.16 Hz, CH_2), 3.07 (*s*, 2H, CH_2), 5.28–5.33 (*t*, 1H, *J* = 5.18 Hz, CH), 7.37–7.43 (dd, 2H, *J* = 7.68 Hz, 4-chlorophenyl), 7.50–7.75 (*m*, 5H, Ar-H), 7.92–7.99 (dd, 2H, *J* = 7.61 Hz, 4-chlorophenyl);^{13}C NMR (DMSO-d_6) δ = 36.3, 36.7 (2C, $2CH_2$), 106.2 (1C,CH), 125.7, 126.2, 127.4, 128.7, 128.8, 129.5, 130.2, 131.2, 132.4158.5, 161.6 (15C, Ar-C), 163.6 (1C,C═O); MS (70 eV): *m/z* = 335(M^+, 30%), 334 (M^+-1100%); Anal. Calc. (Found) for $C_{19}H_{14}ClN_3O$ (335.79): C, 67.96 (67.87); H, 4.20 (4.27); N, 12.51 (12.58).

4.28 | Synthesis of 3-(4-methoxyphenyl)-7-phenyl-4,9-dihydro-5H-pyrrolo [2,1-c] [1,2,4] triazepin-5-one (17c)

The compound was obtained from the reaction of **16c** (3.49 g, 0.01 mol) and DMF, crystallized from benzene as brownish crystals in 76% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3079(CH, aryl), 2976 (CH, alkyl), 1683 (C═O), 1644 (C═N), 1585 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.97(*d*, 2H, *J* = 5.15 Hz, CH_2), 3.09 (*s*, 2H, CH_2), 3.85 (s, 3H, OCH_3), 5.30–5.36 (*t*, 1H, *J* = 5.16 Hz, CH), 7.10–7.17 (dd, 2H, *J* = 7.70 Hz, 4-methoxyphenyl), 7.55–7.80 (*m*, 5H, Ar-H), 7.88–7.97 (dd, 2H, *J* = 7.72 Hz, 4-methoxyphenyl);^{13}C NMR (DMSO-d_6) δ = 34.3, 36.8 (2C, $2CH_2$), 55.5(1C, OCH_3), 106.1 (1C,CH), 127.4, 128.6, 129.1, 129.2, 129.4, 129.6, 129.7, 130.3, 157.5159.1, 161.6 (15C, Ar-C), 163.5 (1C, C═O); MS (70 eV): *m/z* = 331 (M^+, 84%); Anal. Calc. (Found) for $C_{20}H_{17}N_3O_2$ (331.38): C, 72.49 (72.57); H, 5.17 (5.11); N, 12.68 (12.76).

4.29 | Synthesis of 3-(6-(4-substituted-phenyl)-1,2,4-triazin-3-yl)-1-phenylpropan-1-one (18a-c)

General procedure: *Method A*: A mixture of **15a-c** (0.01 mol) and formamide (15 mL) was refluxed with stirring in DMF (45 ml) for 9–11 h under (TLC) checking. The reaction mixture was cooled at room temperature and poured into (100 ml) of water was added and the mixture was neutralized with NH_4OH. The solid precipitate formed was filtered and washed via H_2O, ethanol, then dried and recrystallized from a proper solvent to yielded **18a-c**. *Method B*: A mix of **15a-c** (0.01 mol) and formamide (10 ml) in dimethylformamide (10 ml) was heated under reflux to 22–24 h. The solvent was evaporated under reduced pressure and the residue was

triturated with water. The solid obtained was filtered, dried, and recrystallized from suitable solvent to afford **18a-c**.

4.30 | Synthesis of 1-phenyl-3-(6-phenyl-1,2,4-triazin-3-yl)propan-1-one (18a)

The compound was obtained from the reaction of **15a** (2.80 g, 0.01 mol) and formamide, crystallized from ethanol as yellow crystals in 81% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3093 (CH, aryl), 2933 (CH, alkyl), 1713 (C═O), 1632 (C═N), 1607 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.67–2.73 (*t*, 2H, *J* = 5.20 Hz, CH_2), 2.80–2.85 (*t*, 2H, *J* = 5.21 Hz, CH_2), 7.20–7.93 (*m*, 10H, Ar-H), 8.10 (*s*, 1H, CH, triazine); ^{13}C NMR (DMSO-d_6) δ = 30.2, 39.1 (2C, $2CH_2$), 127.1, 128.3, 128.5, 128.9, 129.1, 133.3, 133.5, 140.4, 149.4, 153.1, 165.8 (15C, Ar-C), 190.4 (1C, C═O); MS (70 eV): *m/z* = 289 (M^+, 92%); Anal. Calc. (Found) for $C_{18}H_{15}N_3O$ (289.34): C, 74.72 (74.61); H, 5.23 (5.30); N, 14.52 (14.64).

4.31 | Synthesis of 3-(6-(4-chlorophenyl)-1,2,4-triazin-3-yl)-1-phenylpropan-1-one (18b)

The compound was obtained from the reaction of **15b** (3.14 g, 0.01 mol) and formamide, crystallized from tetrahydrofuran (THF) as brownish crystals in 88% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3075 (CH, aryl), 2969 (CH, alkyl), 1730 (C═O), 1628 (C═N), 1576 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.70–2.77 (*t*, 2H, *J* = 5.25 Hz, CH_2), 2.85–2.90 (*t*, 2H, *J* = 5.27 Hz, CH_2), 7.45–7.51 (dd, 2H, *J* = 7.62 Hz, 4-chlorophenyl), 7.55–7.90 (*m*, 5H, Ar-H), 7.92–7.97 (dd, 2H, *J* = 7.66 Hz, 4-chlorophenyl), 8.15 (*s*, 1H, CH, triazine); ^{13}C NMR (DMSO-d_6) δ = 30.5, 39.6 (2C, $2CH_2$), 128.2, 128.4, 128.7, 129.2, 129.5, 133.4, 134.5, 140.7, 149.6, 153.4, 165.5 (15C, Ar-C), 192.1 (1C, C═O); MS (70 eV): *m/z* = 323 (M^+, 45%); Anal. Calc. (Found) for $C_{18}H_{14}ClN_3O$ (323.78): C, 66.77 (66.68); H, 4.36 (4.42); N, 12.98 (13.06).

4.32 | Synthesis of 3-(6-(4-methoxyphenyl)-1,2,4-triazin-3-yl)-1-phenylpropan-1-one (18c)

The compound was obtained from the reaction of **15c** (3.10 g, 0.01 mol) and formamide, crystallized from tetrahydrofuran (THF) as yellowish crystals in 83% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3078 (CH, aryl), 2971 (CH, alkyl), 1733 (C═O), 1631 (C═N), 1578 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.73–2.80 (*t*, 2H, *J* = 5.27 Hz, CH_2), 2.89–2.95 (*t*, 2H, *J* = 5.24 Hz, CH_2), 3.77 (*s*, 3H,OCH_3), 7.08–7.15 (dd, 2H, *J* = 7.58 Hz, 4-methoxyphenyl), 7.46–7.52 (dd, 2H, *J* = 7.57 Hz, 4-methoxyphenyl), 7.58–7.96 (*m*, 5H, Ar-H), 8.18 (*s*, 1H, CH, triazine); ^{13}C NMR (DMSO-d_6) δ = 30.8, 39.9 (2C, $2CH_2$), 54.5 (1C, OCH_3), 121.4, 123.8, 128.2, 128.4, 128.7, 133.5, 140.9, 148.2, 153.7, 159.1, 165.3 (15C, Ar-C), 190.2 (1C, C═O); MS (70 eV): *m/z* = 319 (M^+, 91%); Anal. Calc. (Found) for $C_{19}H_{17}N_3O_2$ (319.36): C, 71.46 (71.55); H, 5.37 (5.30); N, 13.16 (13.08).

4.33 | Synthesis of 3-(4-substituted-phenyl)-6-phenyl-4,8-dihydropyrrolo [2,1-c] [1,2,4] triazine (19a-c)

General procedure: *Method A*: A mixture of **18a-c** (0.01 mol) and anhydrous potassium carbonate (K_2CO_3, 2 g, 0.015 mol) in dimethylformamide (DMF, 45 ml) was refluxed for 15–18 h under control (TLC). The solid product of the precipitate was filtered off and washed with ice /cold water (100 ml) and neutralized, dried, and crystallized from the appropriate solvent to give **19a-c**. *Method B*: The stirring of a mixture of **18a-c** (0.01 mol) in glacial acetic acid (40 ml), activated zinc dust (1.3 g, 0.02 mol) was added portionwise at room temperature over a period of 1 h, stirring was continued for an additional 4–6 h. The reaction mixture was heated on a water bath (90–95°C) for 6–8 h, with control (TLC), after allowing the reaction mixture to cool at room temperature, it was poured into cold water (100 mL). The precipitate was filtered, washed with water, dried, and crystallized to produce **19a-c**, respectively.

4.34 | Synthesis of 3,6-diphenyl-4,8-dihydropyrrolo [2,1-c] [1,2,4] triazine (19a)

The compound was obtained from the reaction of **18a** (2.89 g, 0.01 mol) and DMF, crystallized from dioxane as yellowish crystals in 80% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3075(CH, aryl), 2970 (CH, alkyl), 1638 (C═N), 1585 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.11–3.27 (*d*, 2H, *J* = 5.50 Hz, CH_2, pyrrole), 4.17 (*s*, 2H, *J* = 5.60 Hz, CH_2, triazine), 6.58–6.82 (*t*, 1H, *J* = 5.42 Hz, CH, pyrrole), 7.15–7.85 (*m*, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 21.6, 58.5 (2C, $2CH_2$), 79.7 (1C, CH, pyrrole), 121.5, 124.8, 130.2, 130.8, 130.9131.5, 136.1147.7, 158.3, 165.5, 165.7 (15C, Ar-C); MS (70 eV): *m/z* = 273 (M^+, 100%); Anal. Calc. (Found) for $C_{18}H_{15}N_3$ (273.34): C, 79.10 (79.18); H, 5.53 (5.45); N, 15.37 (15.31).

4.35 | Synthesis of 3-(4-chlorophenyl)-6-phenyl-4, 8-dihydropyrrolo [2,1-c] [1,2,4] triazine (19b)

The compound was obtained from the reaction of **18b** (3.23 g, 0.01 mol) and DMF, crystallized from acetone as yellow crystals in 82% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3079(CH, aryl), 2974 (CH, alkyl), 1640 (C═N), 1590 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.05–3.10 (*d*, 2H, *J* = 5.55 Hz, CH_2, pyrrole), 4.35 (*s*, 2H, *J* = 5.65 Hz, CH_2, triazine), 6.15–6.20 (*t*, 1H, *J* = 5.48 Hz, CH, pyrrole), 7.46–7.55 (dd, 2H, *J* = 7.65 Hz, 4-chlorophenyl),7.58–7.85 (*m*, 5H, Ar-H), 7.91–7.98 (dd, 2H, *J* = 7.68 Hz, 4-chlorophenyl);^{13}C NMR (DMSO-d_6) δ = 31.1, 50.5 (2C, $2CH_2$), 95.4 (1C, CH, pyrrole), 127.8, 128.1, 128.5, 128.8, 129.2, 131.9, 134.1, 136.3, 149.2, 160.8, 165.3 (15C, Ar-C); MS (70 eV): *m/z* = 307 (M^+, 40%); Anal. Calc. (Found) for $C_{18}H_{14}ClN_3$ (307.78): C, 70.24 (70.32); H, 4.59 (4.67); N, 13.65 (13.57).

4.36 | Synthesis of 3-(4-methoxyphenyl)-6-phenyl-4,8-dihydropyrrolo [2,1-c] [1,2,4] triazine (19c)

The compound was obtained from the reaction of **18c** (3.19 g, 0.01 mol) and DMF, crystallized from n-hexane as brownish crystals in 77% yield, m. p. > 350°C. IR (KBr): ν_{max} = IR (KBr): ν_{max} = 3073(CH, aryl), 2972 (CH, alkyl), 1635 (C═N), 1583 (C═C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.08–3.13 (*d*, 2H, *J* = 5.52 Hz, CH_2, pyrrole), 3.84(*s*, 3H, OCH_3), 4.38 (*s*, 2H, *J* = 5.63 Hz, CH_2, triazine), 6.19–6.23 (*t*, 1H, *J* = 5.45 Hz, CH, pyrrole), 7.11–7.17 (dd, 2H, *J* = 7.67 Hz, 4-methoxyphenyl), 7.50–7.82 (*m*, 5H, Ar-H), 7.93–7.99 (dd, 2H, *J* = 7.70 Hz, 4-methoxyphenyl);^{13}C NMR (DMSO-d_6) δ = 31.6, 50.7 (2C, $2CH_2$), 56.7 (1C, OCH_3), 95.8 (1C, CH, pyrrole), 122.5, 126.7, 127.8, 128.2, 128.5, 128.9, 134.6149.7, 161.1, 163.2, 165.8 (15C, Ar-C); MS (70 eV): *m/z* = 303 (M^+, 90%); Anal. Calc. (Found) for $C_{19}H_{17}N_3O$ (303.37): C, 75.23 (75.15); H, 5.65 (5.72); N, 13.85 (13.93).

5 | PHARMACOLOGICAL SCREENING

Types of human carcinoma cancer cell line [MGC-803, CNE2, KB and MCF-7] are derived from the (National Cancer institute, Cairo University, Cairo, Egypt).

5.1 | Materials and methods

The in vitro cytotoxicity of the synthesized compounds against different cancer cell lines was performed with the MTT assay according to the method.[46–48] The MTT assay is based on the reduction of the soluble 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) into a blue-purple formazan product, mainly by mitochondrial reeducates activity inside living cells. The cells used in cytotoxicity assay were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum. Cells suspended in the medium (2Y′ 104/ml) were plated in 96-well culture plates and incubated at 37°C in a 5% CO_2 incubator. After 12 h, the test sample (2 ml) was added to the cells (2Y′ 104) in 96-well plates and cultured at 37°C for 3 days. The cultured cells were mixed with 20 ml of MTT solution and incubated for 4 h at 37°C. The supernatant was carefully removed from each well and 100 ml of DMSO was added to each well to dissolve the formazan crystals which were formed by the cellular reduction of MTT. After mixing with a mechanical plate mixer, the absorbance of each well was measured by a microplate reader using a test wavelength of 570 nm. The results were expressed as the IC_{50}, which is the concentration of the drugs inducing a 50% inhibition of cell growth of treated cells when compared to the growth of control cells. Each experiment was performed at least three times. There was a good reproducibility between replicate wells with standard errors below 10%.

6 | CONCLUSION

The target of the recent study is to prepare and evaluate the cytotoxicity activity of the new compounds such as; pyrazoles, 1,3,4-oxadiazoles, 1,2,4-triazoles, 1,2,4-tria zines, pyrrolo [1,2-b] [1,2,4] triazinones, *N*′-(4-sub-benzylidene)-butanehydrazides, 1,2,4-triazepinones, pyrr olo[2,1-c][1,2,4] triazepinones and pyrrolo [2,1-c] [1,2,4] triazines with the hope of finding out new chemical structure can be used as antitumor agents. All the results demonstrated that pyrrolo [2,1-c] [1,2,4] triazepinones **17a-c**, 1,2,4-triazepinones **16a-c**, pyrrolo [2,1-c] [1,2,4] tri-azines **19a-c**, pyrrolo [1,2-b] [1,2,4] triazinones **14** and 1,2,4-triazoles **12** possess promising and wonderful in vitro antitumor activity versus carcinoma cell lines when compared to the 5-fluorouracil drug.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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