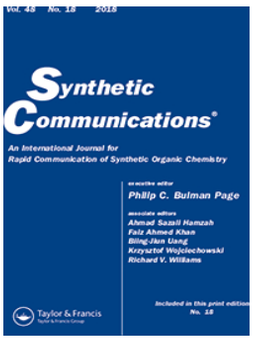

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# Synthesis and antitumor activity evaluation of some 1, 2, 4-triazine and fused triazine derivatives

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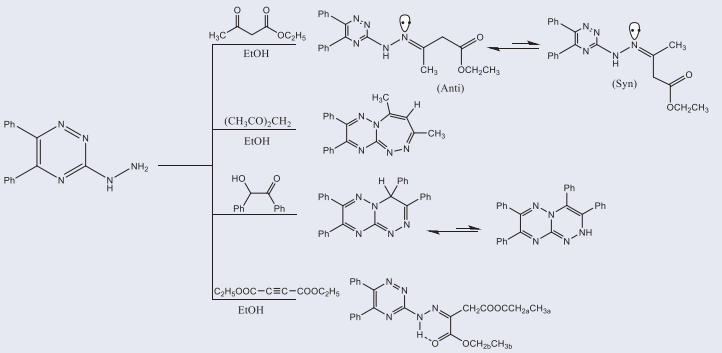
**ABSTRACT**

Reactions of 3-hyrazino-5,6-diphenyl-1,2,4-triazine with various carbonyl compounds such as ethyl acetoacetate, acetylacetone, benzoin, isatin, phthalic anhydride, phenyl isocyanate and acetic anhydride were discussed. Its reactions with α, β unsaturated compounds such as arylidinemalononitrile, diethyl acetylenedicarboxylate, dibenzylidine hydrazine were studied. These reactions led to the formation of various triazine and fused-triazine derivatives. The antitumor activity of the synthesized compounds was tested against **HePG2** and **MCF-7** cell lines. Some of the tested compounds were most active, whereas other compounds exhibited little or no activity.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
1; 2; 4-Triazine; triazolotriazine; triazinotriazepine; triazinotriazine

## Introduction

1,2,4-Triazines and their fused derivatives play an important role in medicinal chemistry due to their high biological activity. They are known to possess a broad spectrum of pharmacological activities such as antiviral,[1] antibacterial, fungicidal, insecticidal, herbicides, hypotensive, hypothermic activities,[2–5] *in vitro* supporting their anti-HIV and anticancer activities,[6–12] biological inhibitors[13–17], anti-epileptic drug.[18] Condensed

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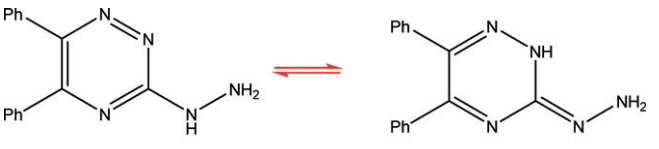
1,2,4-triazines found various applications as pharmaceuticals, herbicides, pesticides, and dyes,[19] growth inhibitory activity against leukemic cell lines and wide range of cancer cells,[20–22] antitumor and antifungal,[23,24] antiviral,[25–30] antimicrobial,[31–33] anti-HIV,[34] antimycobacterial,[35] anxiolytic,[36] and antidepressant agent.[37] These diverse biological activities initiated our interest to synthesize some 1,2,4-triazine and N-bridgehead fused derivatives of anticipated antitumor activities.

## Results and discussion

3-hydrazino-5,6-diphenyl-1,2,4-triazine was synthesized according to the reported procedure[38]and exists as an equilibrium mixture of the two tautomeric forms **1a, b** (Equation 1)



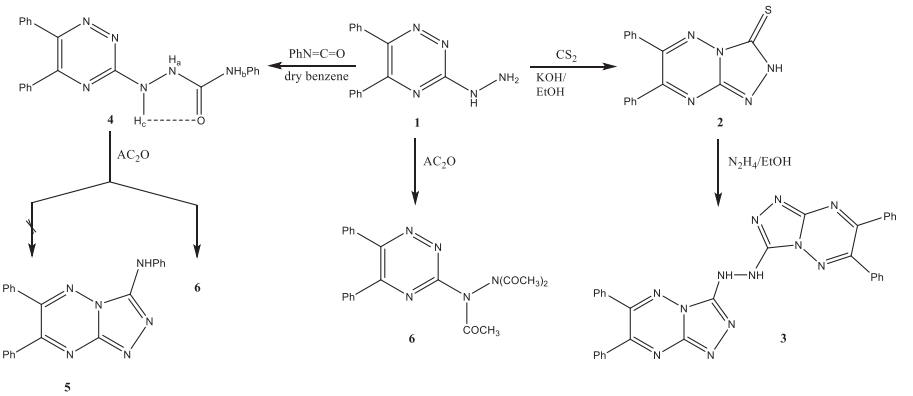

**1a** **1b**

Reaction of **1** with carbondisulfide in ethanol in the presence of a base like KOH, afforded the cycloaddition product triazolotriazine **2**. Its structure is evidenced from microanalytical as well as spectral data. IR spectrum shows two characteristic absorption bands at 3196 and 3114 $cm^{-1}$corresponding to (NH) and 1178 $cm^{-1}$corresponding to (C=S) groups. Further support for the assigned structure is gained by studying its $^{1}$HNMR spectrum that shows one broad singlet signal for (NH) at δ (ppm) 13.52 in addition to multiplet signals for the aromatic protons. The EIMS spectrum of compound **2** does not show the molecular ion peak, but it shows ($M^{\bullet+}$-1) peak in addition to some of abundant peaks. When thione derivative **2** is treated with hydrazine hydrate in boiling dioxane, it gave the dimeric form of hyrazone derivative **3** with a removal of $H_2S$ gas. The structure of compound **3** is substantiated from its infrared and $^{1}$HNMR spectra (cf. Supplementary experimental). Heating of 3-hydrazino derivative **1** with phenyl isocyanate in dry benzene gave the corresponding addition product semicarbazide **4**. The structure of compound **4** is deduced from its microanalytical and spectral data. The IR spectrum exhibits absorption bands for NH and C=O groups. Further proof is gained from its $^{1}$HNMR spectrum which exhibits three exchangeable broad singlet signals for protons of three NH groups. The down field value for the signal of one of the three protons is in accordance with the existence of compound **4** as the chelated form shown in (Scheme 1). Treatment of compound **4** with acetic anhydride yielded the triacetyl derivative **6** instead of the triazolotriazine derivative **5.** Inspection of the $^{1}$HNMR spectrum of compound **6** revealed the appearance of two singlet signals in the up-field region for three methyl groups. The integration value for the signal atδ 2.38 ppm is equivalent to the multiple value of the signal at δ 2.73 ppm. This suggests that the first signal corresponds to protons of two magnetically equivalent methyl groups. Furthermore, the spectrum is devoid of any signals for NH protons. A chemical proof for the suggested structure is gained by preparing an authentic sample, through reacting of compound **1** with acetic anhydride. It was identical in all respects m.p, m.m.p and TLC with compound **6**. Further support is

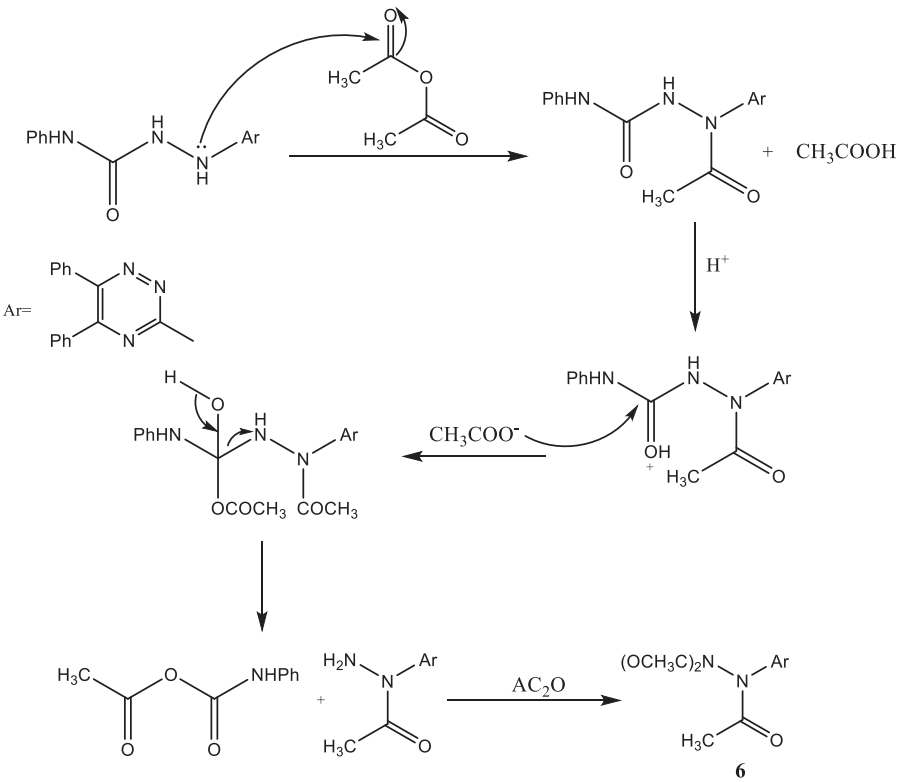
gained from its mass spectrum that revealed the correct molecular ion peak beside some of abundant peaks. All previous reactions are presented in (Scheme 1).

The conversion of compound **4** into **6** is depicted in (Scheme 2)

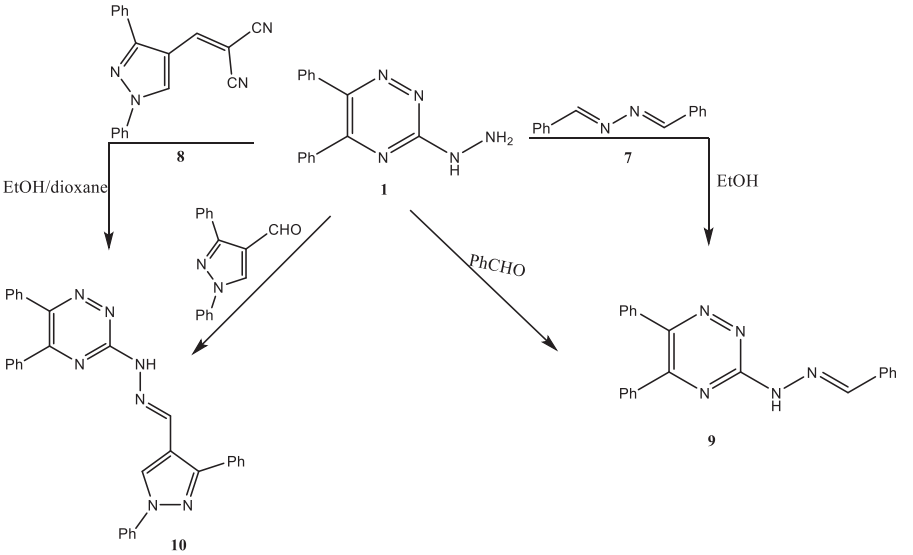
The treatment of compound **1** with dibenzylidene hydrazine **7** and/or pyrazolidine derivative of malononitrile **8** in boiling ethanol, furnished the benzalhydrazone and pyrazolidinehydrazone derivatives **9 and 10,** respectively (Scheme 3). The $^{1}$HNMR spectrum of **9** shows two singlet signals at δ 8.276, 11.933 ppm correspond to protons of




**Scheme 1.** Reactions of **1** with carbon disulfide, phenylisocyante and acetic anhydride.




**Scheme 2.** Mechanistic pathway for the conversion of compound **4** into **6**.



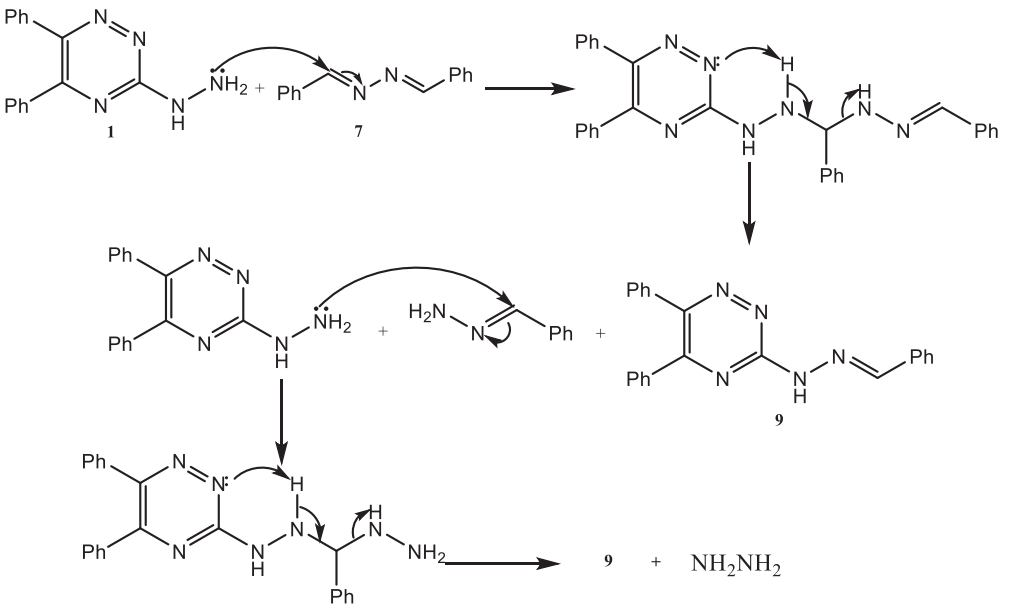

**Scheme 3.** Reactions of **1** with dibenzylidene hydrazine **7** and/or pyrazolidine derivative of malononitrile.

imino methine (CH=N) and (NH) groups. However, the $^1$HNMR spectrum of **10** shows three singlet signals at δ 8.44 ppm (CH=N), 8.943 ppm(CH) of pyrazole and 11.787 ppm (NH). Further evidence for the structures of compounds **9** and **10** is gained from their mass spectra that revealed their molecular ion peaks as well as some of important peaks. The structures of both compounds **9** and **10** were confirmed chemically by preparing authentic samples from reactions of **1** with benzaldehyde and/or 1,3-diphenyl pyrazol-4-carbaldehyde. They were identical in all respects m.p, m.m.p and tlc.

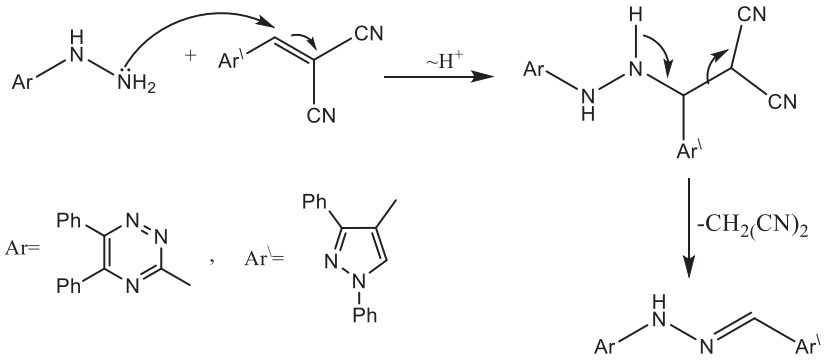
The suggested mechanistic pathways for the formation of hydrazones **9** and **10** are presented in (Scheme 4 and 5).

Heating of compound **1** with phthalic anhydride in acetic acid under reflux condition gives the isoindoline **11** via nucleophilic addition followed by cyclization. The IR spectrum of **11** revealed the presence of one absorption band at 3190 $cm^{-1}$ (NH) and two absorption bands at1791 and 1743 $cm^{-1}$ attributable to the vibrational coupling of two carbonyl groups. The $^1$HNMR spectrum is in accordance with the proposed structure (cf. Supplementary experimental). Reaction of the hydrazino derivative **1** with isatin in DMF as a solvent yielded the Schiff's base derivative **12**. The structure of **12** is established by studying its IR as well as $^1$HNMR spectra. The IR spectrum shows absorption bands characteristic for NH and C=O groups. The $^1$HNMR spectrum shed further light on the proposed structure as it shows two broad singlet signals in the down field region for protons of 2 NH groups in addition to multiple signals for the aromatic protons. The down field value for the signal of $NH_a$ proton as well as the lower absorption frequency of C=O group is a good evidence for existence of compound **12** as the chelated form shown in (Scheme **6**). The mass spectrum of compound **12** does not show the molecular ion peak, probably due to its ready decomposition in the ionization chamber, but it shows some abundant peaks.

Treatment of 3-hydrazinoderivative **1** with ethyl acetoacetate in boiling ethanol afforded the corresponding condensation product **13**. The IR spectrum of **13** revealed



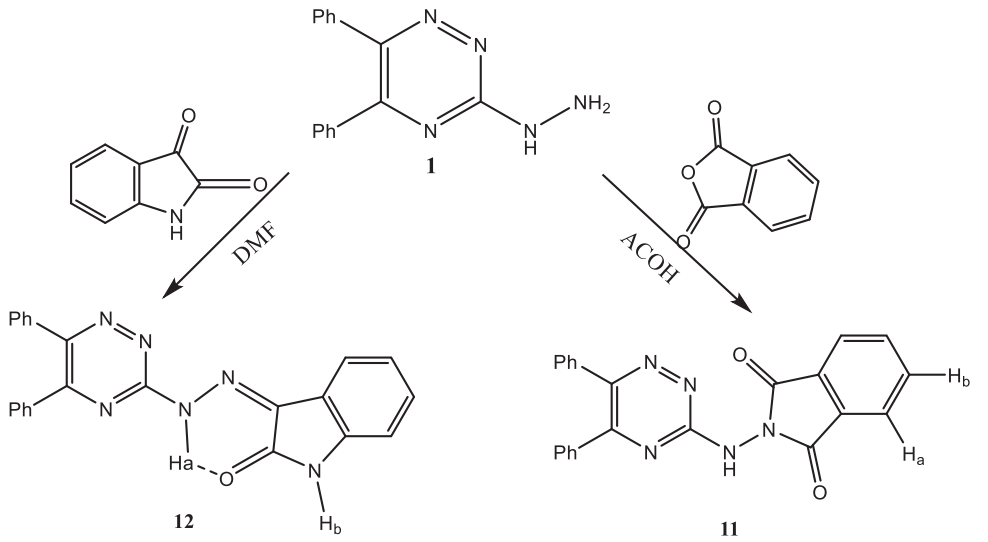
**Scheme 4.** Mechanistic pathway for the formation of hydrazone **9**.



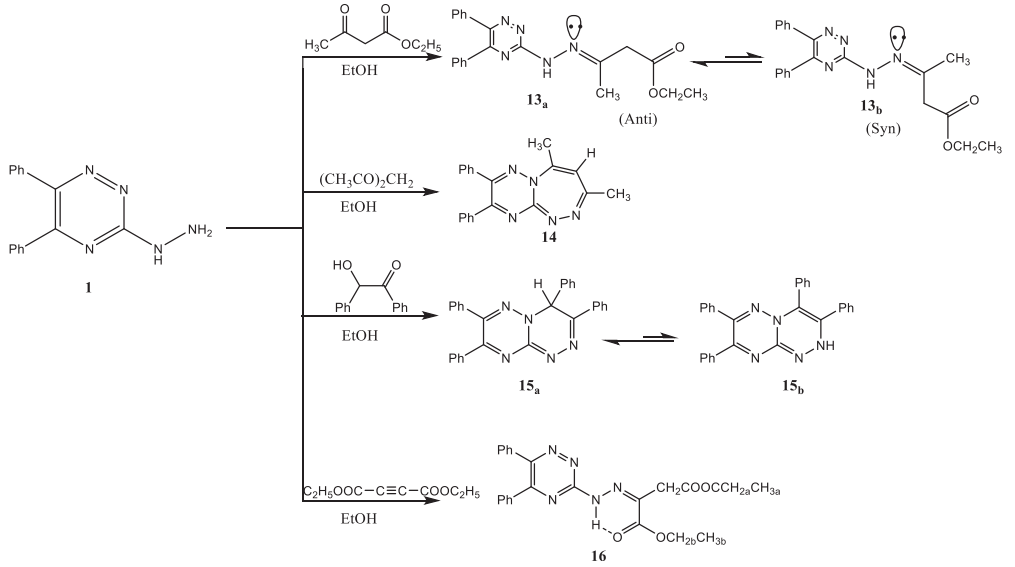
**Scheme 5.** Mechanistic pathways for the formation of hydrazones 9 and 10.

the presence of absorption bands at 3281 $cm^{-1}$ attributable to (NH) and the carbonyl of ester group at 1733 $cm^{-1}$. Inspection of the $^1$HNMR spectrum of compound **13** revealed the existence of signals corresponding to protons of NH, $CH_2$ and $CH_3CH_2$ groups as well as aromatic protons. The appearance of two singlet signals for the methylene protons of N=C–$CH_2$C=O group with integration ratio 1:3 suggests the existence of compound **13** as a mixture of two diasteriomeric forms syn and anti. The lower δ value for the signal of methylene protons of anti-isomer as compared with those of syn isomer is due to the extension of conjugation in the Ar–N=C– moiety that leads to increase the electron density at the carbon bearing the methylene group.

On the other hand, cyclocondensation is produced by reacting of 3-hyrazino derivative **1** with acetylacetone in boiling ethanol to give triazinotriazepine derivative **14**. The IR spectrum shows no absorption bands for (NH) and (C=O) groups. The $^1$HNMR spectrum is in accordance with the proposed structure (cf. Supplementary experimental).




**Scheme 6.** Reactions of **1** with phthalic anhydride and isatin.




**Scheme 7.** Reactions of **1** with Ethyl acetoacetate, acetyl acetone, benzoin and diethyl acetylenedicarboxylate.

Similarly, the cyclocondensation product triazinotriazine derivative **15** was achieved by reaction of 3-hyrazino derivative **1** with benzoin. The $^{1}$HNMR spectrum of compound **15** revealed the appearance of two singlet signals, one in the up-field region for the benzylidene proton (CH) and the other in the down field region for NH proton. This suggests the existence of compound **15** as an equilibrium mixture of toutomers $\mathbf{15_a}$ and $\mathbf{15_b}$ in the ratio of 3:2 (Scheme 7). Compound 1 undergoes Michael addition to diethyl acetylenedicarboxylate to afford the addition product **16**. The structure of **16** is established

**Table 1.** Cytotoxic activity of some compounds against human tumor cells.

| No. | Compounds | *In vitro* cytotoxicity $IC_{50}$ (μM)• | |
|---|---|---|---|
| | | HePG2 | MCF-7 |
| | DOX | 4.50± 0.2 | 4.17 ± 0.2 |
| 1 | 2 | 31.75 ± 2.5 | 35.38 ± 2.4 |
| 2 | 4 | 7.21 ± 0.8 | 9.72 ± 0.9 |
| 3 | 14 | 72.13 ± 3.9 | 68.23 ± 3.8 |
| 4 | 16 | 39.49 ± 2.6 | 45.08 ± 2.8 |
| 5 | 12 | 61.84 ± 3.5 | 67.14 ± 3.7 |
| 6 | 13 | 27.93 ± 2.1 | 26.99 ± 2.0 |
| 7 | 11 | 19.18 ± 1.7 | 21.10 ± 1.8 |
| 8 | 10 | 82.34 ± 4.6 | 72.15 ± 4.1 |
| 9 | 3 | 55.35 ± 3.2 | 49.27 ± 3.0 |
| 10 | 9 | 76.58 ± 4.1 | 91.48 ± 5.2 |
| 11 | 15 | 48.16 ± 2.9 | 58.36 ± 3.4 |
| 12 | 6 | 9.11 ± 1.0 | 12.84 ± 1.1 |

•**$IC_{50}$ (μM)**: 1–10 (very strong). 11–20 (strong). 21–50 (moderate). 51–100 (weak) and above 100 (noncytotoxic).

by studying its IR spectrum that shows absorption bands corresponding to NH and C=O groups. Further evidence for the suggested structure of compound **16** is gained from its $^{1}$HNMR spectrum that exhibits signals for NH, alkyl and aromatic protons. The down field value for the signal of NH proton, as well as the lower absorption frequency of one of the two carbonyl ester groups is in a good agreement with the existence of compound **16** as the chelated form shown in (Scheme 7).

## Evaluation of the antitumor activity

The anti-tumor efficacy of the compounds against **HePG2** and **MCF-7** cell lines was demonstrated compared with doxorubicin. The obtained results revealed that compounds **4**, **11** and **6** were the most active derivatives among the series of tested compounds, whereas other compounds exhibited little or no activity. The effective dose calculated as $IC_{50}$, which correspond to the compound concentration resulted in 50% mortality in the total cells count and presented in (Table 1, Fig 1).

## Experimental

Melting points were determined using an electrothermal Gallenkamp Scientific melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Nicolet 7600 (USA)FT-IR infrared spectrophotometer using the KBr pellet technique at the central laboratory of faculty of science, Ain shams university. $^{1}$HNMR spectra were recorded on a GEMINI 300 BB-400 MHz spectrometer using tetramethylsilane (TMS) as internal standard in dimethyl sulfoxide (DMSO-d6) as a solvent with chemical shift δ expressed in ppm and $^{13}$C-NMR spectra were recorded on the same spectrometer at 75 MHz and referenced to solvent signal δ = 39.50 ppm for DMSO-d6 at the main defence chemical laboratory. Mass spectra were measured on a GC-MSQP 1000-Ex spectrometer at the regional center for Mycology and Biotecnology of Al-Azhar university and on Agilent technologies 5977 AMSD 7890B CTC system at the central laboratory of

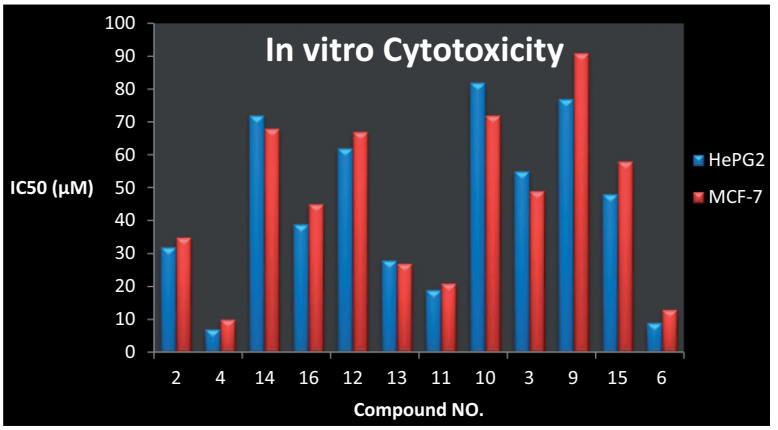



**Figure 1.** Cytotoxic activity of some compounds against human tumor cells. IR spectrum of compound 2.

faculty of science, Ain shams university. Elemental analyses were carried out at the microanalytical center of faculty of science, Cairo University. Follow-up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected aluminum sheets (F254, Merck) and the spots were detected by exposure to UV-lamp. The anticancer activity was done at Micro Analytical Center at Mansoura University.

### General procedure for the reaction of the hydrazino 1 with carbon disulfide

A solution of compound **1** (0.5g, 0.002 mol) in (10 mL) ethanolic potassium hydroxide 10% and carbon disulfide (0.144g, 0.002 mol) was refluxed for 7h. Cooled then neutralized with ice-cold hydrochloric acid. The solid obtained was collected by filtration and recrystallized from a mixture of petroleum 60–80 °C and benzene (1:1).

### 6,7-Diphenyl-[1,2,4] triazolo[4,3-b][1,2,4]triazine-3(2H)-thione2

Orange crystals (50%), mp 208-210 °C, (petroleum 60–80 °C and benzene (1:1)); FTIR (KBr) $cm^{-1}$: 3196, 3114 (NH), 3089, 3054 (Aryl-H), 1664 (C=N), 1178 (C=S).[1] HNMR (DMSO-d6): δ 7.22–7.45 (*m*, 10H, Ar–H), 13.52 (br.s, 1H, NH, exchangeable). MS (70 ev) *m/z* (%): 305.074 ($M^{\bullet}$, missed), 220(36), 192(87), 191(19), 190(20), 178(41), 165(100), 103(19), 104(19), 61(35). Anal. calcd for $C_{16}H_{11}N_5S$ (305.359): C, 62.93; H, 3.63; N, 22.93; S, 10.50. Found: C, 62.78; H, 3.64; N, 22.88; S, 10.52.

### General procedure for the reaction of the semicarbazide 4 with acetic anhydride

***Method A:*** A solution of compound **4** (1g, 0.0026 mol) in acetic anhydride (20 mL) was boiled under reflux for 2h. The resulting solid was poured onto crushed ice and the product that separated was filtered off, washed with water and then recrystallized from petroleum 60–80 °C.

***Method B:*** A solution of compound **1** (0.5 g, 0.002 mol) in acetic anhydride (15 mL) was refluxed for 1 h. The reaction mixture was then poured onto crushed ice and the solid product that separated was filtered off, washed with water and then recrystallized from petroleum 60–80 °C.

### *N, N'-diacetyl-N'-(5, 6-diphenyl-1, 2, 4-triazin-3-yl)-acetohydrazide 6*

Pale yellow crystals (84%), mp138–140 °C (lit.[40] m.p. 143–144 °C), (petroleum 60–80 °C); FTIR (KBr) $cm^{-1}$: 3065, 3011 (Aryl-H), 2937 (Alkyl-H), 1731, 1705 (C=O), 1599 (C=N), 1580 (C=C). $^1$HNMR (DMSO-d6): δ, 2.38 (s, 6H, $2CH_3$), 2.73 (*s*, 3H, $CH_3$), 7.37–7.51 (*m*, 10H, Ar-H) MS(70 ev) *m/z* (%): 389.149 ($M^{\bullet+}$,19), 305(43), 288(27), 276(13), 263(39), 207(16), 179(16), 178(100), 176(15), 165(13), 104(12). Anal.calcd for $C_{21}H_{19}N_5O_3$ (389.415): C, 64.77; H, 4.92; N, 17.98; Found: C, 64.64; H, 4.93; N, 18.04.

## Antitumor bioassay

### *Materials and methods*

#### *Cell line*

Hepatocellular carcinoma HePG-2 and mammary gland MCF-7. The cell line was obtained from ATCC via Holding company for biological products and vaccines (VACSERA), Cairo, Egypt.

#### *Chemical reagents*

The reagents RPMI-1640 medium,MTT and DMSO (sigma co., St. Louis, USA), Fetal Bovine serum (GIBCO, UK) .Doxorubicin was used as a standard anticancer drug for comparison.

#### *MTT assay*

The different cell line mentioned above were used to determine the inhibitory effects of compounds on cell growth using the MTT assay[41,42]. This colorimetric assay is based on the conversion of the yellow tetrazolium bromide (MTT) to a purple formazan derivative by mitochondrial succinate dehydrogenase in viable cells. The cells were cultured in RPMI-1640 medium with 10% fetal bovine serum. Antibiotics added were 100 units/ml penicillin and 100 µg/ml streptomycin at 37 C in a 5% $Co_2$ incubator. The cells were seedes in a 96-well plate at a density of $1.0 \times 10^4$ cells/well. at 37 °C for 48 h under 5% $CO_2$. After incubation, the cells were treated with different concentration of compounds and incubated for 24 h. After 24 h of drug treatment, 20 µl of MTT solution at 5 mg/ml was added and incubated for 4 h. Dimethyl sulfoxide (DMSO) in volume of 100 µl is added into each to dissolve the purple formazan formed. The colorimetric assay is measured and recorded at absorbance of 570 nm using a plate reader (EXL 800). The relative cell viability in percentage was calculated as (A570 of untreated sample/A570 of untreated sample)×100.

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