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# Synthesis: Antioxidant and Antiproliferative Activities of Novel Quinazolinone Derivatives

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***Abstract:***
***Background****: The recent literature reveals that the quinazolinone moiety associated with various aromatic as well as heterocyclic compounds possess wide range of pharmacological properties.*
***Materials and Methods****: The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data (FT-IR, $^{1}$HNMR, $^{13}$CNMR, mass spectra). Antioxidant activity of quinazolinones was determined by diphenyl picryl hydrazyl (DPPH) assay method. Antiproliferative activity of quinazolinones was determined against three cancer cell lines (MCF-7, HCT and HepG-2).*
***Results****: One-pot Biginelli reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone), thiourea and a variety of aldehydes; afforded octahydroquinazolinone derivatives. Treatment of one of them with ethyl bromoacetate, displayed ethyl 2-(quinazolin-2-ylthio)acetate derivative. Moreover, octahydroquinazolinone derivatives on reflux with hydrazine hydrate furnished the hydrazine derivatives. Condensation of these hydrazines with a number of formyl derivatives gave the corresponding hydrazones. On the other hand, cyclization of one of hydrazine derivatives with acetic acid, afforded the [1,2,4]triazolo-[3,4-b]quinazolin-6-one. The prepared compounds were examined as antioxidants that determined in terms of $EC_{50}$ values as well as antiproliferative against cancer cell lines; HepG-2, HCT and MCF-7 in terms of $IC_{50}$.*
***Conclusion:*** *new synthesized quinazolinones showed high antioxidant activity compared to vitamin E as well as moderate antiproliferative activity as compared to Doxorubicin, Doxorubicin and Vinblastine standards.*
***Key Word****: Dimedone; Triazole; Pyrazoloquinoxaline; Quinazolinone; antioxidant; antiproliferative; DPPH; scavenging and cancer cell lines.*

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## I. Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones, named Biginelli compounds and their derivatives have received a great deal of attention, due to their therapeutic and pharmaceutical properties, such as anti-inflammatory [1], antibacterial [2-5], antitumor [6,7], antifungal [2,3,8], antitubercular [2] activities. Moreover, dihydropyrimidinones have been used as calcium channel blockers [9] as well as a calcium antagonist [10-12]. Furthermore, some alkaloids containing the dihydropyrimidine core unit possess a diversity of useful biological effects; among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors [13-15]. Octahydroquinazolinones found to be bioactive analogues because of their potential antibacterial activity against Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa [16-19], as well as a calcium antagonist [16-18,20]. In this work some new quinazolinone derivatives were synthesized and tested for their antioxidant and antiproliferative activities. In the same time these compounds can be used as bases for nucleoside preparation. The current study aims to synthesize new quinazolinone derivatives and test their activities as antioxidant and antiproliferative.

## II. Material And Methods

**Chemistry Part,** melting points were determined with a Melt-temperature apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel 1B-F plates and the spots were detected by UV light absorption. IR spectra were recorded on Perkin Elmer. USA Spectrometer. $^{1}$H NMR, $^{13}$C NMR were recorded on JEOL JNM ECA 500 MHz (faculty of Science, Alexandria University, Alexandria, Egypt) and 300 MHz (Jordan University, Amman, Jordon) using tetramethyl-silane as an internal standard. Mass spectra and elemental analyses were recorded on GCMS solution DI Analysis Shimadzu Qp-2010 Plus, at the faculty of

Science, Cairo University, Cairo, Egypt. Solutions were evaporated under diminished pressure unless otherwise stated. The ChemDraw-Ultra-8.0 has been used in generating the nomenclature of the prepared compounds.

**Procedure methodology (Chemistry part)**

Biginelli reaction.General Method [21]. A mixture of 5,5-dimethylcyclohexan-1,3-dione (dimedone) (1.428 mmol), aromatic aldehyde (1.428 mmol) and thiourea (1.428 mmol) in absolute ethanol (4mL) in presence of concentrated hydrochloric acid (37%, 0.4mL) was refluxed and monitored by TLC, The solid product was filtered off, washed with ammonium hydroxide solution then with water.

*4-(2-Chlorophenyl)-1,2,3,4,7,8-hexahydro-7,7-di-methyl-2-thioxoquinazolin-5(6H)-one* **1**. It was recrystallized from ethanol as colorless needles.

*1,2,3,4,7,8-Hexahydro-7,7-dimethyl-4-(3-nitro-phenyl)-2-thioxoquinazolin-5(6H)-one* **2**. It was recrystallized from ethanol as colorless needles.

*1,2,3,4,7,8-Hexahydro-7,7-dimethyl-4-(4-nitro-phenyl)-2-thioxoquinazolin-5(6H)-one* **3**. It was recrystallized from ethanol as colorless needles.

*4-(4-Bromophenyl)-1,2,3,4,7,8-hexahydro-7,7-di-methyl-2-thioxoquinazolin-5(6H)-one* **4**. It was recrystallized from ethanol as white needles.

*1,2,3,4,7,8-Hexahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)-2-thioxoquinazolin-5(6H)-one* **5**. It was recrystallized from methanol as white needles.

*1,2,3,4,7,8-Hexahydro-7,7-dimethyl-4-(1-phenyl-1H-pyrazolo[4,3-b]quinoxalin-3-yl)-2-thioxoquina-zolin-5(6H)-one* **6.** It was recrystallized from dioxane as canary yellow crystals.

*Ethyl 2-(3,4,5,6,7,8-hexahydro-7,7-dimethyl-5-oxo-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quina-zolin-2-ylthio)acetate* **7**. A mixture of 1,2,3,4,7,8-hexahydro-7,7-dimethyl-4-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-2-thioxoquinazolin-5(6*H*)-one **5** (1.416 mmol), ethyl bromoacetate (1.416 mmol) and anhydrous potassium carbonate (5.664 mmol) in dry acetone (30mL) was refluxed for 5 hours, then it was filtered off, the filtrate was evaporated as yellow syrup. It was recrystallized from ethanol as yellow syrup.

Reaction of 2-thioxo-quinazolin-5(6*H*)-one **2, 4, 5** with hydrazine hydrate. General Method. A suspension of 2-thioxo-quinazolin-5(6*H*)-one **2**, **4** and **5** (10 mmol) in hydrazine hydrate (99%, 20 mL) was stirred under reflux for 8 hours; the solid precipitated was filtered off, washed with ethanol and dried.

*2-Hydrazinyl-3,4,7,8-tetrahydro-7,7-dimethyl-4-(3-nitrophenyl)quinazolin-5(6H)-one* **8**. It was recrystallized from ethanol as yellow needles.

*4-(4-Bromophenyl)-2-hydrazinyl-7,8-dihydro-7,7-dimethylquinazolin-5(1H,4H,6H)-one* **9**. It was recrystallized from ethanol as yellow needles.

*2-hydrazinyl-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one* **10**. It was recrystallized from ethanol as yellow crystals.

Reaction of hydrazines **8** and **10** with aromatic aldehydes. General Method. A suspension of hydrazine compound (0.285mmoL) in ethanol (5mL) was treated with aromatic aldehyde (0.285mmoL) under reflux for 3hours; the solid precipitated was filtered off, washed with ethanol and dried.

*2-Hydrazinyl-N-(3-phenylallylidene)-3,4,7,8-tetra-hydro-7,7-dimethyl-4-(3-nitrophenyl)-quinazolin-5(6H)-one* **11**, it was obtained from compound **8** and cinnamaldehyde. It was recrystallized from ethanol as yellow crystals.

*2-Hydrazinyl-N-[(p-methoxyphenyl-4-yl)methyl-ene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(3-nitro-phenyl)-quinazolin-5(6H)-one* **12**, it was obtained from compound **8** and *4-methoxybenzaldehyde*. It was recrystallized from ethanol as yellow crystals.

*2-Hydrazinyl-N-[(2-phenyl-2H-1,2,3-triazol-4-yl)-methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(3-nitro-phenyl)quinazolin-5(6H)-one* **13**, it was obtained from compound **8** and 2-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde. It was recrystallized from dimethyl formamide as yellow needles.

*2-Hydrazinyl-N-[(2-chlorophenyl-1-yl)methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one* **14**, it was obtained from compound **10** and *o*-chlorobenz-aldehyde. It was recrystallized from ethanol as yellow needles.

*2-Hydrazinyl-N-[(3-nitrophenyl-1-yl)methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one* **15**, it was obtained from compound **10** and *m*-nitrobenzaldehyde. It was recrystallized from ethanol as yellow needles.

*2-Hydrazinyl-N-[(4-nitrophenyl-1-yl)methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one* **16**, it was obtained from compound **10** and *p*-nitrobenzaldehyde. It was recrystallized from ethanol as yellow crystals.

*2-Hydrazinyl-N-[(4-bromophenyl-1-yl)methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one* **17**, it was obtained from compound **10** and *p*-bromobenzaldehyde. It was recrystallized from ethanol as off white needles.
*2-Hydrazinyl-N-[(2-phenyl-2H-1,2,3-triazol-4-yl)-methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one* **18**, it was obtained from compound **10** and 2-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde. It was recrystallized from ethanol as yellow crystals.
*2-Hydrazinyl-N-[(1-phenyl-1H-pyrazolo[4,3-b]-quinoxalin-3-yl)methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quina-zolin-5(6H)-one* **19**, it was obtained from compound **10** and 1-phenyl-1*H*-pyrazolo[4,3-*b*]-quinoxaline-3-carbaldehyde. It was recrystallized from ethanol-DMF as red crystals.
*2-Hydrazinyl-N-[(2-methyl-N'-(2-oxoindolin-3-ylidene)furan-3-carbohydrazide-5-yl)-methylene]-3,4,-7,8-tetra-hydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)-quinazolin-5(6H)-one* **20**, it was obtained from compound **10** and 5-formyl-2-methyl-N'-(2-oxoindolin-3-ylidene)furan-3-carbo-hydrazide. It was recrystallized from ethanol as yellow crystals.

*8,9-Dihydro-3,8,8-trimethyl-5-(2-phenyl-2H-1,2,3-triazol-4-yl)-[1,2,4]triazolo-[3,4-b]-quinazolin-6(5H-,7H,10H)-one* **21.** A mixture of 2-hydrazinyl-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2H-1,2,3-triazol-4-yl)quinazolin-5(6H)-one **10** (1.424 mmoL) and acetic acid (15 mL) was refluxed for 5 hours, the reaction mixture was cooled. The separated solid was filtered off, and dried. It was recrystallized from methanol as yellow crystals.

**Materials (Antiproliferative screening)**

Mammalian cell lines: MCF-7 cells (human breast cancer cell line were obtained from VACSERA Tissue Culture Unit. Chemicals Used: diphenyl picryl hydrazyl (DPH), Dimethyl sulfoxide (DMSO), crystal violet and trypan blue dye were purchased from sigma (St. Louis, Mo., USA). Fetal Bovine serum, DMEM (Dulbecc'o Modefied Eagle's Medium), RPMI-1640, HEPES buffer solution, L-glutamine, gentamycin and 0.25% Trypsin-EDAT were purchased from Lonza. Crystal violet (1%): composed of 0.5% (W/V) crystal violet and 50% methanol, then made up to volume dd $H_2O$ and filtered through a whatmann No. 1 filter paper.

**Cell line propagation:**

The cells were propagated in (DMEM) supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer and 50 µg/mL gentamycin. All cells were mentained at 37 ºC in humidified atmosphere with 5% $CO_2$ and were subcultured two times a week. Cell toxicity was monitored by determining the effect of the examined compound on cell morphology and cell viability.

**Cytotoxicity evaluation using viability assay:**

For cytotoxicity assay, the cells were seeded in 96-well plate at a cell concentration of $1*10^4$ cell per well in 100 µL of growth medium. Fresh medium containing different concentrations of the test sample was added after 24 hours of seeding. Serial two-fold dilutions of the tested chemical compound were added to confluent cell monolayers dispensed into 96-well, flat-bottomed microtiter plates (Falcon, NJ, USA) using a multichannel pipette. The microtiter plates were incubated at 37 ºC in a humidified incubator with 5% $CO_2$ for a period of 48 hour. Three wells were used for each concentration of each tested sample. Control cells were incubated without test sample and with or without DMSO. After incubation of the cells for 24 hours at 37 ºC, various concentrations of each sample (50, 25, 12.5, 6.25, 3.125 and 1.56 µg) were added each separately. The incubation was continued for 48 hours and viable cells yield was determined colorimetrically using MTTB (3,4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide). The water insoluble tetrazolium salt is converted to purple formazon by the mitochondrial dehydrogenase of viable cells. After the end of incubation period, media were aspirated and the crystal violet solution (1%) was added to each well for at least 30 minutes. The stain was removed and plates were rinsed using tap water until all excess stain is removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly, then the absorbance of the plates were measured after gently shaken on Microplate Reader (TECAN, inc.), using a test wavelength of 490 nm. All results were corrected for background absorbance detected in wells without added stain. Treated samples were compared with the cell control in the absence of the tested compounds. All experiments were carried out in the triplicate. The cell cytotoxic effect of each tested compound was calculated [29,30].

## III. Result

### A. Chemical analysis

**Table no 1**. Mass, IR, $^1$H NMR spectral data of compounds **1-21**.

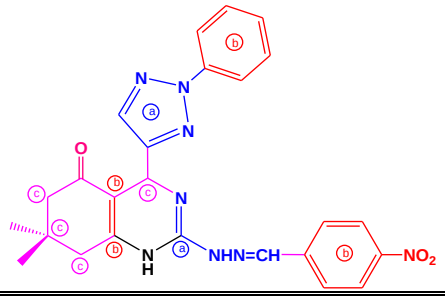
| Comp. no. | Mass (m/z) (%) | IR (γ, cm$^{-1}$) | $^1$H NMR (δ, ppm)(DMSO-d$_6$) |
|---|---|---|---|
| **1** | ------ | 3232 (2NH), 1668 (C=O), 1625 (C=C). | δ: 1.01, 1.04 (2s, 6H, 2CH$_3$), 2.18 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.32 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.58 (s, 2H, CH$_{2(1)}$), 3.38 (s, 1H, NH with H$_2$O of DMSO), 5.60 (s, 1H, CH-methine), 7.08-7.10 (m, 1H, Ar-H$_{(d)}$), 7.27-7.29 (m, 2H, Ar-H$_{(b,c)}$), 7.47-7.49 (m, 1H, Ar-H$_{(a)}$), 10.97 (bs, 1H, NH, D$_2$O exchangeable). |
| **2**[25] | [M$^+$+2] 333 (9.0), [M$^+$+1] 332 (44.4), [M$^+$] 331 (5.3). | 3212 (2NH), 1676 (C=O), 1615 (C=C). | δ: 0.93, 1.03 (2s, 6H, 2CH$_3$), 2.15 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.35 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.47 (d, 1H, CH$_{2(1)}$, *J* 17.55 Hz), 2.61 (d, 1H, CH$_{2(1)}$, *J* 17.55 Hz), 3.33 (s, 1H, NH with H$_2$O of DMSO), 5.65 (s, 1H, CH-methine), 7.62 (t, 1H, Ar-H$_{(d)}$, *J* 7.65 Hz), 7.70 (d, 1H, Ar-H$_{(c)}$, *J* 7.65 Hz), 8.08-8.10 (m, 2H, Ar-H$_{(b,a)}$), 10.98 (s, 1H, NH, D$_2$O exchangeable). |
| **3**[25] | [M$^+$+2], 333 (19.9), [M$^+$+1], 332(100.0), [M$^+$], 331(35.3). | 3190 (2NH), 1669 (C=O), 1628 (C=C). | δ: 0.90, 1.01 (2s, 6H, 2CH$_3$), 2.14 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.32 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.45 (d, 1H, CH$_{2(1)}$, *J* 17.61 Hz), 2.57 (d, 1H, CH$_{2(1)}$, *J* 17.61 Hz), 3.37 (s, 1H, NH with H$_2$O of DMSO), 5.59 (s, 1H, CH-methine), 7.50 (d, 2H, Ar-H$_{(b)}$, *J* 8.40 Hz), 8.16 (d, 2H, Ar-H$_{(a)}$, *J* 8.40 Hz), 10.96 (bs, 1H, NH, D$_2$O exchangeable). |
| **4**[17, 18,26 ,27] | ------ | 3245 (2NH), 1669 (C=O), 1622 (C=C). | δ: 0.90, 1.01 (2s, 6H, 2CH$_3$), 2.13 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.31 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.42 (d, 1H, CH$_{2(1)}$, *J* 17.61 Hz), 2.55 (d, 1H, CH$_{2(1)}$, *J* 17.61 Hz), 3.37 (s, 1H, NH with H$_2$O of DMSO), 5.41 (s, 1H, CH-methine), 7.18 (d, 2H, Ar-H$_{(b)}$, *J* 8.40 Hz), 7.49 (d, 2H, Ar-H$_{(a)}$, *J* 8.40 Hz), 10.86 (bs, 1H, NH, D$_2$O exchangeable). |
| **5** | [M$^+$+2], 355 (15.0), [M$^+$+1], 354 (54.8), [M$^+$], 353(23.6). | 3190 (2NH), 1676 (C=O), 1628 (C=N&C=C). | δ: 1.00, 1.03 (2s, 6H, 2CH$_3$), 2.15 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.36 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz ), 2.39 (d, 1H, CH$_{2(1)}$, *J* 17.56 Hz), 2.61 (d, 1H, CH$_{2(1)}$, *J* 17.56 Hz), 3.33 (s, 1H, NH with H$_2$O of DMSO), 5.68 (s, 1H, CH-methine), 7.36 (t, 1H, Ar-H$_{(c)}$, *J* 7.65 Hz), 7.50 (t, 2H, Ar-H$_{(b)}$, *J* 7.65 Hz), 7.85 (d, 2H, Ar-H$_{(a)}$, *J* 7.65 Hz), 7.93 (s, 1H, CH-triazole), 10.92 (s, 1H, NH, D$_2$O exchangeable). |
| **6** | [M$^+$+2], 456 (21.0), [M$^+$+1], 455 (69.3), [M$^+$], 454 (2.7). | 3224 (2NH), 1669 (C=O), 1619 (C=N&C=C). | δ: 1.08, 1.09 (ss, 6H, 2CH$_3$), 2.15 (d, 1H, CH$_{2(2)}$, *J* 15.30 Hz), 2.44-2.51 (m, 2H, CH$_{2(2,1)}$ with DMSO), 2.76 (d, 1H, CH$_{2(1)}$, *J* 17.61 Hz), 3.51 (s, 1H, NH), 6.12 (s, 1H, CH-methine), 7.28 (t, 1H, Ar-H$_{(g)}$, *J* 7.65 Hz), 7.53 (t, 2H, Ar-H$_{(f)}$, *J* 7.65 Hz), 7.79 (t, 1H, Ar-H$_{(d)}$, *J* 7.65 Hz), 7.88 (t, 1H, Ar-H$_{(c)}$, *J* 7.65 Hz), 8.10 (d, 1H, Ar-H$_{(b)}$, *J* 9.15 Hz), 8.21 (t, 3H, Ar-H$_{(e,a)}$, *J* 8.40 Hz), 11.12 (s, 1H, NH, D$_2$O exchangeable). |
| **7** | ------ | 3290 (NH), 1737 (CO$_2$Et), 1717 (C=O), 1623 (C=N), 1602 (C=C). | $^1$H NMR (δ, ppm) (CDCl$_3$) δ: 1.09, 1.12 (2s, 6H, 2CH$_3$-quinazolinone), 1.21-1.27 (m, 5H, S-CH$_2$, CH$_3$-ester), 2.34 (s, 2H, CH$_{2(2)}$-quinazolinone), 2.44 (s, 2H, CH$_{2(1)}$-quinazolinone), 3.79 (s, 1H, NH, D$_2$O exchangeable), 4.17-4.20 (m, 2H, CH$_2$-ester), 5.66 (s, 1H, CH-methine), 7.28 (t, 1H, Ar-H$_{(c)}$, *J* = 7.65 Hz), 7.40 (t, 2H, Ar-H$_{(b)}$, *J* = 7.65 Hz), 7.77 (s, 1H, CH-triazole), 7.93 (d, 2H, Ar-H$_{(a)}$, *J* = 7.65 Hz). |
| **8** | ------ | 3335&3221 (NH, NH$_2$), 1648 (C=O), 1610 (C=N&C=C), | δ: 0.83, 0.97 (2s, 6H, 2CH$_3$), 1.87 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 1.96 (d, 1H, CH$_{2(2)}$, *J* 16.80 Hz), 2.07 (d, 1H, CH$_{2(1)}$, *J* 16.80 Hz), 2.08 (d, 1H, CH$_{2(1)}$, *J* 16.06 Hz), 3.36 (s, 1H, NH with H$_2$O of DMSO), 5.13 (s, 1H, CH-methine), 5.64 (bs, 2H, NH$_2$, D$_2$O exchangeable), 6.36 (d, 1H, Ar-H$_{(d)}$, *J* 6.90 Hz), 6.41 (d, 1H, Ar-H$_{(c)}$, *J* 7.65 Hz), 6.46 (s, 1H, Ar-H$_{(b)}$), 6.85 (t, 1H, Ar-H$_{(a)}$, *J* 7.65 Hz), 8.67 (s, 1H, NH, D$_2$O exchangeable). |
| **9** | [M$^+$+1], 366, 364(2.88, 9.01), [M$^+$],365, 363 (9.57, 40.41). | 3335&3200 (NH, NH$_2$), 1658 (C=O), 1624 (C=N&C=C). | δ: 0.82, 0.97 (2s, 6H, 2CH$_3$), 2.06 (s, 2H, CH$_{2(2)}$), 2.14 (d, 1H, CH$_{2(1)}$, *J* 15.00 Hz), 2.24 (d, 1H, CH$_{2(1)}$, *J* 15.00 Hz), 4.34 (s, 1H, NH, D$_2$O exchangeable), 5.28 (s, 1H, CH-methine), 5.67 (s, 2H, NH$_2$, D$_2$O exchangeable), 7.14 (d, 2H, Ar-H$_{(b)}$, *J* 9.00 Hz), 7.45 (d, 2H, Ar-H$_{(a)}$, *J* 9.00 Hz), 9.69 (s, 1H, NH, D$_2$O exchangeable). |
| **10** | [M$^+$+2], 353 (6.7), [M$^+$+1], 352 (22.2), [M$^+$], 351 (8.4). | 3327&3259 (NH, NH$_2$), 1685 (C=O), 1649 (C=N), 1605 (C=C). | δ: 0.94, 1.00 (2s, 6H, 2CH$_3$), 2.01 (d, 1H, CH$_{2(2)}$, *J* 16.06 Hz), 2.19-2.25 (m, 2H, CH$_{2(2,1)}$), 2.41 (d, 1H, CH$_{2(1)}$, *J* 17.60 Hz), 3.31 (s, 1H, NH with H$_2$O of DMSO), 4.70 (s, 2H, NH$_2$, D$_2$O exchangeable), 5.50 (s, 1H, CH-methine), 7.36 (t, 1H, Ar-H$_{(c)}$, *J* 7.65 Hz), 7.51 (t, 2H, Ar-H$_{(b)}$, *J* 7.65 Hz), 7.88 (d, 3H, Ar-H$_{(a)}$ and CH-triazole), 9.79 (s, 1H, NH, D$_2$O exchangeable). |
| **11** | [M$^+$+2], 445 (80.39), [M$^+$+1], 444 (60.78), [M$^+$], 443 (50.98). | 3308-3181 (2NH), 1696(C=O), 1655(C=N), 1609(C=C). | …… |
| **12** | [M$^+$+1], 448 (78.23), [M$^+$], 447 (57.26). | 3305&3227 (2NH), 1688(C=O), 1648(C=N), 1603(C=C). | …… |
| **13** | [M$^+$+1], 485(66.67), | 3319 (2NH), 1640 (C=O), | δ: 1.03, 1.07 (2s, 6H, 2CH$_3$), 2.09 (d, 1H, CH$_{2(2)}$, *J* 17.60 Hz), 2.28 (d, |

| | | | |
|---|---|---|---|
| | [$M^+$], 484 (52.25). | 1600 (C=N&C=C). | 1H, $CH_{2(2)}$, *J* 17.60 Hz), 2.43-2.46 (m, 1H, $CH_{2(1)}$ with DMSO), 3.09 (d, 1H, $CH_{2(1)}$, *J* 16.06 Hz), 3.36 (s, 1H, NH with $H_2O$ of DMSO), 6.35 (s, 1H, CH-methine), 7.37-7.44 (m, 2H, Ar-H), 7.53-7.58 (m, 3H, Ar-H), 7.92 (d, 2H, Ar-H, *J* 6.85 Hz), 8.02 (t, 2H, Ar-H, *J* 6.85 Hz), 8.51-8.52 (ss, 2H, CH=N and CH-triazole), 9.60 (s, 1H, NH, $D_2O$ exchangeable). |
| **14** | ------ | 3223 (2NH), 1701 (C=O), 1640 (C=N), 1585 (C=C). | δ: 0.92, 1.03 (2s, 6H, $2CH_3$), 2.09 (d, 1H, $CH_{2(2)}$, *J* = 16.00 Hz), 2.26 (d, 1H, $CH_{2(2)}$, *J* = 16.00 Hz), 2.36 (d, 1H, $CH_{2(1)}$, *J* = 17.56 Hz), 2.49 (d, 1H, $CH_{2(1)}$, *J* = 17.56 Hz), 3.33 (s, 1H, NH with $H_2O$ of DMSO), 6.38 (s, 1H, CH-methine), 7.35-7.39 (m, 3H, Ar-$H_{(e,f,g)}$), 7.46 (dd, 1H, Ar-$H_{(d)}$, $J_{a,d}$ = 7.65 Hz and $J_{d,f}$ = 1.55 Hz), 7.50 (t, 2H, Ar-$H_{(c)}$, *J* = 7.65 Hz), 7.86 (d, 2H, Ar-$H_{(b)}$, *J* = 7.65 Hz), 7.90 (dd, 1H, Ar-$H_{(a)}$, $J_{a,d}$ = 7.65 Hz and $J_{a,e}$ = 2.30 Hz), 8.01 (s, 1H, CH-triazole), 8.78 (s, 1H, CH=N), 10.37 (s, 1H, NH, $D_2O$ exchangeable). |
| **15** | ------ | 3250&3180 (2NH), 1708 (C=O), 1656 (C=N), 1619 (C=C). | δ: 0.90, 1.03 (2s, 6H, $2CH_3$), 2.09 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.28 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.33 (d, 1H, $CH_{2(1)}$, *J* 17.60 Hz), 2.50 (d, 1H, $CH_{2(1)}$, *J* 17.60 Hz), 3.33 (s, 1H, NH with $H_2O$ of DMSO), 6.49 (s, 1H, CH-methine), 7.34 (t, 1H, Ar-$H_{(g)}$, *J* 7.65 Hz), 7.48 (t, 2H, Ar-$H_{(f)}$, *J* 8.40 Hz), 7.68 (t, 1H, Ar-$H_{(e)}$, *J* 8.40 Hz), 7.82 (d, 2H, Ar-$H_{(d)}$, *J* 8.40 Hz), 8.07 (s, 1H, Ar-$H_{(c)}$), 8.15-8.19 (m, 2H, Ar-$H_{(b,a)}$), 8.56 (s, 1H, CH-triazole), 8.63 (s, 1H, CH=N), 10.39 (s, 1H, NH, $D_2O$ exchangeable). |
| **16** | [$M^+$+2], 486 (1.99), [$M^+$+1], 485(4.30), [$M^+$], 484 (1.16). | 3243&3176 (2NH), 1706 (C=O), 1624 (C=N&C=C). | δ: 0.90, 1.01 (2s, 6H, $2CH_3$), 2.09 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.27 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.33 (d, 1H, $CH_{2(1)}$, *J* 16.80 Hz), 2.45-2.51 (m, 1H, $CH_{2(1)}$ with DMSO), 3.33 (s, 1H, NH with $H_2O$ of DMSO), 6.49 (s, 1H, CH-methine), 7.33 (t, 1H, Ar-$H_{(e)}$, *J* 7.65 Hz), 7.46 (t, 2H, Ar-$H_{(d)}$, *J* 7.65 Hz), 7.80 (d, 2H, Ar-$H_{(c)}$, *J* 7.65 Hz), 7.97 (d, 2H, Ar-$H_{(b)}$, *J* 8.40 Hz), 8.06 (s, 1H, CH-triazole), 8.22 (d, 2H, Ar-$H_{(a)}$, *J* 8.40 Hz), 8.62 (s, 1H, CH=N), 10.41 (s, 1H, NH, $D_2O$ exchangeable). |
| **17** | [$M^+$+2], 519 (2.88), [$M^+$+1], 518 (5.66), [$M^+$], 517 (3.16). | 3245&3174 (2NH), 1703 (C=O), 1618 (C=N&C=C). | δ: 0.91, 1.02 (2s, 6H, $2CH_3$), 2.08 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.27 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.32 (d, 1H, $CH_{2(1)}$, *J* 16.85 Hz), 2.46-2.51 (m, 1H, $CH_{2(1)}$ with DMSO), 3.32 (s, 1H, NH with $H_2O$ of DMSO), 6.40 (s, 1H, CH-methine), 7.35 (t, 1H, Ar-$H_{(e)}$, *J* 7.65 Hz), 7.48 (t, 2H, Ar-$H_{(d)}$, *J* 7.65 Hz), 7.58 (d, 2H, Ar-$H_{(c)}$, *J* 8.40 Hz), 7.68 (d, 2H, Ar-$H_{(b)}$, *J* 7.65 Hz), 7.82 (d, 2H, Ar-$H_{(a)}$, *J* 8.40 Hz), 8.05 (s, 1H, CH-triazole), 8.51 (s, 1H, CH=N), 10.31 (s, 1H, NH, $D_2O$ exchangeable). |
| **18** | [$M^+$+1], 507 (3.51), [$M^+$], 506 (18.86). | 3211(2NH), 1689 (C=O), 1654 (C=N), 1600 (C=C). | δ: 0.89, 1.03 (2s, 6H, $2CH_3$), 2.14 (d, 1H, $CH_{2(2)}$, *J* = 18 Hz), 2.29 (d, 1H, $CH_{2(2)}$, *J* = 18 Hz), 2.37 (d, 1H, $CH_{2(1)}$, *J* = 18 Hz), 2.85 (d, 1H, $CH_{2(1)}$), 4.67 (s, 1H, NH, $D_2O$ exchangeable), 5.83 (s, 1H, CH-methine), 7.34 (t, 1H, Ar-$H_{(f)}$, *J* 9.0 Hz), 7.41 (t, 1H, Ar-$H_{(e)}$, *J* 9.0 Hz), 7.49 (t, 2H, Ar-$H_{(d)}$, *J* 9.0 Hz), 7.54 (t, 2H, Ar-$H_{(c)}$, *J* 9.0 Hz), 7.89 (d, 2H, Ar-$H_{(b)}$, *J* 9.0 Hz), 7.97 (d, 2H, Ar-$H_{(a)}$, *J* 9.0 Hz), 8.01 (s, 1H, CH=N), 8.41 (s, 1H, CH-triazole$_{(4)}$), 8.49 (s, 1H, CH-triazole$_{(3)}$), 9.52 (s, 1H, NH, $D_2O$ exchangeable). |
| **19** | [$M^+$+1], 608 (55.56), [$M^+$], 607 (75.93). | 3239 (2NH), 1652 (C=O), 1600 (C=N&C=C). | …… |
| **20** | [$M^+$+1], 631 (61.26), [$M^+$] , 630 (81.08). | 3217 (2NH), 1688 (CO), 1654 (2CONH), 1621 (C=N&C=C). | δ: 0.89, 1.03 (2s, 6H, $2CH_3$), 2.12 (d, 1H, $CH_{2(2)}$, *J* = 18 Hz), 2.27 (d, 1H, $CH_{2(2)}$, *J* = 18 Hz), 2.35 (d, 1H, $CH_{2(1)}$, *J* = 15 Hz), 2.65 (s, 3H, $CH_3$-furan), 2.83 (d, 1H, $CH_{2(1)}$, *J* = 18 Hz), 4.67 (s, 1H, $NH_{(6)}$, $D_2O$ exchangeable), 5.81 (s, 1H, CH-methine), 6.91 (d, 1H, Ar-H-isatin$_{(g)}$, *J* 6.0 Hz), 7.06 (t, 1H, Ar-H-isatin$_{(f)}$, *J* 9.0 Hz), 7.20 (bs, 1H, CH-furan), 7.34 (t, 2H, Ar-H-isatin$_{(e)}$ and Ar-H-triazole$_{(c)}$), 7.50 (t, 2H, Ar-H-triazole$_{(b)}$, *J* 6.0 Hz), 7.56 (d, 1H, Ar-H-isatin$_{(d)}$, *J* 6.0 Hz), 7.89 (d, 2H, Ar-H-triazole$_{(a)}$, *J* 9.0 Hz), 7.92 (s, 1H, CH=N), 8.28 (s, 1H, CH-triazole), 9.48 (s, 1H, $NH_{(5)}$, $D_2O$ exchangeable), 11.25 (bs, 1H, $NH_{(4)}$, $D_2O$ exchangeable), 13.35 (bs, 1H, $NH_{(3)}$, $D_2O$ exchangeable). |
| **21** | [$M^+$+1], 376 (2.0), [$M^+$], 375 (1.2). | 3244 (NH), 1701 (C=O), 1625 (C=N&C=C). | δ: 0.96, 1.02 (2s, 6H, $2CH_3$-quinazolinone), 1.81 (s, 3H, $CH_3$-triazole), 1.99 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.24 (d, 1H, $CH_{2(2)}$, *J* 16.06 Hz), 2.26 (d, 1H, $CH_{2(1)}$, *J* 16.06 Hz), 2.46-2.51 (m, 1H, $CH_{2(1)}$ with DMSO), 5.49 (s, 1H, CH-methine), 7.37 (t, 1H, Ar-$H_{(c)}$, *J* 7.65 Hz), 7.52 (t, 2H, Ar-$H_{(b)}$, *J* 7.65 Hz), 7.90 (d, 2H, Ar-$H_{(a)}$, *J* 7.65 Hz), 7.95 (s, 1H, CH-triazole), 9.98 (s, 1H, NH, $D_2O$ exchangeable). |

**Table no 2.** Physical constants of compounds **1-21**.

| Compound No. | Yield (%) | M.p. (°C) | Mol. Form. (Mol. Wt.) | $R_f$ | Microanalysis (expected/found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **1** | 95 % | 256-257 | $C_{16}H_{17}ClN_2OS$ 320.84 | 0.36(H: EA; 2:1; V/V) | 59.90 60.00 | 5.34 5.28 | 8.73 8.69 |
| **2** | 97 % | 224-225 | $C_{16}H_{17}N_3O_3S$ 331.39 | 0.44(H: EA; 2:1; V/V) | 57.99 58.07 | 5.17 5.11 | 12.68 12.69 |
| **3** | 93 % | 233-234 | $C_{16}H_{17}N_3O_3S$ 331.39 | 0.36(H: EA; 2:1; V/V) | 57.99 57.90 | 5.17 5.15 | 12.68 12.71 |
| **4** | 98 % | 230-231 | $C_{16}H_{17}BrN_2OS$ 365.29 | 0.40(H: EA; 2:1; V/V) | 52.61 52.55 | 4.69 4.60 | 7.67 7.72 |
| **5** | 94 % | 233-234 | $C_{18}H_{19}N_5OS$ 353.44 | 0.32(H: EA; 2:1; V/V) | 61.17 61.20 | 5.42 5.48 | 19.81 19.79 |
| **6** | 94 % | 246-247 | $C_{25}H_{22}N_6OS$ 454.55 | 0.31(H: EA; 2:1; V/V) | 66.06 66.00 | 4.88 4.91 | 18.49 18.52 |
| **7** | 98 % | Yellow syrup | $C_{22}H_{25}N_5O_3S$ 439.53 | 0.41(H: EA; 2:1; V/V) | 60.12 60.09 | 5.73 5.77 | 15.93 15.95 |
| **8** | 65 % | >330 | $C_{16}H_{19}N_5O_3$ 329.35 | 0.45(C:M; 10:1; V/V) | 58.35 58.40 | 5.81 5.77 | 21.26 21.30 |
| **9** | 97 % | 265-266 | $C_{16}H_{19}BrN_4O$ 363.25 | 0.78(C:M; 20:1; V/V) | 52.90 52.87 | 5.27 5.17 | 15.42 15.40 |
| **10** | 98 % | 231-232 | $C_{18}H_{21}N_7O$ 351.41 | 0.53(C:M; 15:1; V/V) | 61.52 61.58 | 6.02 6.00 | 27.90 27.85 |
| **11** | 98 % | 240-241 | $C_{24}H_{25}N_5O_4$ 447.19 | 0.22 (EA: H; 3:1; V/V) | 64.42 64.37 | 5.63 5.60 | 15.65 15.55 |
| **12** | 98 % | 249-250 | $C_{25}H_{25}N_5O_3$ 443.2 | 0.63 (EA: H; 3:1; V/V) | 67.70 67.75 | 5.68 5.59 | 15.79 15.73 |
| **13** | 82 % | 239-240 | $C_{25}H_{24}N_8O_3$ 484.51 | 0.52(C:M; 10:1; V/V) | 61.97 62.00 | 4.99 5.05 | 23.13 23.08 |
| **14** | 89 % | 240-241 | $C_{25}H_{24}ClN_7O$ 473.96 | 0.57(H: EA; 2:1; V/V) | 63.35 63.28 | 5.10 5.00 | 20.69 20.72 |
| **15** | 99 % | 270-271 | $C_{25}H_{24}N_8O_3$ 484.51 | 0.52(H: EA; 2:1; V/V) | 61.97 62.00 | 4.99 4.92 | 23.13 23.06 |
| **16** | 94 % | 293-294 | $C_{25}H_{24}N_8O_3$ 484.51 | 0.57(H: EA; 2:1; V/V) | 61.97 62.03 | 4.99 5.04 | 23.13 23.23 |
| **17** | 95 % | 267-268 | $C_{25}H_{24}BrN_7O$ 518.41 | 0.59(EA: H; 2:1; V/V) | 57.92 57.90 | 4.67 4.69 | 18.91 18.95 |
| **18** | 69 % | 213-214 | $C_{27}H_{26}N_{10}O$ 506.56 | 0.75(C: M; 20:1; V/V) | 64.02 64.07 | 5.17 5.23 | 27.65 27.69 |
| **19** | 98 % | 257-258 | $C_{34}H_{29}N_{11}O$ 607.67 | 0.5(C: M; 15:1; V/V) | 67.20 67.26 | 4.81 4.73 | 25.35 25.30 |
| **20** | 85 % | 224-225 | $C_{33}H_{30}N_{10}O_4$ 630.66 | 0.69(C:M; 10:1; V/V) | 62.85 62.81 | 4.79 4.70 | 22.21 22.30 |
| **21** | 87 % | 161-162 | $C_{20}H_{21}N_7O$ 375.43 | 0.56(C:M; 15:1; V/V) | 63.98 64.00 | 5.64 5.67 | 26.12 26.16 |

**Table no 3.** $^{13}$C NMR spectral data of 2-Hydrazinyl-*N*-[(4-nitrophenyl-1-yl)methylene]-3,4,7,8-tetrahydro-7,7-dimethyl-4-(2-phenyl-2*H*-1,2,3-triazol-4-yl)quinazolin-5(6*H*)-one **16**.



| Compound no. | $^{13}$C NMR (DMSO-$d_6$, δ, ppm) |
|---|---|
| **16** | δ: 26.88, 29.32 (2 $CH_3$), 33.20, 39.51, 48.91, 49.91 (4$sp^3$ $carbons_{(c)}$), 107.31, 118.68, 124.53, 128.41, 128.63, 130.27, 135.55, 139.35, 141.37, 142.66 (10 lines for 14 $sp^2$ $carbons_{(b)}$), 148.12, 148.27, 149.28 (3 $C=N_{(a)}$), 152.28 (CH=N), 193.25 (C=O). |

Tables no 4-9 and Figures no 1-5 show absorbance and free radical scavenging activities of synthesized compounds **1-6**, **8-11**, **14-20** and **21** compared with standard vitamin E.

**Table no 4.** Absorbance and free radical scavenging activities of Vitamine E, compounds **1-3.**

| Conc. (mg/ mL) | Vitamin E | | Compound no. 1 | | Compound no. 2 | | Compound no. 3 | |
|---|---|---|---|---|---|---|---|---|
| | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging |
| 0.150 | 0.756 | 21.25 | 0.651 | 32.18 | 0.465 | 51.56 | 0.615 | 35.93 |
| 0.300 | 0.712 | 25.83 | 0.634 | 33.95 | 0.439 | 54.27 | 0.420 | 56.25 |
| 0.450 | 0.684 | 28.75 | 0.616 | 35.83 | 0.422 | 56.04 | 0.465 | 51.56 |
| 0.600 | 0.615 | 35.93 | 0.593 | 38.22 | 0.375 | 60.93 | 0.439 | 54.27 |
| 0.750 | 0.420 | 56.25 | 0.580 | 39.58 | 0.317 | 66.97 | 0.422 | 56.04 |
| 0.900 | 0.202 | 78.95 | 0.565 | 41.14 | 0.266 | 72.29 | 0.375 | 60.93 |
| 1 | 0.037 | 96.14 | 0.499 | 48.02 | 0.235 | 75.52 | 0.317 | 66.97 |

**Table no 5.** Absorbance and free radical scavenging activities of compounds **4-6**, **8.**

| Conc. (mg/ mL) | Compound no. 4 | | Compound no. 5 | | Compound no. 6 | | Compound no. 8 | |
|---|---|---|---|---|---|---|---|---|
| | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging |
| 0.150 | 0.615 | 35.93 | 0.696 | 27.50 | 0.656 | 31.66 | 0.500 | 47.91 |
| 0.300 | 0.580 | 39.58 | 0.665 | 30.72 | 0.635 | 33.85 | 0.455 | 52.60 |
| 0.450 | 0.502 | 47.70 | 0.631 | 34.27 | 0.593 | 38.22 | 0.439 | 54.27 |
| 0.600 | 0.465 | 51.56 | 0.600 | 37.50 | 0.572 | 40.41 | 0.422 | 56.04 |
| 0.750 | 0.400 | 58.33 | 0.589 | 38.64 | 0.525 | 45.31 | 0.375 | 60.93 |
| 0.900 | 0.375 | 60.93 | 0.570 | 40.62 | 0.488 | 49.16 | 0.317 | 66.97 |
| 1 | 0.317 | 66.97 | 0.557 | 41.97 | 0.465 | 51.56 | 0.266 | 72.29 |

**Table no 6.** Absorbance and free radical scavenging activities of compounds **9-11** and **14.**

| Conc. (mg/ mL) | Compound no. 9 | | Compound no. 10 | | Compound no. 11 | | Compound no. 14 | |
|---|---|---|---|---|---|---|---|---|
| | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging |
| 0.150 | 0.776 | 19.16 | 0.465 | 51.56 | 0.700 | 27.08 | 0.523 | 54.00 |
| 0.300 | 0.722 | 24.79 | 0.439 | 54.27 | 0.656 | 31.66 | 0.405 | 57.81 |
| 0.450 | 0.684 | 28.75 | 0.422 | 56.04 | 0.617 | 35.72 | 0.400 | 58.33 |
| 0.600 | 0.635 | 33.85 | 0.375 | 60.93 | 0.589 | 38.64 | 0.380 | 60.41 |
| 0.750 | 0.572 | 40.41 | 0.317 | 66.97 | 0.565 | 41.14 | 0.325 | 66.14 |
| 0.900 | 0.525 | 45.31 | 0.296 | 69.16 | 0.499 | 48.02 | 0.275 | 71.35 |
| 1 | 0.488 | 49.16 | 0.237 | 75.31 | 0.455 | 52.60 | 0.201 | 79.06 |

**Table no 7.** Absorbance and free radical scavenging activities of compounds **15-18.**

| Conc. (mg/ mL) | Compound no. 15 | | Compound no. 16 | | Compound no. 17 | | Compound no. 18 | |
|---|---|---|---|---|---|---|---|---|
| | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging |
| 0.150 | 0.422 | 55.00 | 0.822 | 14.37 | 0.684 | 28.75 | 0.369 | 42.61 |
| 0.300 | 0.398 | 58.54 | 0.790 | 17.70 | 0.635 | 33.85 | 0.337 | 47.58 |
| 0.450 | 0.375 | 60.93 | 0.722 | 24.79 | 0.608 | 36.66 | 0.303 | 52.87 |
| 0.600 | 0.325 | 66.14 | 0.684 | 28.75 | 0.592 | 38.33 | 0.283 | 55.98 |
| 0.750 | 0.292 | 69.58 | 0.625 | 34.89 | 0.565 | 41.14 | 0.240 | 62.67 |
| 0.900 | 0.222 | 76.87 | 0.597 | 37.81 | 0.499 | 48.02 | 0.196 | 69.51 |
| 1 | 0.199 | 79.27 | 0.549 | 42.81 | 0.455 | 52.60 | 0.177 | 72.47 |

**Table no 8.** Absorbance and free radical scavenging activities of compounds **19-21.**

| Conc. (mg/ mL) | Compound no. 19 | | Compound no. 20 | | Compound no. 21 | |
|---|---|---|---|---|---|---|
| | absorbance | % scavenging | absorbance | % scavenging | absorbance | % scavenging |
| 0.150 | 0.485 | 24.57 | 0.615 | 35.93 | 0.465 | 51.56 |
| 0.300 | 0.451 | 29.86 | 0.585 | 39.06 | 0.439 | 54.27 |
| 0.450 | 0.420 | 34.68 | 0.500 | 47.91 | 0.422 | 56.04 |
| 0.600 | 0.399 | 37.94 | 0.465 | 51.56 | 0.375 | 60.93 |
| 0.750 | 0.369 | 42.61 | 0.439 | 54.27 | 0.317 | 66.97 |
| 0.900 | 0.337 | 47.58 | 0.422 | 56.04 | 0.266 | 72.29 |
| 1 | 0.312 | 51.47 | 0.375 | 60.93 | 0.137 | 75.01 |

**Table no 9.** $EC_{50}$ values of the prepared compounds **1-6**, **8-11** and **14-21.**

| Compound no. | $EC_{50}$ (mg) | Cpd no. | $EC_{50}$ (mg) |
|---|---|---|---|
| **Vitamine E** | 0.705 | **11** | 0.925 |
| **1** | > 1 | **14** | 0.035 |
| **2** | 0.220 | **15** | 0.017 |
| **3** | 0.525 | **16** | > 1 |
| **4** | 0.550 | **17** | 0.933 |
| **5** | > 1 | **18** | 0.380 |
| **6** | 0.952 | **19** | 0.943 |
| **8** | 0.275 | **20** | 0.612 |
| **9** | 1.025 | **21** | 0.150 |
| **10** | 0.140 | **…** | … |

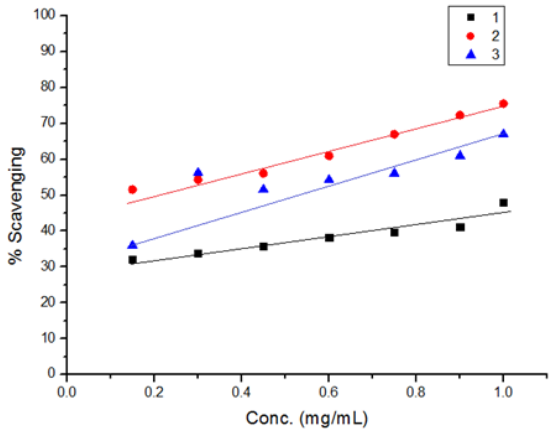



**Figure 1.** Free radical scavenging activity of compounds **1-3**

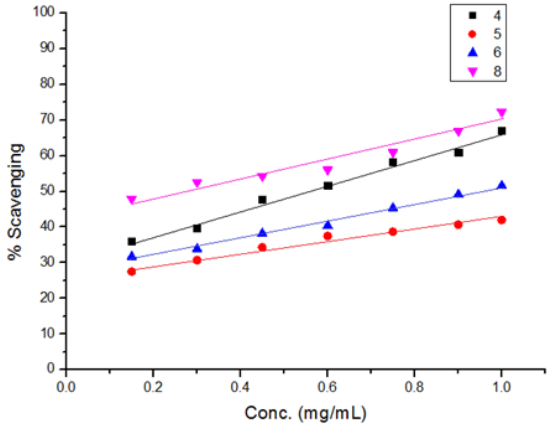



**Figure 2.** Free radical scavenging activity of compounds **4-6, 8**

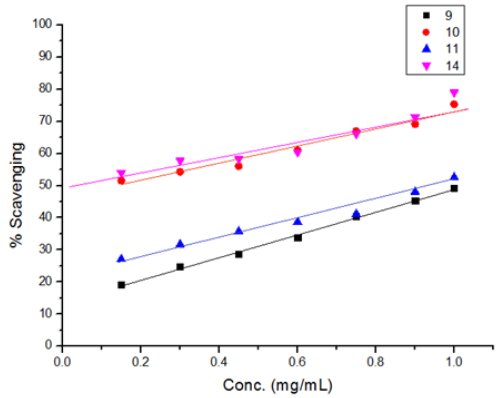



**Figure 3.** Free radical scavenging activity of compounds **9**-**11** and **14.**

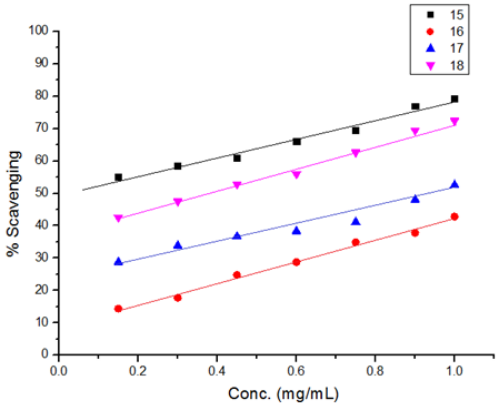



**Figure 4.** Free radical scavenging activity of compounds **15**-**18.**

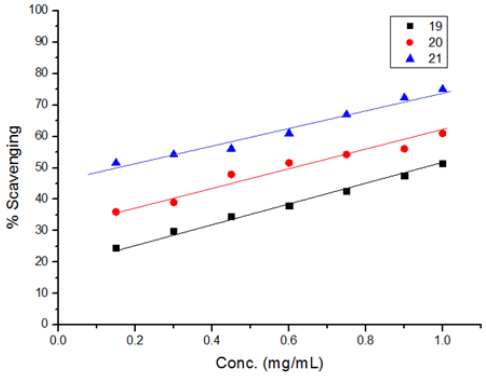



**Figure 5.** Free radical scavenging activity of compounds **19**-**21**.

***Antiproliferative activity screening (cytotoxicity against three cancer cell line):***

**HepG-2**: Human Hepatocellular Liver Carcinoma Cells, **HCT**: Human Colon Carcinoma Cells and **MCF-7**: Human Breast Adrenocarcinoma Cells.

Tables no 10-15 and Figures no 6-17 show cytotoxicity of the examined compounds **14**, **15**, **18** and **21** standards at different concentrations (50-1.56 µg/mL) against breast cancer (MCF-7), colon cancer (HCT) and hepatocellular (HepG-2) cell lines.

**Table no 10.** Effect standard compounds on cell viability using cytotoxic assay.

| **Conc. (µg/mL)** | Doxorubicin for HEPG-2 | Doxorubicin for HCT | **Vinblastine** for MCF-7 |
|---|---|---|---|
| | **Viability %** | **Viability %** | **Viability %** |
| 50.00 | 10.95 | 6.82 | 7.82 |
| 25.00 | 14.29 | 8.89 | 15.18 |
| 12.50 | 16.90 | 14.83 | 29.6 |
| 6.250 | 21.03 | 16.16 | 48.75 |
| 3.125 | 30.32 | 22.28 | 60.35 |
| 1.560 | 48.25 | 34.64 | 76.24 |
| 0.780 | 57.44 | 45.78 | …. |
| 0.390 | …. | 51.08 | …. |
| 0.000 | 100 | 100 | 100 |

**Table no 11.** Effect of different concentrations of compound **14** on cell viability using cytotoxic assay.

| **Conc. (µg/mL)** | **Viability % for HCT** | **Viability % for HEPG-2** | **Viability % for MCF-7** |
|---|---|---|---|
| 50.00 | 6.87 | 8.97 | 7.45 |
| 25.00 | 14.92 | 24.16 | 19.73 |
| 12.50 | 31.24 | 41.62 | 36.38 |
| 6.250 | 42.85 | 58.80 | 51.74 |
| 3.125 | 68.62 | 77.31 | 69.28 |
| 1.560 | 85.14 | 84.28 | 84.26 |
| 0.000 | 100.00 | 100.00 | 100.00 |

**Table no 12.** Effect of different concentrations of compound **15** on cell viability using cytotoxic assay.

| Conc. (µg/mL) | Viability % for HEPG-2 | Viability % for HCT | Viability % for MCF-7 |
|---|---|---|---|
| 50.00 | 9.74 | 9.78 | 8.28 |
| 25.00 | 29.42 | 20.64 | 27.43 |
| 12.50 | 48.68 | 28.42 | 43.72 |
| 6.250 | 64.31 | 36.58 | 59.20 |
| 3.125 | 79.12 | 58.93 | 70.91 |
| 1.560 | 89.53 | 76.35 | 83.49 |
| 0.000 | 100.00 | 100.00 | 100.00 |

**Table no 13.** Effect of different concentrations of compound **18** on cell viability using cytotoxic assay.

| Conc. (µg/mL) | Viability % for HEPG-2 | Viability % for HCT | Viability % for MCF-7 |
|---|---|---|---|
| 50.00 | 12.45 | 8.63 | 10.92 |
| 25.00 | 23.58 | 19.58 | 21.78 |
| 12.50 | 36.29 | 28.36 | 34.53 |
| 6.250 | 67.34 | 41.74 | 53.49 |
| 3.125 | 84.23 | 69.82 | 64.72 |
| 1.560 | 95.42 | 88.49 | 81.86 |
| 0.000 | 100.00 | 100.00 | 100.00 |

**Table no 14.** Effect of different concentrations of compound **21** on cell viability using cytotoxic assay.

| Conc. (µg/mL) | Viability % for HEPG-2 | Viability % for HCT | Viability % for MCF-7 |
|---|---|---|---|
| 50.00 | 10.97 | 4.95 | 6.04 |
| 25.00 | 28.13 | 11.43 | 14.85 |
| 12.50 | 42.56 | 22.38 | 30.94 |
| 6.250 | 59.28 | 33.62 | 41.16 |
| 3.125 | 74.16 | 46.41 | 58.22 |
| 1.560 | 83.72 | 59.05 | 69.75 |
| 0.000 | 100.00 | 100.00 | 100.00 |

**Table no 15.** $IC_{50}$ values of tested compounds **14**, **15**, **18** and **21** compared with that of standard materials.

| Compound no. | HCT ($IC_{50}$, µg/mL) | HEPG-2 ($IC_{50}$, µg/mL) | MCF-7 ($IC_{50}$, µg/mL) |
|---|---|---|---|
| | *Standard* 0.469 | *Standard* 1.2 | *Standard* 6.1 |
| **14** | 5.4 | 9.5 | 7.0 |
| **15** | 4.4 | 12.0 | 10.0 |
| **18** | 5.3 | 9.7 | 7.4 |
| **21** | 2.7 | 9.7 | 4.6 |

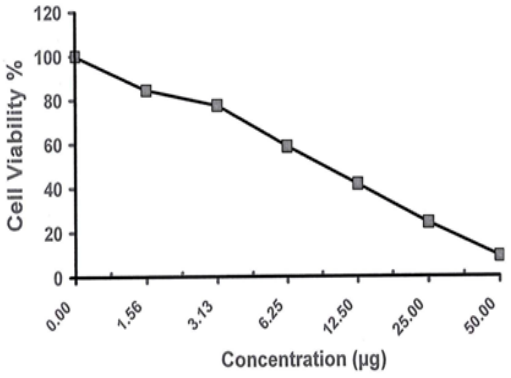



**Figure 6.** Viability activity against HepG-2 of compound **14**.

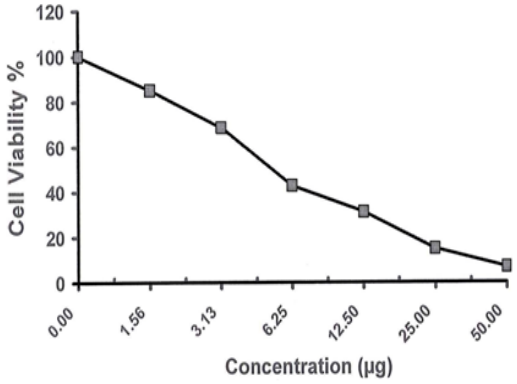



**Figure 7.** Viability activity against HCT-116 of compound **14.**

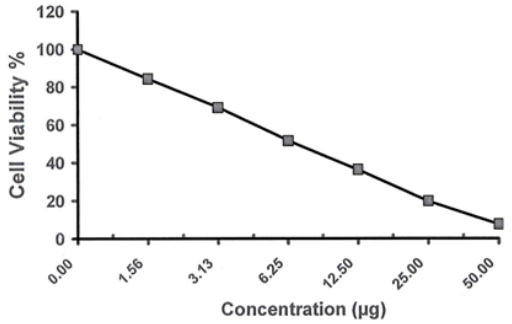



**Figure 8.** Viability activity against MCF-7 of compound **14.**

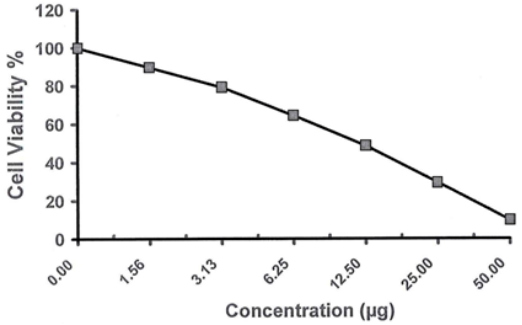



**Figure 9.** Viability activity against HepG-2 of compound **15.**

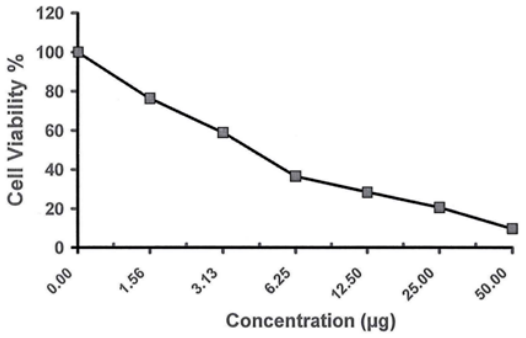



**Figure 10.** Viability activity against HCT-116 of compound **15.**

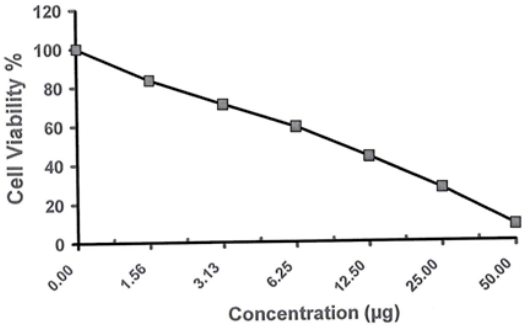



**Figure 11.** Viability activity against MCF-7 of compound **15.**

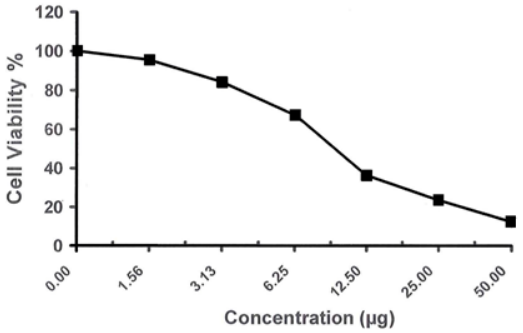



**Figure 12.** Viability activity against HepG-2 of compound **18.**

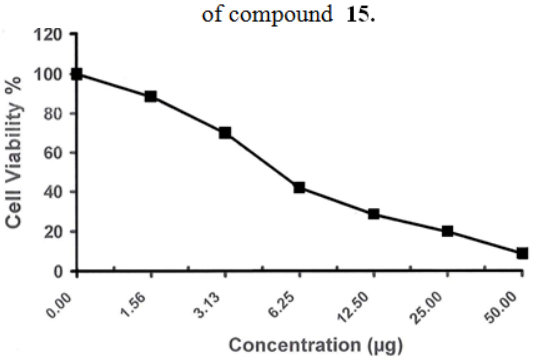



**Figure 13.** Viability activity against HCT-116 of compound **18.**

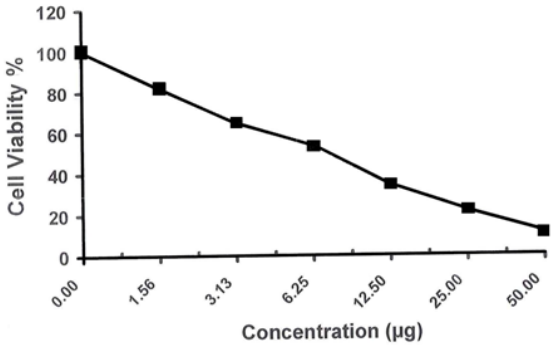



**Figure 14.** Viability activity against MCF-7 of compound **18.**

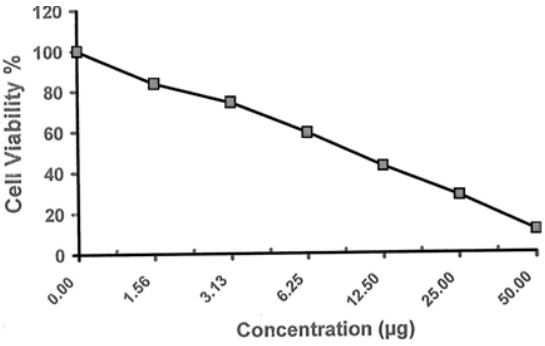



**Figure 15.** Viability activity against HepG-2 of compound **21.**

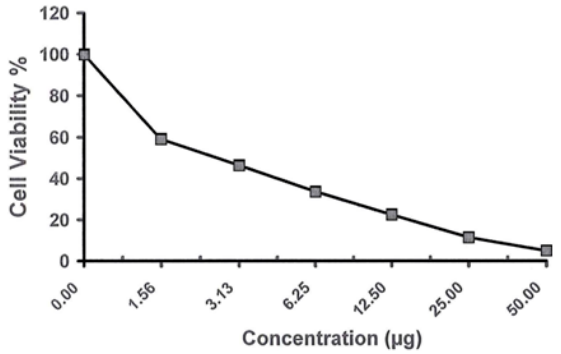



**Figure 16.** Viability activity against HCT-116 of compound **21.**

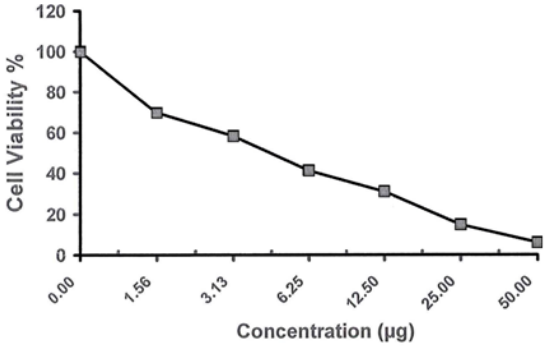



**Figure 17.** Viability activity against MCF-7 of compound **21.**

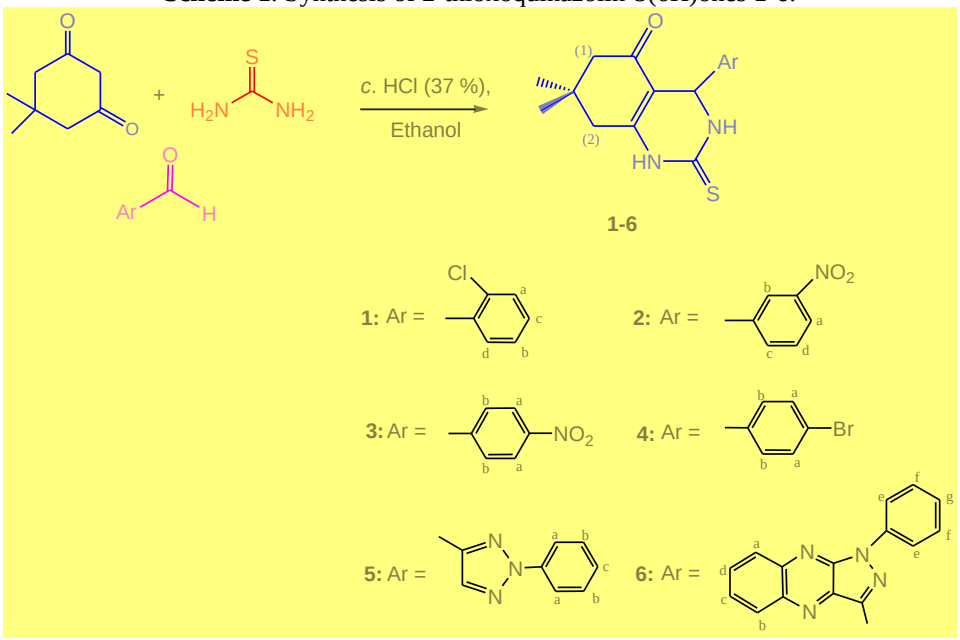
## IV. Discussion

Scheme no 1 showed that 2-Thioxoquinazolin-5(6*H*)ones **1-6** were synthesized in 93-98% yield via one-pot Biginelli reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone), thiourea and a number of aldehydes in absolute ethanol in presence of hydrochloric acid 37% as a catalyst. Tables no 1 and 2 showed infrared spectra of these quinazolinones, as intense peaks at γ (3245-3190), (1676-1668) and (1628-1615) $cm^{-1}$ for (2NH), (C=O) and (C=C&C=N), respectively. The $^1$H NMR (DMSO-$d_6$) spectrum of compound **5** as an example, displayed two singlets at δ 10.92 and 7.93 ppm for one NH proton, and CH-triazole, respectively. The aromatic protons showed as a doublet at δ 7.85 ($J$ = 7.65 Hz) ppm for Ar-$H_{(a)}$ and two triplets at δ 7.50 ($J$ = 7.65 Hz) and 7.36 ($J$ = 7.65 Hz) ppm corresponding to Ar-$H_{(b)}$ and Ar-$H_{(c)}$, respectively. Two singlets appeared at δ 5.68 and 3.33 ppm for CH-methine and the second NH proton [21], respectively. Four doublets appeared at δ 2.61, 2.39, 2.36 and 2.15 ppm with coupling constants $J$ =17.6, 17.6, 16.1 and 16.06 Hz due to the two methylene groups ($CH_{2(1)}$ and $CH_{2(2)}$), respectively. Two singlets at δ 1.03 and 1.00 ppm were assigned to the two methyl groups. As well as the mass spectra of compounds **2**, **3**, **5** and **6** showed their molecular ion peaks at m/z 331(5.3), 331(35.3), 353(23.6) and 454(2.7), respectively.

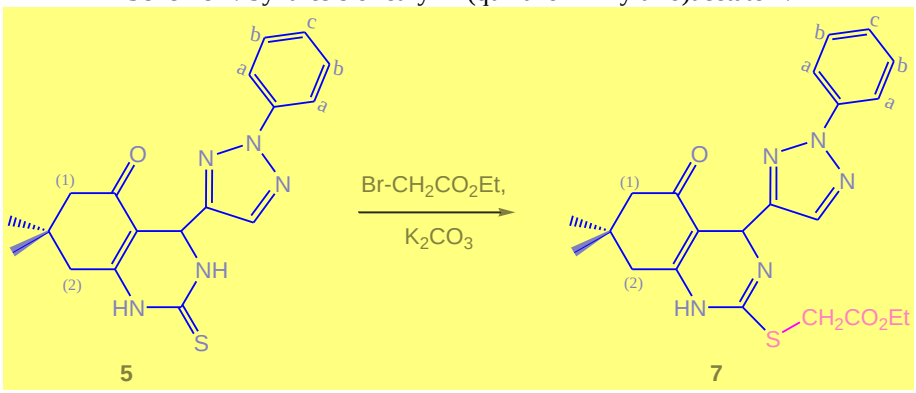
Scheme no 2 showed that treatment of 2-thioxoquinazolin-5(6*H*)-one **5** with ethyl bromoacetate, afforded ethyl 2-(quinazolin-2-ylthio)acetate **7** as confirmed from previously reported results on other systems [22]. Tables 1 and 2 showed infrared spectrum of this compound as ($CO_2$Et) and (C=O) at γ 1737 and 1717 $cm^{-1}$, respectively. $^1$HNMR ($CDCl_3$) spectrum revealed a multiplet at δ (4.20-4.17) ppm for methylene (ester) and another multiplet at δ (1.27-1.21) ppm due to five protons of (S-C$\underline{H}_2$) and (C$\underline{H}_3$-ester).

Scheme 3 showed that 2-thioxoquinazolin-5(6H)-ones **2**, **4** and **5** on reflux with hydrazine hydrate (99%) yielded the corresponding hydrazine derivatives **8-10** in 65-98% yield. Tables 1 and 2 showed infrared spectra of these compounds as (NH, $NH_2$), (C=O) and (C=N, C=C) at γ (333-320), (168-165) and (165-160) $cm^{-1}$, respectively, as well as, $^1$H NMR (DMSO-$d_6$) of compounds **8-10**, showed two singlets at δ (9.79-8.67) and (4.34-3.31) ppm corresponding to two NH protons, the aromatic protons at δ (7.88-6.36) ppm and $NH_2$ protons at δ (5.67-4.703) ppm. A singlet resonated at δ (5.50-5.13) due to methine proton. The methylene protons showed at δ (2.41-1.87) ppm, followed by two singlets at δ (1.00-0.82) ppm for the two methyl protons. The molecular ion recorded in the mass spectra for compounds **9** and **10** at m/z 365/363 (9.57/40.41) and 351 (8.4), respectively are also in agreement with their molecular weights.

**Scheme 1**. Synthesis of 2-thioxoquinazolin-5(6H)ones **1-6**.

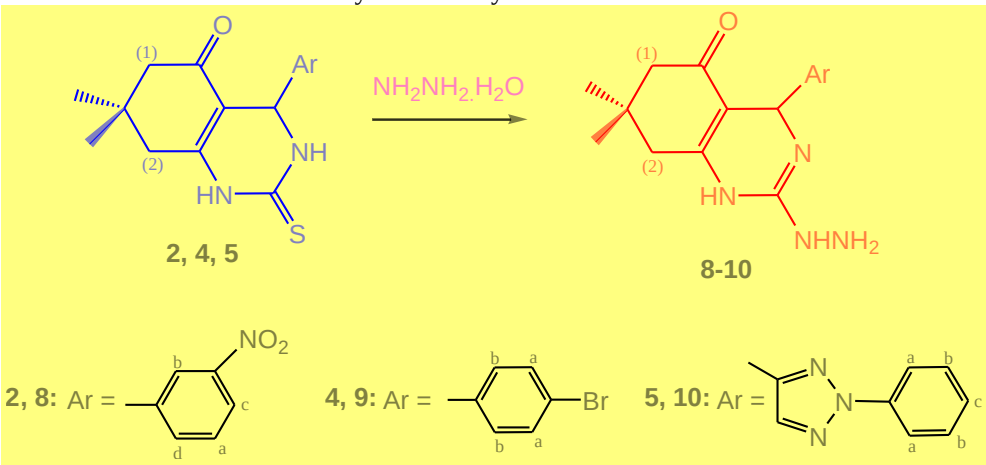



**Scheme 2**. Synthesis of ethyl 2-(quinazolin-2-ylthio)acetate **7**.



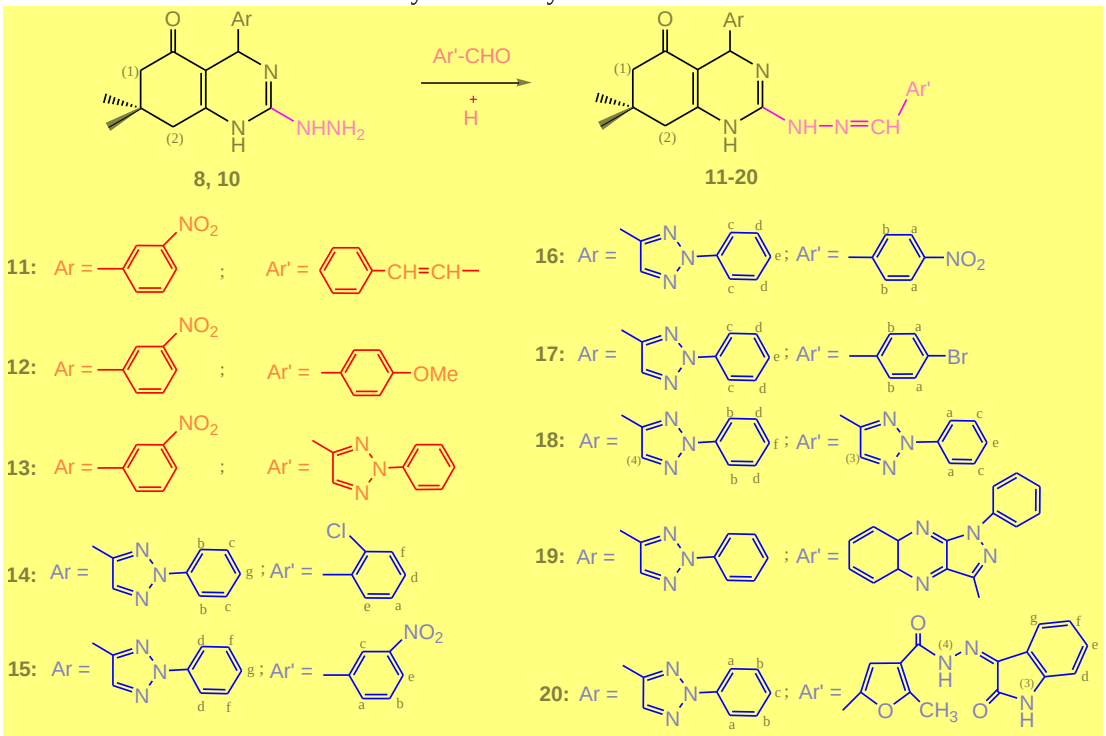

Scheme 4 showed that treatment of hydrazines **8** and **10** with a number of simple aromatic aldehydes as well as 5-formyl-2-methyl-3-(N-(2-oxoindolin-3-ylidene))carbohydra-zide [23] and 1-phenyl-1H-pyrazolo[4,3-b]-quino-xaline-3-carbaldehyde [24], resulted in the corresponding hydrazones **11-20** in yields of (69-99%). Tables no 1-3 showed infrared spectra of these compounds, as NHs, (C=O) and (C=N&C=C) at γ (3319-3174), (1708-1640) and (1655-1585) $cm^{-1}$, respectively. $^{1}H$ NMR (DMSO-$d_6$) spectrum of **16** as an example showed three singlets at δ 10.41, 3.33 and 8.62 ppm for two NH protons and azomethine proton (CH=N), respectively. The aromatic protons (9H) appeared as three doublets at δ 8.22 ($J$ = 8.40 Hz), 7.97 ($J$ = 8.40 Hz) and 7.80 ppm ($J$ = 7.65 Hz) for Ar-$H_{(a)}$, Ar-$H_{(b)}$ and Ar-$H_{(c)}$, respectively, two triplets at δ 7.46 ($J$ = 7.65 Hz) and 7.33 ppm ($J$ = 7.65 Hz) for Ar-$H_{(d)}$ and Ar-$H_{(e)}$, respectively, and a singlet at δ 8.06 ppm due to CH-triazole. A singlet appeared at δ 6.49 ppm due to CH-methine. A multiplet and three doublets at δ (2.51-2.45), 2.33 ($J$ = 16.80 Hz), 2.27 ($J$ = 16.06 Hz) and 2.09 ppm ($J$ = 16.06 Hz) for methylene protons (4H); $CH_{2(1)}$ and $CH_{2(2)}$, respectively. The two methyl groups appeared as two singlets at δ 1.01 and 0.90 ppm. The molecular ion recorded in the mass spectrum is also in agreement with the molecular weight of **16**. Furthermore, $^{13}C$ NMR (DMSO-$d_6$) revealed the signal corresponding to the CH=N at δ 152.28 ppm.

**Scheme 3.** Synthesis of hydrazine derivatives **8-10**.

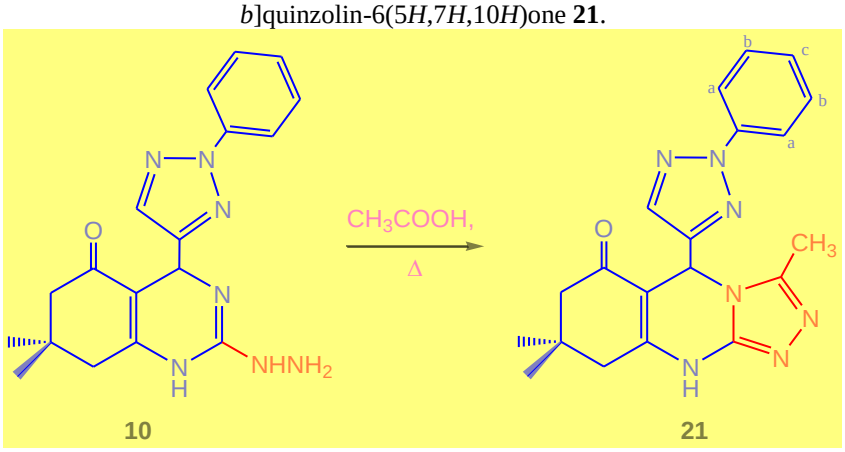



Scheme no 5 showed cyclization of hydrazine **10** with acetic acid to furnish the [1,2,4]triazolo[3,4-*b*]quinzolin-6-one **21**. Tables no 1 and 2 showed infrared bands as (NH), (C=O) and (C=N) at γ 3244, 1701 and 1625 $cm^{-1}$, respectively. $^{1}H$ NMR (DMSO-$d_6$) spectrum displayed two singlets at δ 9.98 and 7.95 ppm for NH and CH-triazole, respectively. The aromatic protons appeared as a doublet at δ 7.90 ppm ($J$ = 7.65 Hz) due to Ar-$H_{(a)}$ and two triplets at δ 7.52 ($J$ = 7.65 Hz) and 7.37 ppm ($J$ = 7.65 Hz) for Ar-$H_{(b)}$ and Ar-$H_{(c)}$, respectively. Methine proton resonated as a singlet at δ 5.49, followed by a multiplet and three doublets at δ (2.506-2.458), 2.26 ($J$ = 16.06 Hz), 2.24 ($J$ = 16.06 Hz) and 1.99 ppm ($J$ = 16.06 Hz) for the methylene protons (4H); $CH_{2(1)}$ and $CH_{2(2)}$, respectively. Three singlets at δ 1.81, 1.02 and 0.96 ppm displayed for the methyl protons (at triazole ring) and the two methyl groups (at quinazoline ring), respectively. In addition, the molecular ion peak recorded in the mass spectrum in accordance with its molecular weight.

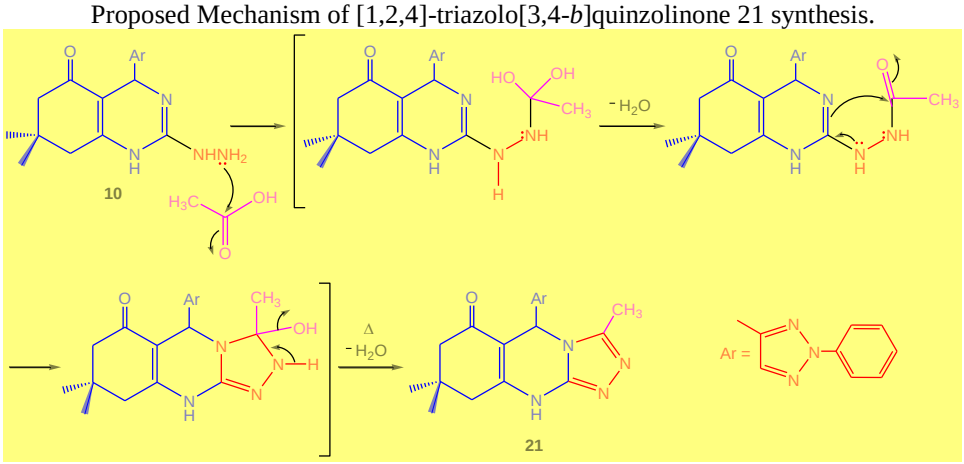
**Scheme 4**. Synthesis of hydrazone derivaties **11-20**.



**Scheme 5**. Synthesis of 8,9-dihydro-3,8,8-trimethyl-5-(2-phenyl-2*H*-1,2,3-triazol-4-yl)-[1,2,4]-triazolo[3,4-*b*]quinzolin-6(5*H*,7*H*,10*H*)one **21**.




Proposed Mechanism of [1,2,4]-triazolo[3,4-*b*]quinzolinone 21 synthesis.




**Bioactivity screening of synthesized quinazolinone derivatives:**

**Antioxdant activity screening (using DPPH):**

The DPPH (diphenyl picryl hydrazyl) assay method was based on the reduction of DPPH. The free radical DPPH with an odd electron gives a maximum absorption at 517 nm. When antioxidants react with DPPH, giving DPPD-H and as consequence the absorbance decreased due to decoulorization with respect to the number of electrons captured. $EC_{50}$ values for each examined compound as well as standard preparations were calculated according to the Shahwar et al method [28] that showed that $EC_{50}$ of compounds **10**, **14**, **15** and **21** had the highest values; 0.140, 0.035, 0.017 and 0.150 mg, respectively compared to $EC_{50}$ of vitamin E standard; 0.705 mg. As well as higher activities revealed in case of compounds **2**, **8** and **18** with $EC_{50}$; 0.220, 0.275 and 0.380 mg, respectively. Moderate activities showed for compounds **3, 4** and **20** with $EC_{50}$; 0.525, 0.550 and 0.612 mg, respectively, meanwhile lower activities observed in case of compounds **1**, **5**, **6**, **9**, **11**, **16**, **17** and **19** with $EC_{50}$ equal to > 1, > 1, 0.952, 1.025, 0.925, > 1, 0.933, 0.943 mg, respectively compared to the standard.

**Antiproliferative activity screening (cytotoxicity against three cancer cell line):**

The obtained data revealed that the maximum cell growth inhibitory effects on MCF-7 was obtained from compound **21** with $IC_{50}$ equal to 4.6 µg compared to Vinblastine standard with $IC_{50}$ 6.1 µg; whereas, compounds **14, 15 and 18** with $IC_{50}$ equal to 7,10, 7.4 µg, respectively showed moderate activity. In addition, the examined compounds showed moderate cytotoxicity against HCT cell line and lower activity against HepG-2 cell line.

## V. Conclusion

In conclusion, some quinazolinone derivatives have been prepared. Their physical and chemical properties were studied, indeed these compounds showed potential antioxidant activities. Four of these compounds showed excellent antiproliferative activities.

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