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Synthesis, Characterization and Anticancer Activity of Novel 1, 3, 4-Oxadiazolyl- and Pyrazolylquinoxalines

Omaima O. M. Farahat[1] and Kamal F. M. Atta[2]

Abstract

Synthesis of 2-[3-(5-hydroxymethyl)-1-phenyl-1H-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (3) was accomplished by the reaction of 3-(5-acetoxymethyl-1-phenyl-1H-pyrazol-3-yl)-1,2-dihydroquinoxalin-2-one (1) with ethyl bromoacetate followed by treatment with hydrazine hydrate under reflux. The key starting material 3 was used for the preparation of the target oxadiazolylpyrazolyl- and dipyrazolylquinoxalines. Thus, the reaction of 3 with ethyl formate or acetic acid afforded the acyl carbohydrazide derivatives 4 and 5 respectively. Moreover, benzoylation of 3 with benzoyl chloride in pyridine yielded the N-,O-dibenzoyl derivative 6 which, upon boiling with acetic anhydride or dimethyl formamide gave the O-benzoyl derivative 11. Furthermore, treatment of 3 with formic acid or acetic acid in the presence of phosphoryl chloride yielded the respective oxadiazolylpyrazolylquinoxalines 9 or 10. O-Acetylation of 4 and 9 or 3, 5 and 8 give the corresponding 1,3,4-oxadiazolylpyrazolyl quinoxalines 7 or 8. Additionally, synthesis of [3-(5-hydroxymethyl)-1-phenyl-1H-pyrazol-3-yl]-1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (12) was performed by refluxing the carbhydrazide 3 with carbon disulphide which upon acetylation afforded the O-,S-diacetyl derivative 13. On the other hand, the dipyrazolylquinoxalines 14 and 16 were obtained upon heterocyclization of the hydrazide 3 with acetylacetone or ethyl acetoacetate respectively. Acetylation of 14 and 16 gave the monoacetyl derivatives 15 and 17, respectively. The structural investigation of the new compounds is based on chemical and spectroscopic evidences. Anti-tumor evaluation of the synthesized compounds in vitro against three cell lines HCT-116 (colon carcinoma), HEPG2 (liver carcinoma) and MCF-7 (breast carcinoma) revealed that they possess high anti-tumor activities.

Keywords: Quinoxaline•oxadiazole•pyrazole• cytotoxicity• carcinoma• growth inhibition

[1] Chemistry Department, Faculty of Science, Alexandria University, Ibrahimia P.O. Box 426, Alexandria 21321, Egypt.
[2] Chemistry Department, Faculty of Science, Alexandria University, Ibrahimia P.O. Box 426, Alexandria 21321, Egypt. E-mail: prof.kf_atta@yahoo.com, Tel.: 002035917883, Fax: 002035932488.

1. Introduction

The mortality of patients suffering from various types of cancer has become an important issue worldwide. Resistance to chemotherapeutic agents used in the treatment of different cancers has become a common obstacle [1, 2]. Several important drugs including tamoxifen (TAM), 5-flurouracil (5FU), adriamycin (ADR) and vincristine (VCR) with different structures and mechanisms of anti-tumor treatment fail to alleviate such problem. Due to the several side effects, drug resistance, and failure of anti-tumor drugs to exert their effects in certain cases of cancers [3-5], searching for new chemotherapeutic agents whether of synthetic or natural origins is one of the hot topics. 1,3,4-Oxadiazole derivatives have attracted significant attention in the field of drug discovery due to the wide array of pharmacological activities they possess, which includes anti-bacterial anti-fungal, analgesic, anti-inflammatory, anti-hypertension, muscle relaxing and anticancer activities [6-16]. Additionally, pyrazole scaffolds represent a common in target pharmaceutical researches due to wide range of activities; the most important of which are anti-inflammatory [17, 18], anti-bacterial, anti-fungal [19, 20], hypoglycemic [21, 22], anti-hyperlipidemic [23], cyclooxigenase-2 inhibition [24], p38 MAP kinase [25], CDK2/Cyclin A [26, 27] and anti-angiogenic [28]. Heterocyclic rings particularly, pyrazoles, represent an advantageous choice for the synthesis of pharmaceutical compounds with different activities and good safety profiles [29]. Different pyrazole derivatives have also been tested for their anti-proliferative activities in vitro and antitumor activity in vivo, often resulting in promising lead compounds [30-36]. The above mentioned biological activities together with our interest in the synthesis of biologically active compounds [37-39] gave in the stimulus to synthesize several new 1,3,4-oxadiazolylpyrazolyl- and dipyrazolylquinoxaline derivatives and studying their anticancer effect

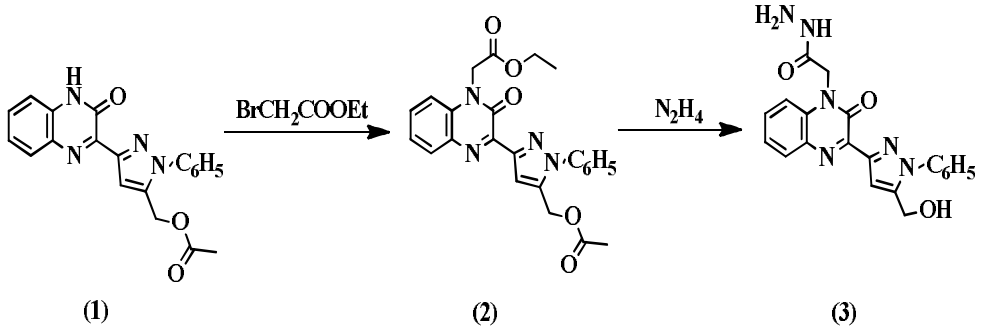
2. Results and Discussions

2.1. Chemistry

The starting compound for the synthesis of the title compounds, namely 3-(5-acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1,2-dihydroquinoxalin-2-one (**1**) was obtained as previously described [37, 39] from L-ascorbic acid.

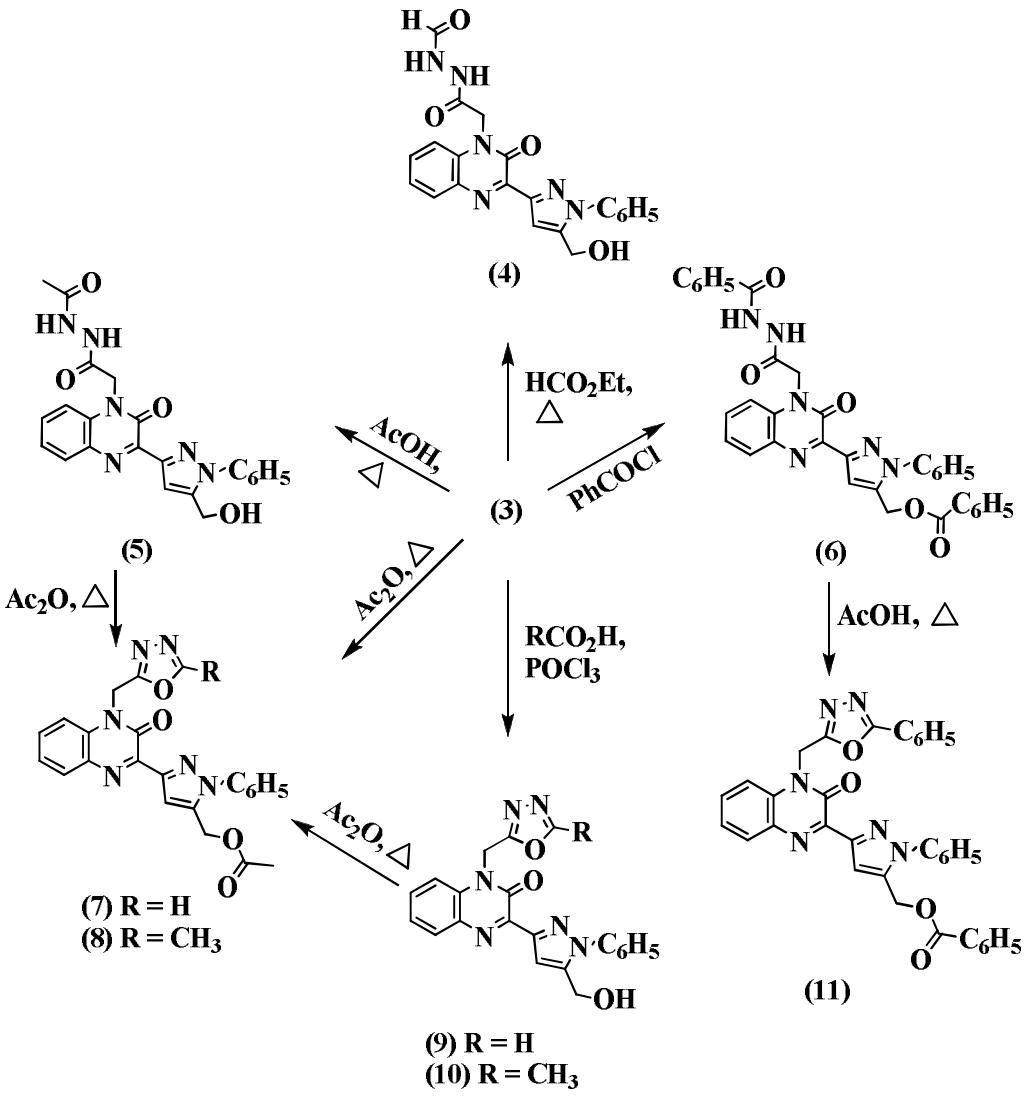
Stirring **1** with ethyl bromoacetate in the presence of anhydrous potassium carbonate afforded 3-(5-acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-ethoxycarbonyl methylquinoxalin-2-one (**2**) in 92% yield (Scheme 1). The structure of **2** was deduced from its spectral analysis. Its IR spectrum **2** showed an ester absorption band at 1746 cm^{-1}. It's ^1H NMR spectrum revealed the absence of NH signal and the presence of the ethyl ester group as a triplet at δ_H 1.26 ppm (CH_3) and a quartet at δ_H 4.21ppm (CH_2), in addition to a singlet at δ_H 3.31ppm (NCH_2), while it's MS exhibited a molecular ion peak at m/z 446.

Heating a methanolic solution of **2** with hydrazine hydrate under reflux yielded the key compound 2-[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**3**) which showed the absence of ester IR absorption band and the presence of amide absorption band at 1656 cm^{-1}. It's ^1H NMR spectrum showed the disappearance of the ethyl ester group of the precursor and the presence of an amino group as two singlets at δ_H 2.73, 2.89 ppm (exchangeable) in addition to a singlet at δ_H 9.44 ppm (exchangeable, NH). The MS spectrum showed the molecular ion peak at m/z 390.



Scheme 1.Formation of 2-[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide

Heating **3** with ethyl formate afforded N'-formyl-2-[3-(5-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**4**) (Scheme 2). Its ^1H NMR spectrum showed a new characteristic singlet at δ_H 8.82 ppm corresponding to the formyl proton in addition to the singlet at δ_H 9.43 ppm for the exchangeable two NH protons.



Scheme 2. Synthesis of 1,3,4-Oxadiazolylpyrazolyl Quinoxalines

On the otherhand, heating **3** with acetic acid under reflux gave the corresponding N'-acetyl-2-[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**5**) which showed two amide absorption bands at 1739 and 1662 cm^{-1}. The ^1H NMR spectrum of **5** revealed a three-proton singlet at δ_H 2.01 corresponding to the acetyl group in addition to two one-proton singlets at δ_H 9.90, 10.25 ppm (exchangeable, 2 NH). The MS spectrum of **5** confirmed the assigned structure.

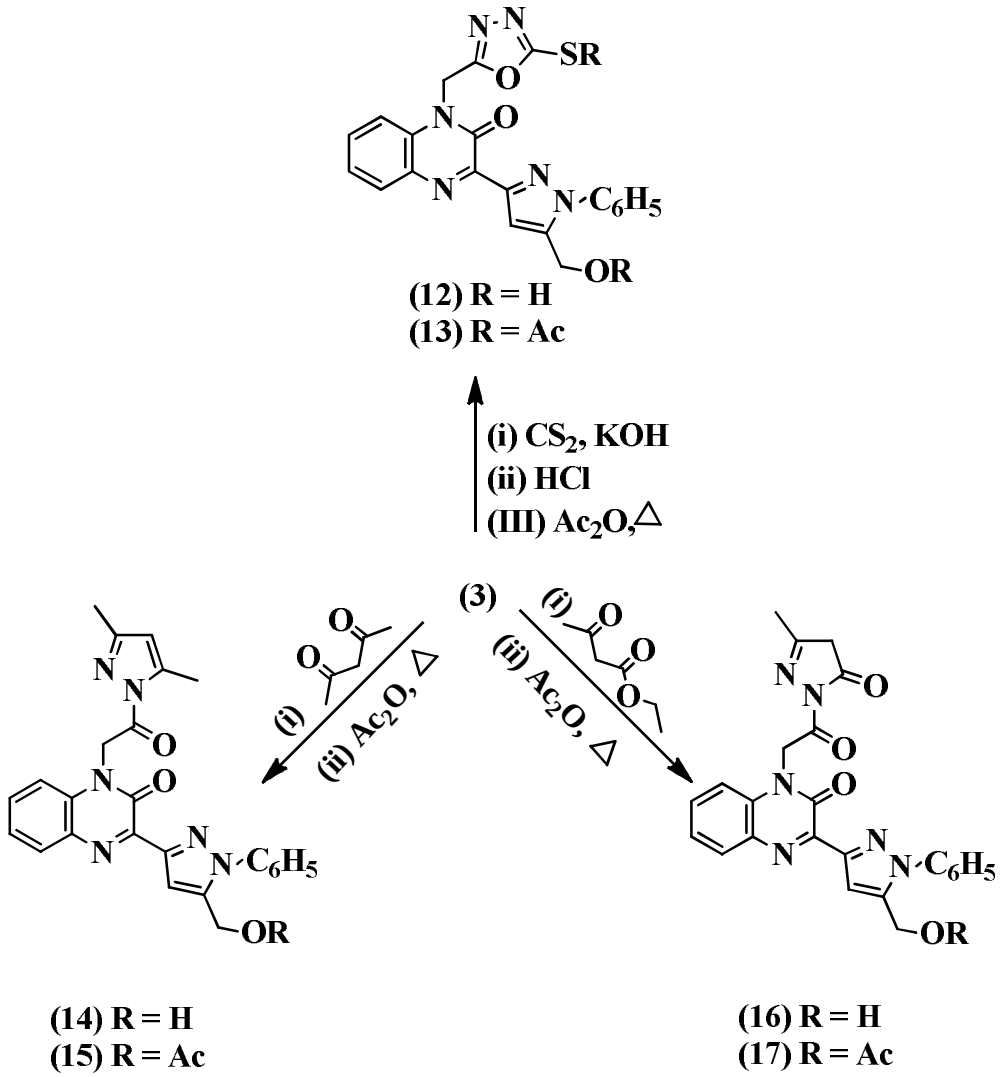
Dehydrative cyclisation of (**4**) and (**5**) by boiling acetic anhydride gave 3-(5-acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(1,3,4-Oxadiazol-2-yl)methyl]quinoxalin-2-one (**7**) and 3-(5-acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]quin-oxalin-2-one (**8**), respectively. Their formation can be explained to be a consequence of dehydrative cyclisation of the acylhydrazide residue to form 1,3,4-oxadiazole ring followed by acetylation of the hydroxylmethyl group. The IR spectra of **7** and **8** showed the presence of a new ester absorption band at 1745 and 1739 cm^{-1}, respectively. Furthermore, the ^1H NMR spectra of **7** and **8** revealed the absence of the two NH singlets of their precursors (**4** and **5**) and the presence of the three-proton singlets at δ_H 2.49 and 2.44 ppm, respectively corresponding to the acetyl protons, in addition to the one-proton singlet at δ_H 7.93 ppm (oxadiazole-H) and the three-proton singlet at δ_H 2.37 ppm (oxadiazole-CH_3). The MS spectrum of **8** exhibited the molecular ion peak at m/z 456.

Ring closure of **3** with phosphoryl chloride in the presence of formic or glacial acetic acid afforded the corresponding 3-(5-hydroxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (**9**) and 3-(5-hydroxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (**10**). Structures **9** and **10** were confirmed by their spectral data; their ^1H NMR spectra showed the absence of the three singlets for the three exchangeable NH protons of their precursor (**3**) but showed the presence of the oxadiazole-H as singlet at δ_H 7.94 ppm for **9**, whereas **10** showed the oxadiazole-CH_3 as singlet three-proton at δ_H 2.50 ppm. The structures of and **9** and **10** were also, confirmed by their MS. Acetylation of **9** and **10** with acetic anhydride under reflux gave the two O-acetyl derivatives **7** and **8,** respectively. In addition, treatment of **3** with benzoyl chloride in pyridine at room temperature afforded **11**. The IR spectrum of **11** showed an ester carbonyl absorption band at 1717 cm^{-1} and an amide absorption at 1656 cm^{-1}. The two NH protons appeared in the ^1H NMR spectrum as two exchangeable singlets at δ_H 10.47 ppm. Furthermore, its MS showed the molecular ion peak. Compound **6** underwent dehydrative cyclization upon treatment with boiling acetic anhydride to give a product identical to **11**.

The synthesis of 3-(5-hydroxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (**12**) was achieved by refluxing hydrazide**3** with carbon disulfide in the presence of methanolic potassium hydroxide (Scheme 3).

The ^{1}H NMR spectrum of **12** showed an exchangeable SH singlet at δ_H 14.55 ppm. In addition, its MS showed the molecular ion peak at m/z 432. Acetylation of **12** withacetic anhydride yielded **13**. Its IR spectrum showed an ester absorption at 1745 cm^{-1}, in addition to an amide absorption at 1656 cm^{-1}. Its ^{1}H NMR spectrum showed two singlets three-proton at δ_H 2.01 and 2.49 ppm due to $OCOCH_3$ and $SCOCH_3$ groups. The MS and elemental analysis confirmed the presence of the two acetyl groups.

The dipyrazolylquinoxalines**14** and **15** were obtained by heterocyclization of hydrazide**3** with 1,3-dicarbonyl compounds. Thus, heating with acetylacetone afforded 1-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]-3-[5-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoxalin-2-one (**14**). The ^{1}H NMR data of **14** showed the protons of the two pyrazole rings as two one-proton singlets at δ_H 7.73 and 7.75 ppm and the two methyl groups as two three-proton singlets at δ_H2.30 and 2.46 ppm. The MS of **14** showed its molecular ion peak at m/z 454. Acetylation of **14** by boiling with acetic anhydride gave 1-[2-(3, 5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]-3-[5-(acetoxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoxalin-2-one (**15**). It showed an ester carbonyl absorption band at 1744 cm^{-1} and an amide absorption at 1656 cm^{-1}. The ^{1}H NMR spectrum of **15** revealed acetyl group protons as singlet at δ_H2.46 ppm and its MS showed the molecular ion peak.



Scheme 3. Formation of 1,3,4-Oxadiazolylpyrazolyl- and Dipyrazolyl Quinoxalines

Refluxing **3** with ethylacetoacetate in dimethylformamide afforded the expected 3-[5-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-1-[2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl]quinoxalin-2-one (**16**). It's ^{1}H NMR spectrum revealed an exchangeable, OH singlet at δ_H 5.51 ppm, in addition to two singlets characterizing three pyrazole-H at δ_H4.58(2H) and 7.72 ppm. Also, the assigned structure was confirmed from MS.

Acetylation of **16** by boiling acetic anhydride yielded 3-[5-(acetoxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-1-[2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl]quinoxalin-2-one (**17**). The structure of **17** was deduced from its spectral data. Thus, the IR showed the existence of a new absorption band at 1749 cm^{-1} characteristic for an ester group. Also, the ^1H NMR showed that the exchangeable, OH proton has disappeared and instead of it the protons of the acetyl group appeared as singlet at δ_H 2.50 ppm. Furthermore, the MS spectrum showed the molecular ion peak at m/z 498 agreeing with mono acetyl derivative.

2.2. Biological Screening: Anticancer Activity Tests

2.2.1. Materials and Methods

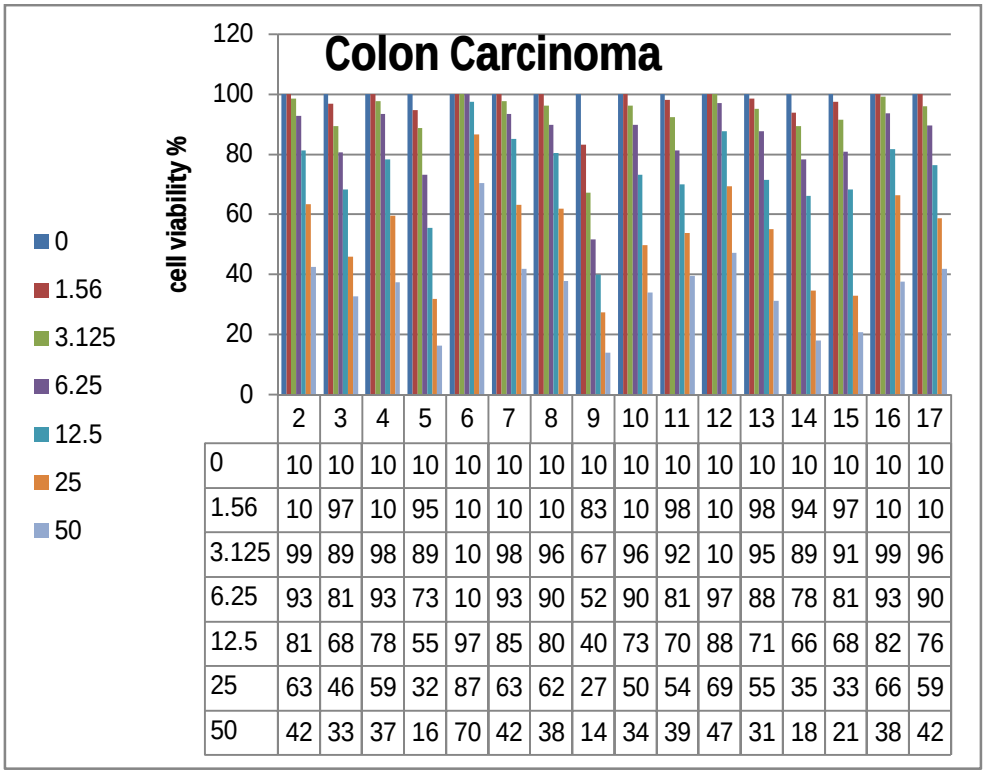
Potential cytotoxicity effect of the newly synthesized compounds in six concentrations, were evaluated in the Regional Center for Mycology & Biotechnology, Al-Azhar University, Cairo, Egypt by SRB assay [40]. Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of plate. Different concentrations of each compound under test (0, 1.56, 3.125, 6.25, 12.5, 25 and 50 μg/mL) were added to the cell monolayer triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 h at 37 ^0C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with sulfo-rhodamine B strain. Excess stain was washed with acetic acid and attached stain was recovered with tris EDTA buffer. Coor intensity was measured in an ELISA reader. Finally, the relation between surviving fraction and drug conc. is plotted to get the survival curve of each tumor cell line after the specified compound.

2.2.2. Anticancer Screening Studies

Sixteen of the newly synthesized compounds were screened for their anticancer activities. The three cell lines used in the present investigation are HCT-116 (colon carcinoma), HEPG2 (liver carcinoma) and MCF-7 (breast carcinoma).

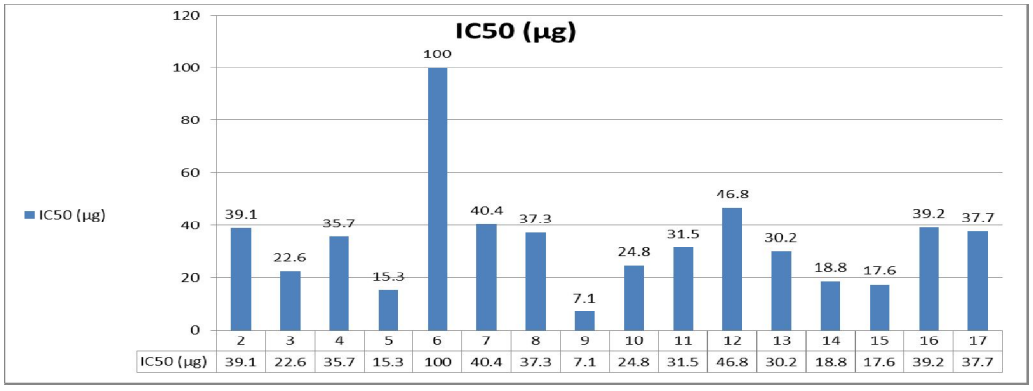
The analyses of concentration-response curves obtained from each cell line treated with our 16 compounds (Figures 1-6) together with the resulting calculation of mean

IC_{50}s (Figures 2, 4 and 6) displaced high or moderate anticancer activity in terms of growth inhibitory effect on cancer cell lines.



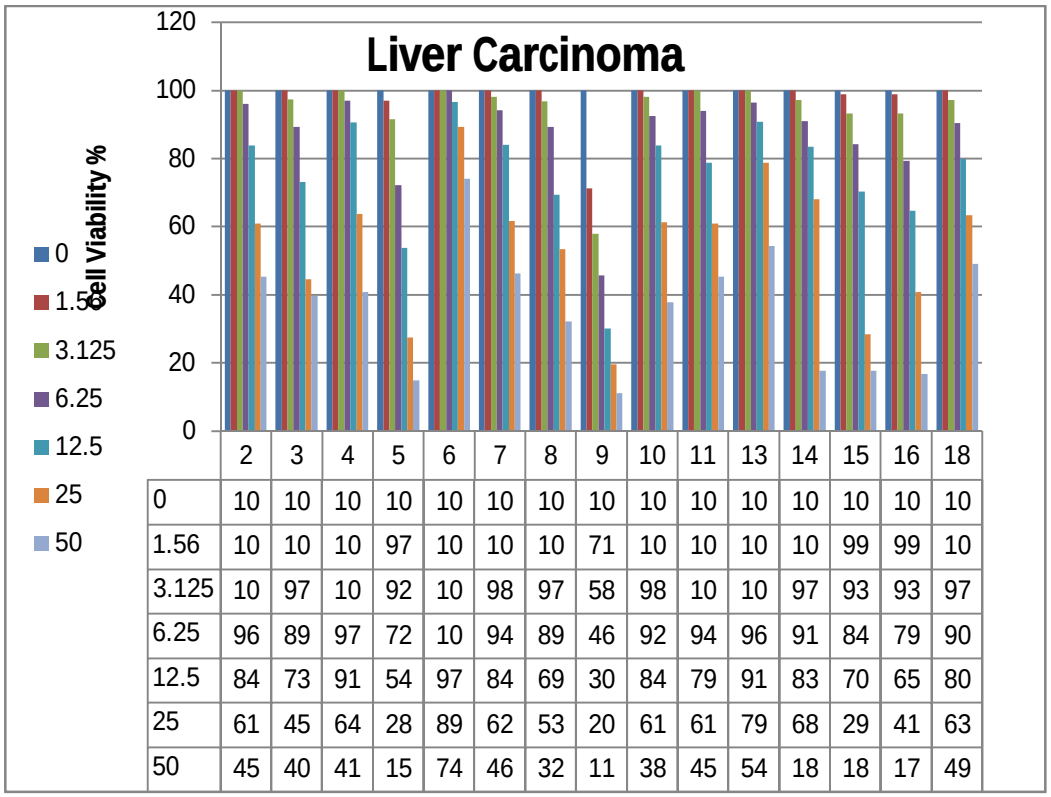
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
0	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.56	10	97	10	95	10	10	10	83	10	98	10	98	94	97	10	10
3.125	99	89	98	89	10	98	96	67	96	92	10	95	89	91	99	96
6.25	93	81	93	73	10	93	90	52	90	81	97	88	78	81	93	90
12.5	81	68	78	55	97	85	80	40	73	70	88	71	66	68	82	76
25	63	46	59	32	87	63	62	27	50	54	69	55	35	33	66	59
50	42	33	37	16	70	42	38	14	34	39	47	31	18	21	38	42

Fig. 1: **Evaluation of cytotoxicity against HCT-116 (colon carcinoma) cell line**



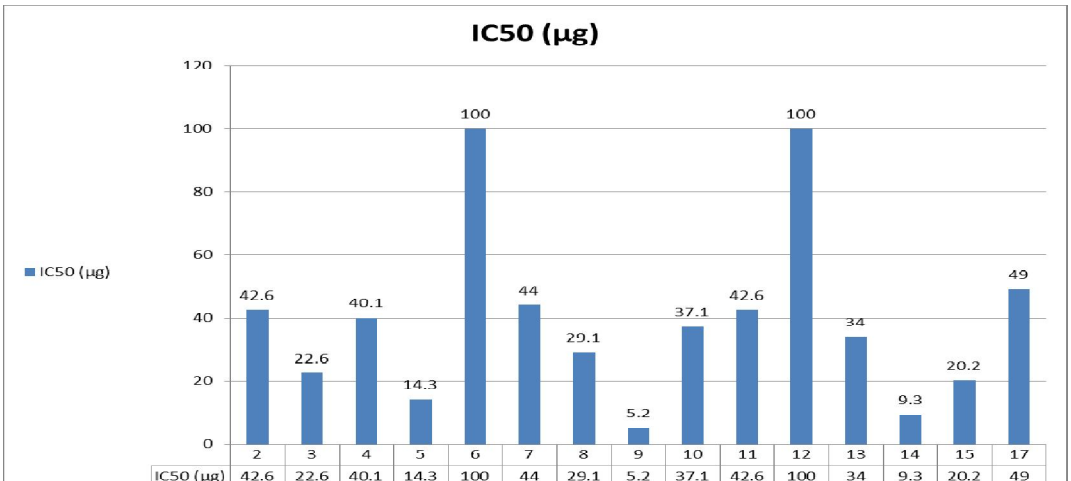
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
IC50 (µg)	39.1	22.6	35.7	15.3	100	40.4	37.3	7.1	24.8	31.5	46.8	30.2	18.8	17.6	39.2	37.7

Fig. 2: E**valuation of cytotoxicity against HCT-116 (colon carcinoma) cell line**



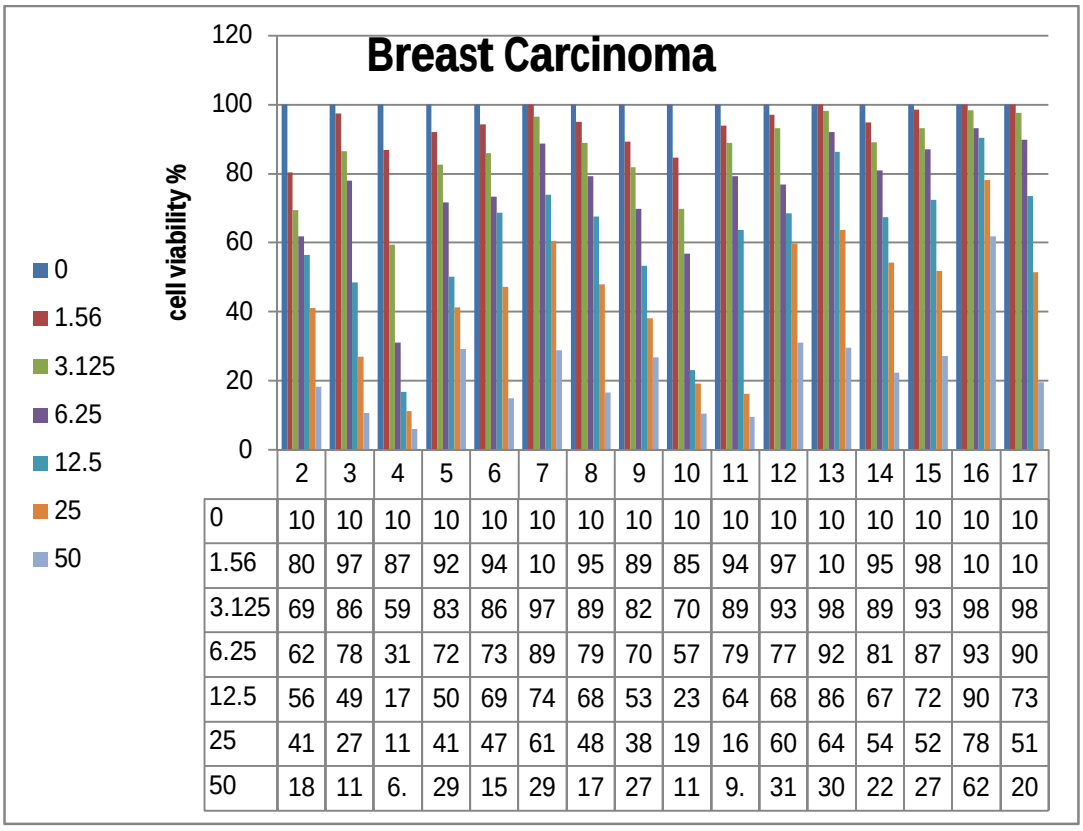
	2	3	4	5	6	7	8	9	10	11	13	14	15	16	18
0	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.56	10	10	10	97	10	10	10	71	10	10	10	10	99	99	10
3.125	10	97	10	92	10	98	97	58	98	10	10	97	93	93	97
6.25	96	89	97	72	10	94	89	46	92	94	96	91	84	79	90
12.5	84	73	91	54	97	84	69	30	84	79	91	83	70	65	80
25	61	45	64	28	89	62	53	20	61	61	79	68	29	41	63
50	45	40	41	15	74	46	32	11	38	45	54	18	18	17	49

Fig. 3: Evaluation of Cytotoxicity Against HEPG2 (Liver Carcinoma) Cell Line



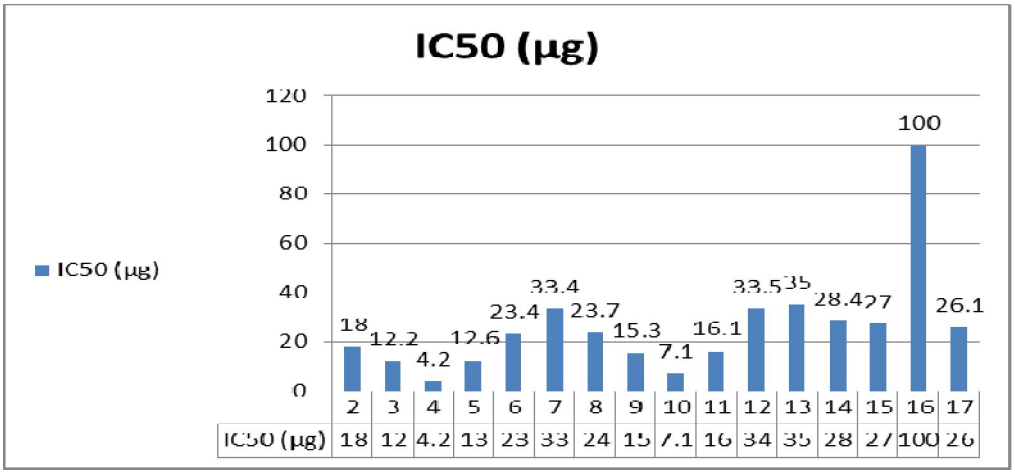
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17
IC50 (µg)	42.6	22.6	40.1	14.3	100	44	29.1	5.2	37.1	42.6	100	34	9.3	20.2	49

Fig. 4: Evaluation of cytotoxicity against HEPG2 (liver carcinoma) cell line



	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
0	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.56	80	97	87	92	94	10	95	89	85	94	97	10	95	98	10	10
3.125	69	86	59	83	86	97	89	82	70	89	93	98	89	93	98	98
6.25	62	78	31	72	73	89	79	70	57	79	77	92	81	87	93	90
12.5	56	49	17	50	69	74	68	53	23	64	68	86	67	72	90	73
25	41	27	11	41	47	61	48	38	19	16	60	64	54	52	78	51
50	18	11	6.	29	15	29	17	27	11	9.	31	30	22	27	62	20

Fig. 5: Evaluation of cytotoxicity against MCF-7 (Breast carcinoma) cell line



	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
IC50 (µg)	18	12	4.2	13	23	33	24	15	7.1	16	34	35	28	27	100	26

Fig. 6: Evaluation of Cytotoxicity Against MCF-7 (Breast Carcinoma) Cell Line

3. Experimental

3.1. General Methods

Melting points were determined on a Kofler Block and are uncorrected. Elemental analyses were carried out in the microanalytical laboratory of the faculty of science, Cairo University. The IR spectra of the prepared compounds were recorded on a Tensor 37 Bruker IR spectrophotometer as potassium bromide pellets. The ^{1}H NMR spectra were recorded on a Bruker AC (500 MHz) spectrometer at the faculty of science, Al-Azhar University; chemical shifts δ are reported in ppm and Hz relative to tetramethylsilane as internal standard. Mass spectra were recorded at 70 ev with GCMS-QP 1000 EX spectrometer at the faculty of science, Cairo University. Reactions were routinely followed by thin layer chromatography (TLC) using Merck Kiesel gel; 60-F254 precoated plastic plates. The spots were detected by UV exposition to light.

3-(5-acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-ethoxycarbonylmethylquinoxalin-2-one (2):

To a solution of 3-(5-acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1,2-dihydro-quinoxalin-2-one [37, 39] (**1**, 3.60 g, 0.01 mol) in dry dimethylformamide (20 mL), anhydrous potassium carbonate (2.76 g, 0.02 mol) and ethyl bromoacetate (5 mL) were added and the mixture was stirred at room temperature for 6 h. the solid mass poured onto crushed ice and the product was filtered, washed with water, dried and crystallized from dioxan to give the title compound as colorless needles (4.10 g, 92% yield); m.p. 190-192^{0}C; IR: 1746 (COO), 1646 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 3H, $CH_2\underline{CH_3}$), 2.49 (s, 3H, $COCH_3$), 3.31 (s, 2H, NCH_2), 4.21 (q, 2H, $\underline{CH_2}CH_3$), 5.19 (s, 2H, OCH_2), 7.65 (s, 1H, pyrazole-H) and 7.42-7.95 (m, 9H, Ar-H); MS (m/z, %): 446 (5, $M^{+\cdot}$), 417 (9, $M^{+\cdot}$-C_2H_5), 376 (7, $M^{+\cdot}$-$C_3H_2O_2$), 289 (7, $M^{+\cdot}$-$C_7H_9O_4$) and 258 (7, $M^{+\cdot}$-$C_9H_{12}O_5$); Anal. Calcd for $C_{24}H_{22}N_4O_5$ (446.46): C, 64.57; H, 4.97; N, 12.55%. Found: C, 64.30; H, 4.87; N, 12.65%.

2[3-(5-Hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (3):

A mixture of **2** (4.46 g, 0.01 mol) and hydrazine hydrate (99%, 10 mL) in methanol (50 mL) was heated under reflux for 15 h.

The solid mass formed after cooling the reaction mixture was filtered, washed with methanol, dried and crystallized from dimethylformamide to give the title compound as colorless needles (3.32 g, 85% yield); m.p. 300-302^{0}C; IR: 3432, 3351 (NH_2), 3296 (NH), 1656 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.73, 2.89 (2s, 2H, exchangeable, NH_2), 3.31 (s, 2H, NCH_2), 4.31 (s, 1H, exchangeable, OH), 4.97 (s, 2H, OCH_2), 7.75 (s, 1H, pyrazole-H), 7.36-7.92 (m, 9H, Ar-H) and 9.44 (s, 1H, exchangeable, NH); MS (m/z, %): 390 (2, $M^{+\cdot}$), 359 (3, $M^{+\cdot}$-N_2H_3), 331 (2, $M^{+\cdot}$-CH_3N_2O), 318 (3, $M^{+\cdot}$-$C_2H_4N_2O$) and 317 (3, $M^{+\cdot}$-$C_2H_5N_2O$); Anal. Calcd for $C_{20}H_{18}N_6O_3$ (390.40): C, 61.53; H, 4.65; N, 21.53%. Found: C, 61.59; H, 4.57; N, 21.66%.

N'-Formyl-2-[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (4)

A suspension of **3** (0.78g,0.002 mol) in ethyl formate was heated under reflux for 8 h. The product which separated upon cooling was filtered off and crystalized from aqueous dimethylformamide to give the title compound as colorless needles (0.71 g, 85% yield). m.p. 308-310 ^{0}C; IR: 3350 (OH), 3299 (NH), 1749 (CON) and 1659 cm^{-1} (CON); ^{1}H NMR ($CDCl_3$): δ = 3.30 (s, 2H, NCH_2), 4.57 (s, 1H, exchangeable OH), 5.56 (s, 2H, OCH_2), 7.36-7.92 (m, 9H, Ar-H), 7.75 (s, 1H, pyrazole-H), 8.82 (s, 1H, CHO) and 9.43 (s, 2H, exchangeable 2NH); MS (m/z, %): 418 (31, $M^{+\cdot}$), 382 (30, $M^{+\cdot}$- $2H_2O$) and 276 (82, $M^{+\cdot}$-$C_4H_4N_3O_3$); Anal. Calcd for $C_{21}H_{18}N_6O_4$ (418.41): C, 60.28; H, 4.34; N, 20.09%. Found: C, 60.20; H, 4.63; N, 20.12%.

N'-Acetyl-2-[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (5)

A mixture of **3(**0.78g,0.002 mol) and glacial acetic acid (10 ml) was heated at reflux for 8 h. After cooling the reaction mixture was poured onto crushed ice and the product which separated was filtered off, washed with water, dried and crystalized from ethanol to give the title compound as colorless needles. m.p. 272-274 ^{0}C; IR: 3437 (OH), 1739 (CON), 1662 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.01 (s, 3H, $COCH_3$), 3.30 (s, 2H, NCH_2), 5.19 (s, 2H, OCH_2)7.57 (s, 1H, pyrazole-H), 7.40-7.63 (m, 9H, Ar-H), 9.90 (s, 1H, exchangeable NH) and 10.25 (s, 1H, exchangeable NH); MS (m/z, %): 430 (89, $M^{+\cdot}$-2H), 414 (19, $M^{+\cdot}$-H_2O), 404 (53, $M^{+\cdot}$-

CO), 396 (56, $M^{+\cdot}$-$2H_2O$) and 367 (100, $M^{+\cdot}$-CH_5O_3); Anal. Calcd for $C_{22}H_{20}N_6O_4$ (432.43): C, 61.10; H, 4.66; N, 19.43%. Found: C, 60.80; H, 4.43; N, 19.32%.

N'-Benzoyl-2-[3-(5-benzoyloxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (6):

A solution of 2-[3-(5-Hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl aceto-hydrazide(**3**,0.78 g,0.002 mol) in pyridine (10 ml) was treated with benzoyl chloride (0.3 ml) and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice and the product was filtered off, washed with water and dried. It was crystalized from ethanol to give the title compound as colorless needles (1.08 g, 90% yield). m.p. 253-255^{0}C; IR: 1717 (COO), 1656 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 3.30 (s, 2H, NCH_2), 5.17 (s, 2H, OCH_2), 7.92 (s, 1H, pyrazole-H), 7.43-7.94 (m, 19H, Ar-H) and 10.47 (s, 2H, 2NH); MS (m/z, %): 599 (24, $M^{+\cdot}$), 494 (2, $M^{+\cdot}$-C_6H_5CO), 464 (22, $M^{+\cdot}$-$C_7H_7N_2O$), 436 (27, $M^{+\cdot}$-$C_8H_7N_2O_2$), and 422 (29, $M^{+\cdot}$-$C_9H_9N_2O_2$); Anal. Calcd for $C_{34}H_{26}N_6O_5$ (598.61): C, 68.22; H, 4.38; N, 14.04%. Found: C, 68.19; H, 4.45; N, 14.00%.

Reaction of Compound 3 with Aliphatic Acids

A mixture of **3** (0.78 g,0.002 mol), formic or acetic acid (5 ml) and phosphoryl chloride (10 ml) was gently heated at 70 ^{o}C for 8 h. After cooling it was poured onto ice-water mixture (50 ml) and the solid that separated out was filtered, washed with water, dried and crystalized from aqueous dimethylformamide to give the title compound as colorless needles.

3-(5-Hydroxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (9):

Yield: 0.68 g (85%); m.p. 208-210 ^{0}C; IR: 3434 (OH), 1720 (CON), 1662 (CON) and 1605 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 3.32 (s, 2H, NCH_2), 3.73 (s, 1H, exchangeable OH), 7.33-7.68 (m, 9H, Ar-H), 7.91 (s, 1H, pyrazole-H) and 7.94 (s, 1H, oxadiazole-H); MS (m/z, %): 400 (9, $M^{+\cdot}$), 372 (6, $M^{+\cdot}$-CO), 369 (8, $M^{+\cdot}$-CH_2OH), 357 (8, $M^{+\cdot}$-CHNO), 317 (9, $M^{+\cdot}$-$C_3H_3N_2O$) and 303 (, $M^{+\cdot}$-$C_3H_3N_3O$); Anal. Calcd for $C_{21}H_{16}N_6O_3$ (400.39): C, 62.99; H, 4.03; N, 20.99%. Found: C, 62.80; H, 4.13; N, 21.02%.

3-(5-Hydroxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (10):

Yield: 0.70 g (85%); m.p. 228-230 ^{0}C; IR: 3440 (OH), 1649 (CON) and 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.33 (s, 2H, NCH_2), 4.68 (s, 1H, exchangeable OH), 7.75 (s, 1H, pyrazole-H), and 7.32-7.92 (m, 9H, Ar-H); MS (m/z, %): 414 (9, $M^{+\cdot}$), 400 (6, $M^{+\cdot}$-CH_2), 399 (6, $M^{+\cdot}$-CH_3), 383 (9, $M^{+\cdot}$-CH_2OH), 318 (8, $M^{+\cdot}$-$C_4H_4N_2O$) and 316 (13, $M^{+\cdot}$-$C_4H_6N_2O$); Anal. Calcd for $C_{22}H_{18}N_6O_3$ (414.42): C, 63.76; H, 4.38; N, 20.28%. Found: C, 63.80; H, 4.33; N, 20.32%.

3-(5-Benzoyloxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (11)

Method A. N'-benzoyl-2-[3-(5-benzoyloxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**6**,0.60 g,0.001 mol) and glacial acetic acid (10 ml) was heated at reflux for 8 h. The reaction mixture was cooled, poured onto crushed ice and the product which separated was filtered off, washed with water, dried and crystalized from ethanol to give the title compound as colorless needles (0.49 g, 85% yield).m.p. 248-250^{0}C; IR: 1726 (COO), 1649 (CON) and 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 3.31 (s, 2H, NCH_2), 5.20 (s, 2H, OCH_2), 7.97 (s, 1H, pyrazole-H), and 7.41-8.19 (m, 19H, Ar-H); MS (m/z, %): 581 (26, $M^{+\cdot}$), 580 (14, $M^{+\cdot}$-1), 477 (16, $M^{+\cdot}$-C_7H_4O), 461 (64, $M^{+\cdot}$-$C_7H_4O_2$), 446 (23, $M^{+\cdot}$-$C_8H_8O_2$), 304 (23, $M^{+\cdot}$-$C_{17}H_{13}N_2O_2$) and 276 (26, $M^{+\cdot}$-$C_{18}H_{13}N_2O_3$); Anal. Calcd for $C_{34}H_{24}N_6O_4$ (580.19): C, 70.34; H, 4.17; N, 14.47%. Found: C, 70.40; H, 4.13; N, 14.52%.

Method B. N'-benzoyl-2-[3-(5-benzoyloxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**6**, 0.60 g,0.001 mol) and dimethylformamide (10 ml) was heated at reflux for 8 h. The product that separated on cooling was filtered off, dried and crystalized from ethanol to give the title compound as colorless needles (0.52 g, 90% yield).m.p. and mixed m.p. with that prepared according to Method A. 248-250^{0}C; the IR and ^{1}H NMR spectra of **11** obtained according Method A and B were identical.

3-(5-Hydroxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (12):

A mixture of 2[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**3**,0.78 g,0.002 mol), a solution of methanolic potassium hydroxide (0.50 g KOH and 20 ml MeOH) and carbon disulphide (2 ml, excess) was refluxed for 8 h. After cooling, it was poured onto ice-water mixture (50 ml), acidified with diluted HCl to P^H 6 and the colorless precipitate was formed. The precipitate was filtered off and crystalized from dimethylformamide to give the title compound as colorless needles (0.34 g, 80% yield). m.p. 262-264 ^{0}C; IR: 3485 (OH), 3149 (NH), 1656(CON) and 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 3.30 (s, 2H, NCH_2), 4.58 (s, 1H, exchangeable OH), 5.69 (s, 2H, OCH_2), 7.41-7.96 (m, 9H, Ar-H), 7.75 (s, 1H, pyrazole-H) and 14.55 (s, 1H, exchangeable SH); MS (m/z, %): 432 (1, $M^{+\cdot}$), 360 (1, $M^{+\cdot}$-C_2N_2S) and 318 (75, $M^{+\cdot}$-$C_3H_2N_2OS$); Anal. Calcd for $C_{21}H_{16}N_6O_3S$ (432.46): C, 58.32; H, 3.73; N, 19.43; S, 7.41%. Found: C, 58.40; H, 3.63; N, 19.52; S, 7.50%.

1-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]-3-[5-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoxalin-2-one (14):

A mixture of 2[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**3**,0.78 g,0.002 mol) and acetylacetone (10 ml) was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure, ethanol was added and the product separated out was filtered, washed with ethanol and crystalized from ethanol to give the title compound as colorless needles (0.77g, 85% yield). m.p. 170-172 ^{0}C; IR: 3408 (OH), 1736 (CON), 1649 (C=O) and 1595 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.31 (s, 2H, NCH_2), 4.58 (s, 1H, exchangeable, OH), 5.55 (s, 2H, OCH_2), 7.73 (s, 1H, pyrazole-H), 7.75 (s, 1H, pyrazole-H) and 7.36-7.96 (m, 9H, Ar-H); MS (m/z, %): 454 (38, $M^{+\cdot}$), 331 (48, $M^{+\cdot}$-$C_6H_7N_2O$), 318 (38, $M^{+\cdot}$-$C_6H_7N_2O$), 304 (43, $M^{+\cdot}$-$C_7H_8N_3O$) and 245 (48, $M^{+\cdot}$-$C_9H_{11}N_3O_3$); Anal. Calcd for $C_{25}H_{22}N_6O_3$ (454.48): C, 66.07; H, 4.88; N, 18.49%. Found: C, 66.15; H, 4.95; N, 18.60%.

3-[5-(Hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-1-[2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl]quinoxalin-2-one (16):

A solution of 2[3-(5-hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-oxoquinoxalin-1-yl acetohydrazide (**3**,0.78 g,0.002 mol) in dimethylformamide (25 ml) and ethylacetoacetate (0.27 g, 0.002 mol) was heated under reflux for 8 h. The reaction mixture was evaporated under reduced pressure, ethanol was added and the solid separated out was filtered, washed with ethanol and crystalized from ethanol to give the title compound as colorless needles (0.77g, 85% yield). m.p. 266-268 ^{0}C; IR: 3411 (OH), 1646 (CON) and 1592 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.35 (s, 2H, NCH_2), 4.58 (s, 2H, pyrazole-H), 5.21 (s, 2H, OCH_2), 5.51 (s, 1H, exchangeable, OH), 7.72 (s, 1H, pyrazole-H) and 7.40-7.95 (m, 9H, Ar-H); MS (m/z, %): 456 (37, $M^{+\cdot}$), 380 (27, $M^{+\cdot}$-C_6H_4), 318 (42, $M^{+\cdot}$-$C_6H_7N_2O_2$) and 250 (27, $M^{+\cdot}$-$C_7H_{10}N_3O_3$); Anal. Calcd for $C_{24}H_{20}N_6O_4$ (456.45): C, 63.15; H, 4.42; N, 18.41%. Found: C, 63.09; H, 4.50; N, 18.36%.

Reaction of Compounds 3, 4, 5, 9, 10, 12, 14 or 16 with Acetic Anhydride

A suspension of compounds **3**, **4**, **5**, **9**, **10**, **12**, **14** or **16**(0.001 mol) in acetic anhydride (5 ml) was heated under reflux for 2 h., and the mixture was cooled and poured onto crushed ice. The product that separated out was filtered off, successively washed with water, ethanol and ether and then dried. It was crystallized from ethanol to give the title compound as colorless needles**.**

3-(5-Acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(1,3,4-Oxadiazol-2-yl)methyl]quinoxalin-2-one (7):

Yield: 0.40 g(90%); m.p. 214-216 ^{0}C; IR: 1745 (COO), 1656 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 3H, $COCH_3$), 3.32 (s, 2H, NCH_2), 5.80 (s, 2H, OCH_2), 7.41-7.71 (m, 9H, Ar-H), 7.90 (s, 1H, pyrazole-H) and 7.93 (s, 1H, oxadiazole-H); Anal. Calcd for $C_{23}H_{18}N_6O_4$ (442.43): C, 62.44; H, 4.10; N, 19.00%. Found: C, 62.50; H, 4.13; N, 18.82%.

3-(5-Acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (8):

Yield: 0.41 g (90%); m.p. 130-131^{0}C; IR: 1739 (COO), 1653 (CON) and 1605 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.37 (s, 3H, CH_3), 2.44 (s, 3H, $CO\underline{CH_3}$), 3.30 (s, 2H, NCH_2), 5.19 (s, 2H, OCH_2), 7.66 (s, 1H, pyrazole-H) and 7.44-7.95 (m, 9H, Ar-H); MS (m/z, %): 456 (1, $M^{+\cdot}$), 441 (2, $M^{+\cdot}$-CH_3), 373 (5, $M^{+\cdot}$-$C_3H_3N_2O$) and 359 (3, $M^{+\cdot}$-$C_4H_5N_2O$); Anal. Calcd for $C_{24}H_{20}N_6O_4$ (456.45): C, 63.15; H, 4.42; N, 18.41%. Found: C, 63.59; H, 4.57; N, 18.66%.

3-(5-Acetoxymethyl-1-phenyl-1*H*-pyrazol-3-yl)-1-[(5-acetylmercapto-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2-one (13):

Yield: 0.47 g (90%); m.p. 274-276 ^{0}C; IR: 1745(COO), 1656 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.01 (s, 3H, $COCH_3$), 2.49 (s, 3H, $SCOCH_3$), 3.31 (s, 2H, NCH_2), 5.19 (s, 2H, OCH_2), 7.44-7.95 (m, 9H, Ar-H) and 7.73 (s, 1H, pyrazole-H); MS (m/z, %): 474 (1, $M^{+\cdot}$-CH_2CO), 432 (2, $M^{+\cdot}$- $2CH_2CO$), 400 (2, $M^{+\cdot}$-$C_4H_4O_2S$) and 371 (2, $M^{+\cdot}$-$C_5H_3O_3S$); Anal. Calcd for $C_{25}H_{20}N_6O_5S$ (516.53): C, 58.13; H, 3.90; N, 16.27; S, 6.21%. Found: C, 58.20; H, 3.83; N, 16.32; S, 6.30%.

1-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]-3-[5-(acetoxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]quinoxalin-2-one (15):

Yield: 0.45g (90%); m.p. 218-220 ^{0}C; IR: 1744 (COO), 1656 (CON) and 1602 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.46 (s, 3H, CH_3), 2.50 (s, 6H, $2CH_3$), 3.31 (s, 2H, NCH_2), 5.26 (s, 2H, OCH_2), 7.72 (s, 1H, pyrazole-H), 7.74 (s, 1H, pyrazole-H) and 7.40-7.95 (m, 9H, Ar-H); MS (m/z, %): 496 (8, $M^{+\cdot}$), 482 (5, $M^{+\cdot}$-CH_2), 481 (14, $M^{+\cdot}$-CH_3), 453 (25, $M^{+\cdot}$-CH_3CO), 437 (9, $M^{+\cdot}$-$OCOCH_3$), 423(20, $M^{+\cdot}$-CH_2OCOCH_3), 409 (16, $M^{+\cdot}$-$C_4H_7O_2$), 408 (6, $M^{+\cdot}$-$C_4H_8O_2$) and 394 (8, $M^{+\cdot}$-$C_5H_{10}O_2$); Anal. Calcd for $C_{27}H_{24}N_6O_4$ (496.52): C, 65.31; H, 4.87; N, 16.93%. Found: C, 65.19; H, 4.95; N, 16.75%.

3-[5-(Acetoxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-1-[2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl]quinoxalin-2-one (17):

Yield: 0.45 g (90%); m.p. 188-190 ^{0}C; IR: 3443 (OH), 1749 (COO), 1646 (CON) and 1589 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 3H, CH_3), 2.50 (s, 3H, CO$\underline{CH_3}$), 3.30 (s, 2H, NCH_2), 5.19 (s, 2H, pyrazole-H), 5.21 (s, 2H, OCH_2), 7.44-7.65 (m, 9H, Ar-H) and 7.92 (s, 1H, pyrazole-H); MS (m/z, %): 498 (5, $M^{+\cdot}$), 446 (2, $M^{+\cdot}$-CH_2CO), 415 (9, $M^{+\cdot}$-$C_3H_5O_2$), 401 (2, $M^{+\cdot}$-$C_4H_5N_2O$) and 359 (3, $M^{+\cdot}$-$C_6H_7N_2O_2$); Anal. Calcd for $C_{27}H_{24}N_6O_4$ (496.52): C, 65.31; H, 4.87; N, 16.93%. Found: C, 65.19; H, 4.95; N, 16.75%.

4. Conclusion

The synthesis of the targeted 1,3,4-oxadiazolyl- and pyrazolylquinoxalines was accomplished through simple synthetic routes . Pharmacological evaluation of compounds **2-17** against three cell lines HCT-116 (colon carcinoma), HEPG2 (liver carcinoma) and MCF-7 (breast carcinoma) revealed that these compounds possess high or moderate anti-tumor activities. Most of the synthesized compounds showed very good anticancer activity in terms of growth inhibitory effect on the three cancer cell lines. Hence, it could be a potential drug candidate for cancer treatment.

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