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Design, Synthesis and *In Vitro* Anticarcinogenic Activity of Novel 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4H)-yl)-methyl]-1, 3, 4-oxadiazol-2-yl) phenyl acetate

Fatma A. M. Mohamed [1, 2*], Saleha Y. M. Alakilli[1], Eman F. El Azab[1, 3] and Bi Bi Zainab Mazhari [1]

[1]Department of Clinical Laboratory Science, College of Applied Medical Sciences, Jouf University, **Kingdom of Saudi Arabia**
[2]Lecturer of Organic Chemistry, Faculty of Sciences, Alexandria University, **Egypt**
[3] Lecturer of Biochemistry, Faculty of Sciences, Alexandria University, **Egypt**

***Correspondence:** f_ahmed84@yahoo.com **Received: 09-10-2019, Revised: 03-11-2019, Accepted: 07-11-2019 e-Published: 24-11-2019**

Synthesis of 2-(4-oxoquinazolin-3(4*H*)-yl) acetohydrazide 3 was accomplished by the reaction of quinazolin-4(3H)-one 1 with ethyl bromoacetate followed by treatment with hydrazine hydrate. The key starting materials 3 was used for synthesis of the target 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4*H*)-yl)-methyl]-1, 3, 4-oxadiazol-2-yl) phenyl acetate 5. Thus, the reaction of 3 with salicylaldehyde afforded N'-(2-hydroxybenzylidene)-2-(4-oxoquinazolin-3(4*H*)-yl) acetohydrazide 4. Cyclization of 4 with acetic anhydride leading to the formation of 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4*H*)-yl) methyl]-1, 3, 4-oxa-diazol-2-yl) phenyl acetate 5. The structure of 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4H)-yl) methyl]-1, 3, 4-oxadiazol-2-yl) phenyl acetate 5 was established by elemental analysis, infrared, mass spectra, and nuclear magnetic resonance. Also, anti-tumor estimation of the new compounds *in vitro* through three cell lines HepG2 (liver carcinoma), HCT-116 (colon carcinoma), and MCF-7 (breast carcinoma) revealed that they own high anti-tumor activities.

Keywords: Quinazolinone, oxadiazol, carcinoma, cytotoxicity

INTRODUCTION

Quinazolone derivatives are synthesized mainly beginning from anthranilic acid with an appropriate substituent in order to have a specific substituent in three to four steps. Thus, numerous analogues of quinazolones have been produced and subjected to screening for biological activity using various animal models. Several derivatives of quinazoline characterize as one of the utmost active classes of compounds (Asif, 2014 and Srivastava & Sujiti, 2015). Quinazolines and its derivatives own extensive scope of biological activities like antibacterial (Nagar et al., 2013), anti-inflammatory (Mohamed et al., 2011), antioxidant activity (Al-Omar et al., 2006), antitumor (El-Azab et al., 2010), cytotoxic activity (Sinha et al., 2013), antifungal (Vashi et al., 2010), antihypertensive (Patel et al., 2013), anti-HIV (Mohamed et al., 2012), analgesic effect (Sinha et al., 2013), anticonvulsant (Mukherjee et al., 2014), anti-tubercular activities (Srivastav et al., 2013), antimalarial activity (Sen et al., 2010) and antibacterial activity (Kale and Durgade, 2017).

The goal of current study is to scrutinize

a novel compound of quinazolone derivatives, which possess most biological activity.

MATERIALS AND METHODS

Experimental

Determination of melting points were done by using a Kofler Block and are uncorrected. Also, elemental analyses were done in the micro analytical laboratory of the Faculty of Science, Cairo University, Egypt. The IR spectra of compounds were recorded on a Tensor 37 Bruker infrared spectrophotometer as potassium bromide pellets and frequencies are informed in cm^{-1}. The IR spectra was carried out in the faculty of science, Alexandria University, Egypt. The ^1H NMR spectra were recorded on a Bruker AC (500 MHz) spectrometer of the Faculty of Science, Jordan University, Jordan. Chemical shifts δ are in ppm and Hz relative to tetramethylsilane as an internal standard. Mass spectra were recorded at 70 ev by 5980 series II GC coupled with 5989 B mass spectrometer of the Faculty of Science, Cairo University, Egypt. Reactions were normally followed by thin layer chromatography (TLC) using Merck Kiesel gel; 60-F254 precoated plastic plates. The spots were detected by UV Lamp.

Quinazolin-4(3H)-one 1:

A solution of 2-aminobenzoic acid (10 g, 0.0729 mol) and formamide (50 mL) was heated under reflux for 90 minutes. The reaction mixture was cooled and the solid that separated out was filtered, then washed with methanol, dried and crystallized from methanol to give the title compound (**1**) as colorless needles (10 g, 93% yield); m.p. and mixed m.p. 186-188°(Sen and Singh, 1959, Armarego, 1961, and Armarego, 1962).

Ethyl 2-(4-oxoquinazolin-3(4*H*)-yl) acetate 2:

To a solution of quinazolin-4(3*H*)-one (**1**, 5 g, 0.0344 mol) in dry dimethyl-formamide (20 mL), anhydrous potassium carbonate (10 g, 0.0723 mol) and ethyl bromoacetate (5 mL) was whiskered at room temperature for 6 h. The solid mass dispensed onto crumpled ice and the product was filtered, washed well with water, dried and crystallized from ethanol to give the title compound **2** as colorless needles (7.3 g, 92% yield); m.p. 68-70˚(Mali *et al*., 2009); IR: 1739 (COOEt) and 1676 cm^{-1}(amide group of quinazolinone ring); ^1H NMR ($CDCl_3$): δ 1.35 (t, 3H, -$CH_2\underline{CH_3}$), 4.31 (q, 2H, -$\underline{CH_2}CH_3$), 4.35 (s, 1H, CH_2CO), 7.55 (t, 1H, aromatic-H), 7.82 (t, 1H, aromatic-H), 7.76 (d, 1H, aromatic-H), 8.35 (d, 1H, aromatic-H) and 8.02 (s,1H, pyrimidine-H); MS: (m/z, %): 232 (M^+, 5), 187 (M^+-OEt, 6), 186 (M^+-OC_2H_6, 7), 160 (M^+-$C_3H_4O_2$, 3), 159 (M^+-$C_3H_5O_2$, 32), 103 (M^+-$C_4H_7O_3N$, 2), 102 (M^+-$C_4H_8O_3N$, 5), 114 (M^+-C_7H_4NO, 30) and 85 (M^+-C_9H_9NO, 15); Anal. Calcd for $C_{12}H_{12}N_2O_3$ (232.24): C, 62.06; H, 5.21; N, 12.06%. Found: C, 62.30; H, 5.03; N, 12.40%.

2-(4-Oxoquinazolin-3(4H)-yl) acetohydrazide 3:

A solution of ethyl 2-(4-oxoquinazolin-3(4*H*)-yl) acetate (**2**, 5 g, 0.0215 mol) and hydrazine hydrate (15 mL) in methanol (50 mL) was stirred at room temperature for 30 min. The product which separated after cooling, was filtered, washed with methanol, dried and crystallized from methanol-benzene to give the title compound **3** as colorless needles (4 g, 85% yield); m.p.225-226˚(18);IR: 3463 (NH), 3291 and 3162 (asymmetric and symmetric NH stretching frequencies of the primary amino group) 1680 (carbonyl group of quinazolinone ring) and 1630 cm^{-1} (carbonyl absorption band of pyrrolidine ring);MS: (m/z, %):218 (M^+, 91), 203(M^+-NH, 1), 202(M^+-NH_2, 9), 201 (M^+-NH_3, 64), 126 (M^+-C_6H_6N, 100), 125 (M^+-C_6H_7N, 33), 160 (M^+-CON_2H_2, 8), 142 (M^+-C_6H_4, 15), 114 (M^+-C_7H_4O, 49), 103(M^+-$C_3H_5N_3O_2$, 2), 102 (M^+-$C_3H_6N_3O_2$, 15) and 76 (M^+-$C_4H_6N_4O_2$, 21); Anal. Calcd for $C_{10}H_{10}N_4O_2$ (218.21): C, 55.04; H, 4.62; N, 25.68%. Found: C, 55.21; H, 4.30; N, 26.01%.

N'-(2-Hydroxybenzylidene)-2-(4-oxoquinazolin-3(4*H*)-yl) aceto-hydrazide 4:

A mixture of 2-(4-oxoquinazolin-3(4H)-yl)acetohydrazide (3, 0.21 g, 0.001 mol), salicylaldehyde (0.2 mL) in ethanol (50 mL) and two drops of acetic acid was heated under reflux for 6 hours. The precipitated solid formed was filtered, washed with ethanol and crystallized from dimethylformamide to give the title compound 4 as colorless needles (0.28 g, 90% yield) ; m.p. 280-282°;IR: 3642 (broad strong band of OH), 3384 (stretching band of NH), 1698(carbonyl absorption of quinazolinone ring) and 1670 cm1 (carbonyl absorption of pyrrolidine ring); MS: (m/z, %): 323 (M^++1, 3), 322 (M^+, 14), 263(M^+-CH_3N_2O, 17), 262(M^+- CH_4N_2O, 100), 245 (M^+-$CH_5N_2O_2$, 2), 172 (M^+- $C_8H_6O_3$, 8), 169 (M^+-$C_7H_9N_2O_2$, 4), 96 (M^+- $C_{14}H_{10}O_3$, 4), 95 (M^+-$C_{14}H_{11}O_3$, 50) and 67 (M^+-$C_{14}H_{11}N_2O_3$, 79); Anal. Calcd for $C_{17}H_{14}N_4O_3$ (322.32): C, 63.35; H, 4.38; N, 17.38 %. Found: C, 63.40; H, 4.42; N, 17.39%.

2-(3-Acetyl-2, 3-dihydro-5-[{(4-oxoquinazolin-3(4*H*)-yl} methyl)-1, 3, 4-oxadiazol-2-yl) phenyl acetate 5:

A solution of N'-(2-hydroxybenzylidene)-2-(4-oxoquinazolin-3(4*H*)-yl) aceto-hydrazide (4, 0.32 g, 0.001 mol) in anhydrase acetic (5 mL) was boiled under reflux for one hour. The outcome solution was discharged onto crumpled ice, then the output product was separated out, filtered off, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The output product was crystallized from dimethyl-formamide to yield the new compound 5 as colorless needles (0.33 g, 83% yield); m.p. 280-282°; IR: 1761 (a broad strong absorption of carbonyl acetyl group), 1673 (carbonyl band of quinazolinone ring) and 1609 cm^{-1} (oxadiazole C=N absorption); ^1H NMR (DMSO-d_6): δ 2.21 (s, 3H, -CO$\underline{CH_3}$), 2.42 (s, 3H, -CO$\underline{CH_3}$), 7.08 (s, 1H, oxadiazole-H), 5.01 (s, 2H, CH_2), 7.35 (t, 1H, aromatic-H), 7.52 (t, 1H, aromatic-H), 7.57 (t, 1H, aromatic-H), 7.86 (t, 1H, aromatic-H), 7.25 (d, 1H, aromatic-H), 7.53 (d, 1H, aromatic-H), 7.70 (d, 1H, aromatic-H) 8.14 (d, 1H, aromatic-H) and 8.25 (s,1H, pyrimidine-H); MS: (m/z, %): 408 (M^++2, 3), 407 (M^++1, 19), 406 (M^+, 79), 276 (M^+-$C_4H_6N_2O_3$,17), 249(M^+- $C_5H_5N_2O_4$, 100), 248 (M^+-$C_5H_6N_2O_4$, 16), 247 (M^+- $C_9H_7N_2O$, 5), 205 (M^+-$C_{11}H_9N_2O_2$, 95), 204 (M^+-$C_{11}H_{10}N_2O_2$, 51),178 (M^+-$C_{12}H_{10}O_2N_3$, 17) and 152 (M^+-$C_{13}H_{10}O_2N_4$, 46; Anal. Calcd for $C_{21}H_{18}N_4O_5$ (406.39): C, 62.06; H, 4.46; N, 13.79%. Found: C, 62.21; H, 4.61; N, 13.50%.

Biological Screening

***In vitro* anticancer activity**

The newly synthesized compound was estimated for its growth inhibition potential against three aggressive cancer cell lines, namely human colon tumor HCT, hepatocellular carcinoma HepG2, and MCF-7 breast cancer using the sulforhodamine B (SRB) colorimetric assay (Skehan et al., 1990).

Different concentrations were formed from the mew compound and evaluated for its *in vitro* anticancer activity by SRB Cells in the Regional Center for Mycology& Biotechnology, Al-Azhar University, Cairo, Egypt. SRB Cells were coated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compound to permit attachment of cell to the wall of the plate.

Different concentrations of the new compound were added to the cell monolayer. Monolayer cells incubated with the compound for 48 h at 37°C and in atmosphere of 5% CO_2. After 48 h, cells were fixed then washed and stained with SRB strain. Removing the extra stain by washing with acetic acid and attached stain was recovered with tris EDTA buffer. Color intensity was estimated by an ELISA reader. Finally, plot the relation among surviving fraction and drug concentration to develop the survival curve of each tumor cell line. The anticancer activities are expressed as the median growth inhibitory concentration (IC_{50}).

RESULTS AND DISCUSSION

In a program in our laboratory devoted to the synthesis of heterocyclic compound from hydrazion- and hydrazide heterocycles.

Stirring of quinazolin-4(3H)-one 1 with ethyl bromoacetate at room temperature afforded ethyl 2-(4-oxoquinazolin-3(4H)-yl) acetate 2 in excellent yield. The structure of the ester derivatives 2 was deduced from its spectral analysis. The IR spectrum showed two absorption bands at 1739 and 1676 cm-1 for the ester and cyclic amide groups, respectively. The1H -NMR spectrum revealed a triplet at δ 1.35 for CH_3 group as well as a quartet at δ 4.31 for CH_2 group, in addition to a singlet at δ 4.35 for methylene group. Furthermore, its mass spectrum showed molecular ion peak and fragment at ion pattern agreeing with the structure (cf. Experimental).

Hydrazinolysis of ethyl 2-(4-oxoquinazolin-3(4*H*)-yl) acetate 2 with hydrazine hydrate led to the formation of 2-(4-oxoquinazolin-3(4*H*)-yl) acetohydrazide 3 in good yield. The infrared spectrum of compound 3 showed the absence of the ester group of the former and the presence of carbonyl absorption band of quinazolinone ring at 1680 cm^{-1} and carbonyl absorption band of amide group at 1630 cm^{-1}. The carbohydrazide 3 gives a strong intense molecular ion peak at m/z 218.

The carbohydrazidoquinazoline 3 appeared attractive intermediate for the synthesis of heterocyclic compound. Treatment of compound 3 with salicylaldehyde led to the formation of afforded N'-(2-hydroxybenzylidene)-2-(4-oxoquinazolin-3(4*H*)-yl) acetohydrazide 4. The IR spectrum of compound 133 showed a broad strong band of OH at 3642 cm^{-1},a stretching band of NH at 3384 cm^{-1}, carbonyl absorption of quinazolinone ring at 1698 cm^{-1} and carbonyl absorption of amide group at 1670 cm^{-1}. Although, the acetohydrazidequinazoline 4 gives a weak intense molecular ion peak at m/z 322 (14%).

On the other hand, cyclization of N'-(2-hydroxybenzylidene)-2-(4-oxoquinazolin-3(4*H*)-yl) acetohydrazide 4 with acetic anhydride afforded

2-(3-acetyl-2,3-dihydro-5-[(4-oxoquinazolin-3(4*H*)-yl) methyl]-1, 3, 4-oxa-diazol-2-yl) phenyl acetate 5. The infrared spectrum of the compound 5 showed a broad strong absorption of carbonyl acetyl group at 1761 cm^{-1}, carbonyl band of quinazolinone ring at 1673 cm^{-1} and oxadiazole C=N absorption at 1609 cm^{-1}. The ^1H -NMR spectrum of 2-(3-acetyl-2,3-dihydro-5-[(4-oxoquinazolin-3(4*H*)-yl)-methyl]-1,3,4-oxadiazol-2-yl)phenyl acetate 5, in DMSO-d_6, exhibited two singlet signals at δ 2.21 (3H) and 2.42 (3H) for two methyl protons of acetyl group, as well as a singlet at δ 7.08 for oxadiazole-H (1H) proton. Also, it showed a singlet at δ 5.01 for CH_2 (2H) group, in addition to four triplets at δ 7.35 (1H), 7.52 (1H), 7.57(1H) and 7.86 (1H) and four doublets at δ 7.25 (1H), 7.52 (1H),7.70 (1H) and 8.14 (1H) for phenyl protons. Moreover, it showed a singlet at δ 8.25 for H-2 pyrimidine proton. The oxadiazoloquinazoline 5 gives a strong intense molecular ion peak at m/z 406 (79%) for the mass spectrum (Scheme.1).

Anticancer Screening Studies

The newly synthesized 2-(3-acetyl-2,3-dihydro-5-[(4-oxoquinazolin-3(4H)-yl)methyl]-1,3,4-oxa-diazol-2-yl)phenyl acetate was evaluated for its growth inhibition potential against three aggressive cancer cell lines, specifically HT-29 colon cancer, HepG2 hepatocellular carcinoma, and MCF-7 breast cancer cells using the SRB colorimetric test (Skehan et al., 1990). Doxorubicin (Dox) was utilized as positive control as it is one of the most effective anticarcinogenic agents that owns wide-ranging spectrum against different types of solid tumors and is known to have potent pro-apoptic effects (Panaretakis *et al*., 2002).

Evaluation of cytotoxicity against colon carcinoma cell lines

In case of HCT-116 cells as demonstrated in table (1), it exhibited low viability cells about 21.75 % for compounds 5 at 50 µg but the remained compounds showed lower sensitivity.

The inhibitory concentration that inhibits the viable cells for human colon tumor HCT by 50% (IC_{50}) table (1) of the compound 5 were exhibited a strong growth inhibition (IC_{50}= 31.2 µg) for compound 5. The compound 5 give a good result because carbonyl group of the compound 5.

Evaluation of cytotoxicity against hepatocellular carcinoma cell lines

In case of HepG2 cells, it indicated low viability cells about 38.29 % for compound 5 at 50 µg but the remained compounds exhibited lower sensitivity as shown in table (1). Also, when the tumor cells was treated with 25 µg of each compound showed 47.54 % inhibition against HepG2 for compound 5.

Furthermore, when the concentration of compound 5 was decreased to 6.25 µg showed 20.85 % inhibition against liver tumor for these compounds 5. That explains the decreasing of the concentration of compound used led to decrease of the inhibition against hepatocellular carcinoma tumor.

The inhibitory concentration that inhibits the viable cells for HepG2 by 50% (IC_{50}) of the new compound exhibited a strong growth inhibition (IC_{50}=29.3 µg) for compound 5. The above results showed that compound 5 give a good result because the presence of carbonyl group.

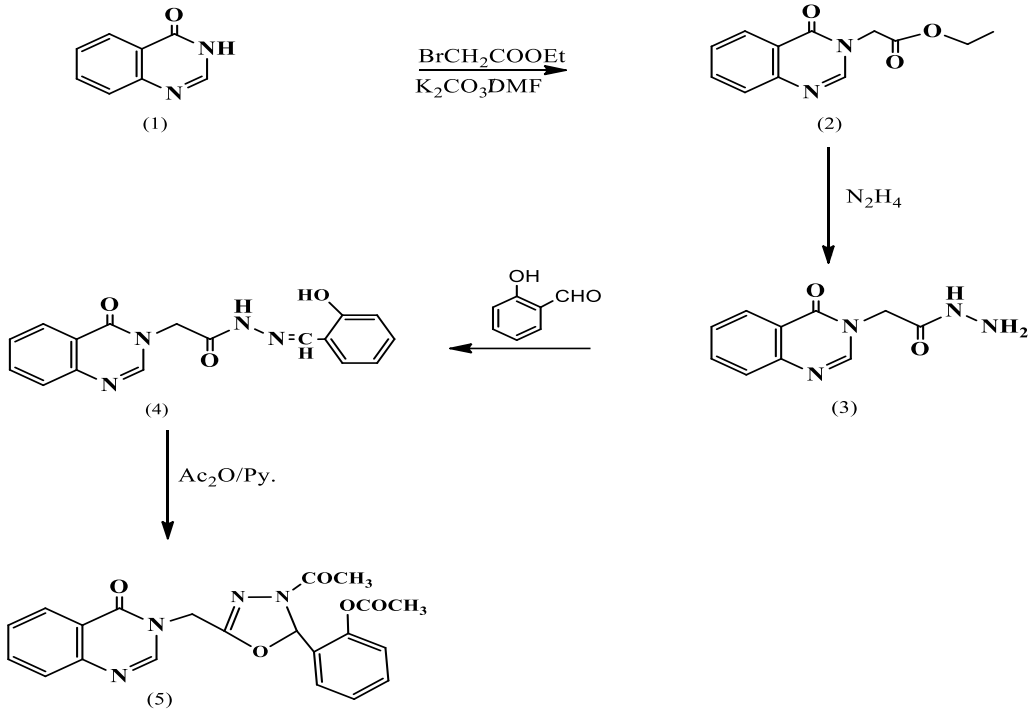
Evaluation of cytotoxicity against breast carcinoma cell lines

In case of HCF-7 cells as in table (1), it displayed 84.64 % very strong inhibition against HCF-7 for compound 5 at 50 µg. Moreover, when the breast tumor cells was treated with 25 µg from each compound in showed low viability cells about 31.59 % for compound 5.

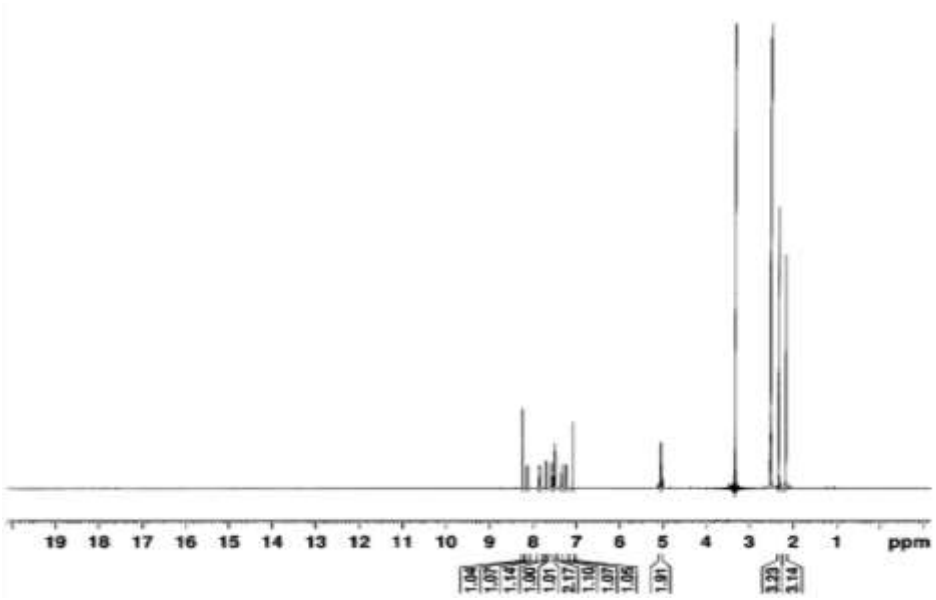
Also, treatment of the breast tumor with 12.5 µg of the above compound showed 46.9 % inhibition against HCF-7 for compound 5. Furthermore, when the concentration of our compound decreased to 6.25 µg showed 32.68 % inhibition against HCF-7. In addition, the inhibitory concentration that inhibits the viable cells for HCF-7 by 50% (IC_{50}) of the compound 5 were exhibited a very strong growth inhibition (IC_{50}= 14.3 µg).

Table 1: *In vitro* anticancer activities of the newly synthesized compound against hepatocellular carcinoma (HepG2), colon cancer (HT-29), and breast cancer (MCF-7) cell lines.

Sample Concentration (µg)	Human colon tumor (HCT)	Hepatocellular carcinoma (HepG2)	Breast cancer (MCF-7)
50	21.75	38.29	15.36
25	59.37	52.46	31.59
12.5	82.43	72.62	53.1
6.25	91.56	79.15	67.32
3.12	97.85	93.84	80.27
1.56	100	97.52	89.14
0	100	100	100



Scheme 1: the synthesis of 2- (4-oxoquinazolin-3(4H)-yl) acetohydrazide a



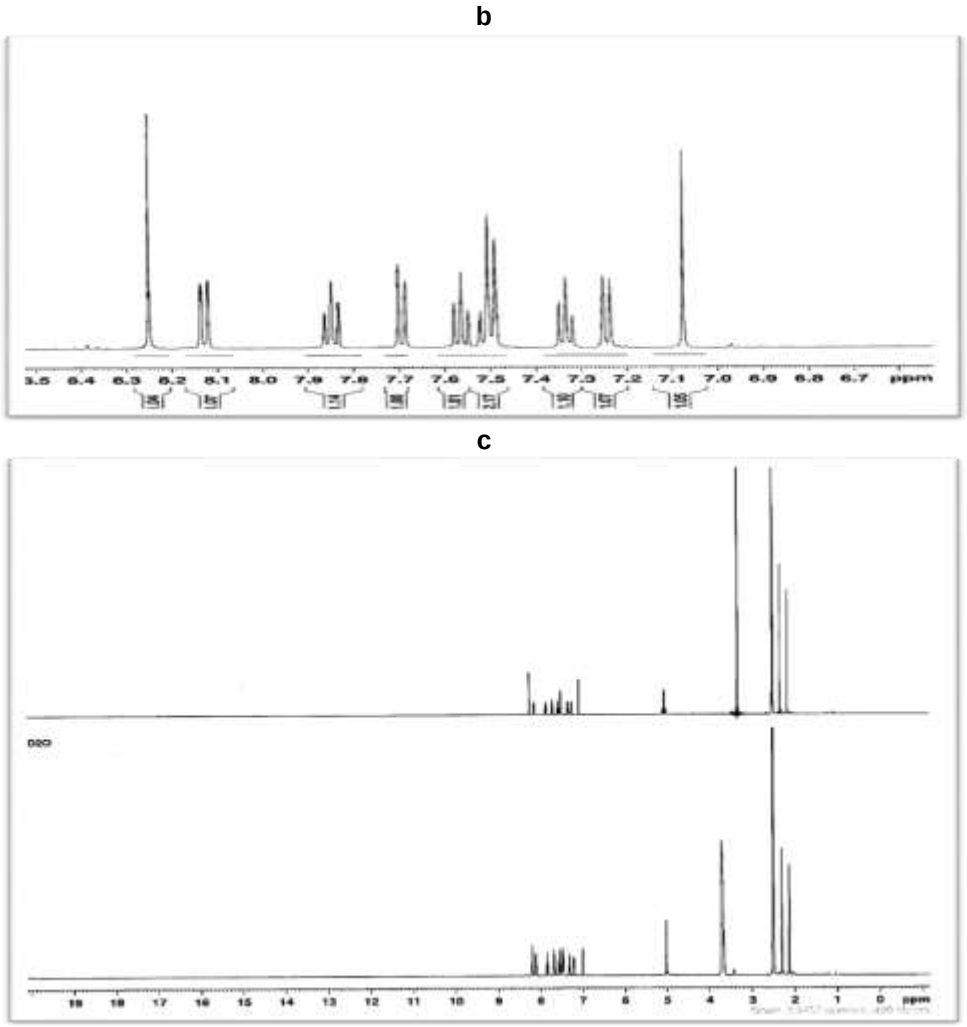


Figure 1 $_{a,b,c}$:1H nmr spectrum of 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4H)-yl) methyl]-1, 3, 4-oxadiazol-2-yl) phenyl acetate in DMSO-d) 5.

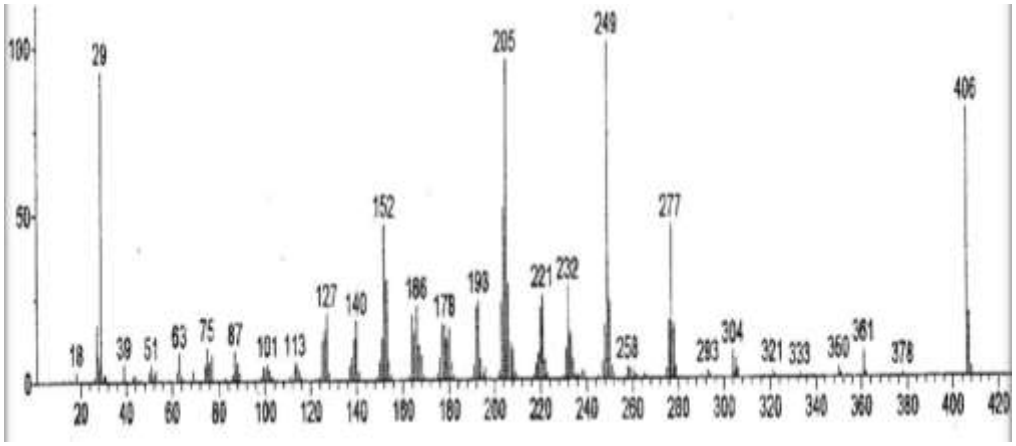


Figure 2: Mass Spectrum of 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4H)-yl) methyl]-1, 3, 4-oxadiazol-2-yl) phenyl acetate 5.

The present result was in the same line with a previous study conducted by Mohamed et al., (2016) who developed novel antitumor molecules containing 4-substituted quinazoline pharmacophore. Also, a another study done by Chen et al., (2016) reported that 30 novel quinazolinyl–diaryl urea derivatives were planned, produced, and screened for their biological data by measuring there antitumor activities against three cancer cell lines A549(denocarcinomic human alveolar basal epithelial cells), HepG2, and MGC-803(human gastric cancer).

In addition, a recent mini-review conducted by Solyanik (2019) reported that the pharmacological effects of quinazolines basically depend on their structure. The restrictive factor is certainly the poor solubility of many quinazoline compounds. Also, high chemical reactivity can thwart the study of their specific antitumor or antimetastatic activities. Although quinazolines symbolize promising “chemical construction set” for creating anticancer drugs with an extensive arsenal of targets for therapeutic intervention.

CONCLUSION

We have presented one synthetic approaches for the synthesis of the 2-(3-acetyl-2, 3-dihydro-5-[(4-oxoquinazolin-3(4H)-yl)-methyl]-1, 3, 4-oxadiazol-2-yl) phenyl acetate. The anticancer activity of the newly synthesized compound was evaluated against liver HepG2, breast MCF-7, and colon HT-29 cancer cell lines. The new compound exhibited relatively potent and selective growth inhibition against the HCF-7 cell line.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors have read and agreed to the content and the publication of this paper.

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