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Synthesis of some novel quinoline-2-one derivatives*with anticipated biological activities

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Abstract

In this work, different functionalized quinoline-2-one derivatives have been synthesized. The targeted compounds were designed to bear chloro, azido, fused tricycle, glycine, and sugar moieties. The synthesized derivatives have been screened for anticancer activity against HCT-116 cell line (human colon carcinoma) using MTT viability assay, for antioxidant activity using in vitro H_2O_2 scavenging activity method basing on iodometric titration with a modification and for antimicrobial activity against Gram-positive bacteria Staphylococcus aureus and Gram-negative bacteria Escherichia coli and against fungus strain of Candida albicans. Quinolone acylated arabinose hydrazone derivative **8** have the privilege amongst all the synthesized derivatives as it showed the best activity as an anticancer with IC_{50} 23.5 μg/mL and it was the sole derivative that exhibited good antibacterial activity against the two strains of the tested bacteria. Results of antioxidant test revealed that quinolinonyl-glycine derivative **10** exhibited excellent H_2O_2 scavenging activity with IC_{50} 20.92 μg/mL that surpassed the activity of ascorbic acid which is used as a reference. All the derivatives exhibited no antifungal activity against Candida albicans.

Keywords: quinoline2one, anticancer, antioxidant, antimicrobial activity

1. Introduction

Quinolines are naturally plant-derived, and a wide variety of their derivatives can be synthesized [1, 2]. The quinolone (oxo-quinoline) ring system is one of the most common heterocycles in drug research [3]. Quinolone derivatives have been utilized extensively in medicinal chemistry due to its privileged structure that shows various pharmacological activities such as anti-bacterial [4], anti-tubercular [5], anti-malarial [6], anti-HIV [7], anti-HCV [8], antitumor [9], anti-cancer [10] and many other biological activities [11, 12].

Presence of various functional groups were always the main reason that bestowed the quinoline ring its biological significance. For instance, presence of chloro-group in the quinoline containing compounds had revealed a great significance since discovery of chloroquine (CQ) as the first antimalarial drug. Furthermore, chlorine is found in the structure of anticancer drug tipifarnib which is basically containing a quinoline -2-one nucleus [13].

Previously published study [14] revealed that substitution of quinoline systems by azido groups enhanced their inhibitory effect on human platelet aggregation. Furthermore, the considerable biological and pharmacological activities of functionalized pyrazoloquinolines have attracted much attention over the past two decades. Also, the pyrazolo[4,3-c]quinoline heterocyclic ring system is a very attractive scaffold in medicinal chemistry as anticancer [15] and anti-inflammatory [16] and anti-oxidant agents [17]. Accordingly, several synthetic approaches have been reported, based on the annulation of the pyrazole ring onto a quino-

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line motif [18] or the quinoline ring onto a pyrazole scaffold [19].

Meanwhile, the synthesis of polycyclic heterosystems derivatives linked to Sugar moieties was reported to possess high antitumor and anti-inflammatory activities [20].

Our object from this study is to introduce different groups to the quinoline-2-one (2-quinolone) ring to investigate the variation in biological activity of it.

2. Experimental

3. Materials and Methods

Thin layer chromatography (TLC) was carried out on silica gel 60 F254 aluminum sheets (E. Merck, layer thickness 0.2 mm) in the following solvent systems, S_1: ethyl acetate/petroleum ether (2:1); S_2: ethyl acetate/petroleum ether (1:1); S_3: methanol/chloroform (1:10). The spots on thin layer plates were detected by UV lamp. Melting points were determined on a Buchi 510 melting-point apparatus. Elemental analyses were performed on a Flash EA-1112 instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. ^{1}H NMR spectra were measured on Bruker spectrometer (300 MHz) NMR Laboratory, Chemistry Department, Faculty of Science, Sohag University. Mass and IR spectra were measured on GC-MS - 2010 Plus W/0230 Shimadzu and FT-IR Spectrometer 4100 JASCO respectively at Micro Analytical Center, Laboratory, Cairo University.

3.1. Synthesis of ethyl 4-chloro-1-(4-methoxyphenyl)-2-oxo-1, 2-dihydroquinoline -3- carboxylate (2).

4-Hydroxy-1-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) (0.44 g, 1.3 mmol) was suspended in $POCl_3$ (3 mL) and heated at 80^{o}C for 1 hr. Then, the mixture was cooled to 0^o C, diluted with water, and neutralized with NaOH (10 N). The resulting solid was filtered and dried.

Faint orange powder (0.36 g, 76.82%), m.p. 148-150^o C R_f=0.19 (S_1).^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J=6.0 Hz , CH_3); 3.80 (3H, s, OCH_3); 4.35 (2H, q, J=6.0 Hz, CH); 6.66 (2H, d, J=6.0 Hz, Ar-H); 6.97-7.18 (5H, m, Ar-H); 7.84 (1H, d, J=6.0 Hz, Ar-H). MS (EI, 70 eV): m/z (%): 357 $[M]^+$. Anal. Calcd. For $C_{19}H_{16}ClNO_4$ (Mol. wt. 357.5): C, 63.78; H, 4.58; N, 3.92; Found C, 64.05; H, 4.76; N, 4.15.

3.2. Synthesis of ethyl 4-azido-1-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (3).

4-Choroquinolinone (**2**) (0.034 g, 0.06 mmol) and sodium azide (0.04 g, 0.6 mmole) were stirred in DMF (30 mL) at 50-60° C for 24 hrs. Then the reaction mixture was poured into 150 mL of ice-water, then kept in refrigerator for 12 hrs. The formed precipitate was filtered washed with water and dried.

Faint brown powder (0.12 g, 50.2%), m.p. 150-154^o C R_f=0.21 (S_1). ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J=6.0 Hz, CH_3); 3.80 (3H, s, OCH_3); 4.39 (2H, q, J=6.0 Hz, CH); 6.67 (2H, d, J=6.0 Hz, Ar-H); 6.99-7.18 (5H, m, Ar-H); 7.93 (1H, d, J=6.0 Hz, Ar-H). MS (EI, 70 eV): m/z (%): 364 $[M]^+$. Anal. Calcd. For $C_{19}H_{16}N_4O_4$ (Mol. wt. 364): C, 62.64; H, 4.40; N, 15.38; Found C, 63.04; H, 4.75; N, 14.95.

3.3. Synthesis of 5-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline-3,4(2H,5H)-dione (4).

4-Choroquinolinone (**2**) (0.034 g, 0.01mmol) was refluxed with hydrazine hydrate (5–7 equiv) in ethanol for 6 hrs., then allowed to cool to room temperature. The precipitate obtained was filtered and dried to yield the desired compound.

Orange powder (0.0123 g, 47.86%), m.p. 220-224^o C R_f=0.08 (S_1). ^{1}H NMR (DMSO) δ 6.51 (1H, d, J=9 Hz Ar-H); 7.10-7.26 (5H, m, Ar-H); 7.46 (1H, t, J=6 Hz, Ar-H); 8.12 (1H, d, J=6 Hz, Ar-H). Anal. Calcd. For $C_{17}H_{13}N_3O_3$ (Mol. wt. 307): C, 66.45; H, 4.23; N, 13.68; Found C, 65.97; H, 4.70; N, 13.96.

3.4. Synthesis of [4-Hydroxy-N-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline]-3-carbohydrazide (5).

Quinoline ester derivative 1 (1 g, 2.9 mmol) was stirred in ethanol with hydrazine hydrate (2.4 mL, 50.0 mmol) for 1 hr., afterwards, the formed precipitate was filtered off, washed with ethanol and

crystallized from methanol to yield the hydrazide **5.**

White powder (0.87g, 90.6%), m.p. 230^o C R_f=0.96 (S_3).^{1}H NMR (DMSO) δ 3.85 (3H, s, OCH_3); 6.63(1H, d, J=8.4 Hz, Ar-H); 7.13-7.61 (5H, m, Ar-H); 8.12 (1H, d, J=8.1 Hz, Ar-H); 10.81 (1H, bs, NH). IR spectrum, ν cm^{-1}: 3431 (OH), 3345 and 3249 (NH_2), 3073 (NH), 1779, 1617 (C=O). Anal. Calcd. For $C_{17}H_{15}N_3O_4$ (Mol. wt. 325): C, 62.77; H, 4.62; N, 12.92; Found C, 62.52; H, 4.92; N, 12.65.

3.5. Synthesis of (E)-4-hydroxy-1-(4-methoxyphenyl)-2-oxo-N'-(arabinose)-ylidene-1,2-dihydroquinoline-3-carbohydrazide (7).

Hydrazide **5** (0.33 g, 1.01 mmol) was refluxed with D-arabinose (0.168 g, 1.12 mmol) and 0.1 mL of glacial acetic acid in methanol in water bath for about 6 hrs. The reaction mixture was set aside to cool to room temperature, then the formed precipitate was filtered off and washed with cold methanol to yield derivative **7**.

Faint yellow powder (0.238 g, 51.3%), m.p. 230^o C R_f=0.14 (S_2). ^{1}H NMR ($CDCl_3$) δ 3.50-3.77-3.82 (5H, m, 3CH, CH_2); 3.87 (3H, s, OCH_3); 4.53-5.68 (4H, m, 4OH); 6.65 (1H, d, J=6.0 Hz, Ar-H); 7.15-7.37 (5H, m, Ar-H); 7.62 (1H, d, J=9.0 Hz, Ar-H); 7.66 (1H, s, CH); 8.17 (1H, d, J=9.0 Hz, Ar-H); 11.23 (1H, bs, NH); 12.87 (1H, s, OH). (EI, 70 eV): m/z (%): 457 [M]$^+$Anal. Calcd. For $C_{22}H_{23}N_3O_8$ (Mol. wt. 457): C, 57.77; H, 5.03; N, 9.19; Found C, 58.01; H, 5.28; N, 9.

3.6. Synthesis of 4-acetoxy-1-(4-methoxyphenyl)-2-oxo-N'-(5-arabinose-1,2,3,4-tetrayltetraacetate)-ylidene-1,2-dihydroquinoline-3-carbohydrazide (8).

4-Hydroxy-1-(4-methoxyphenyl)-2-oxo-N'-(arabinose)-ylidene-1,2-dihydroquinoline-3-carbohydrazide (**6**) (0.136 g, 0.3 mmol) was stirred over night with (0.5 mL, 5 mmol) acetic anhydride in pyridine. Afterwards mixture was poured onto water and the formed precipitate was filtered off.

Yellow powder (0.08 g, 52.4%), m.p. 180-182^o C R_f=0.41 (S_2).^{1}H NMR ($CDCl_3$) δ 2.19 (15H, s, $5CH_3$); 3.87 (3H, s, OCH_3); 6.69 (1H, d, J=6.0 Hz, Ar-H); 6.77 (1H, d, J=6.0 Hz, Ar-H); 7.18-7.6 (5H, m, Ar-H); 7.81 (1H, d, J=6.0 Hz, Ar-H); 8.17 (1H, s, CH); 11.74 (1H, bs, NH). (EI, 70 eV): m/z (%): 668 [M+H] +. IR spectrum, ν cm^{-1}: 2924 (NH), 1782 (C=O), 1736 (C=O), 1648 (C=O). Anal. Calcd. For $C_{32}H_{33}N_3O_{13}$ (Mol. wt. 667): C, 57.57; H, 4.95; N, 6.3; Found C, 57.25; H, 5.25; N, 5.99.

3.7. Synthesis of N-[(4-hydroxy-1-(4-methoxyphenyl)-2-oxo-1,2dihydro-3-quinolinyl)carbonyl] glycine methyl ester (9).

Equimolar amount of ethyl 4-hydroxy-1-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) and glycine ester hydrochlorides are refluxed in toluene in the presence of catalytic amount of triethyl amine using Dean-Stark apparatus for about 6 hrs. After completion, the reaction solvent was evaporated and the residue was dissolved in methyelne chloride, washed with water and dried over anhydrous (Na_2SO_4). The solvent was evaporated to dryness, and the residue was crystallized from petroleum ether/ ethyl acetate to give the desired product.

White powder (0.8 g, 72.7%), m.p. 160^{o}C R_f=0.23 (S_1). ^{1}H NMR ($CDCl_3$): δ 3.76 (3H, s, CH_3); 3.90 (3H, s, OCH_3); 4.18 (2H, d, J=3.0 Hz, CH_2); 6.73 (1H, d, J=9.0 Hz, Ar-H); 7.10-7.28 (5H, m, Ar-H); 7.45 (1H, t, J=9.0 Hz , Ar-H); 8.23 (1H, d, J=9.0 Hz, Ar-H); 10.57 (1H, bs, NH); 16.58 (1H, s, OH). 13C NMR δ 40.9 (CH_2); 52.3 (CH_3); 55.6(O-CH_3); 96.9; 115.5; 115.8; 116.2 (C-7); 122.6; 130; 133.5; 142.7 (aromatic carbons); 159.9; 169.4; 172.8 (C=O). IR spectrum, ν cm^{-1}: 3441 (OH), 3212 (NH), 1629 (C=O), 1297 (C-O). Anal. Calcd. For $C_{20}H_{18}N_2O_6$ (Mol. wt. 382): C, 62.83; H, 4.71; N, 7.33; Found C, 63.27; H, 5.03; N, 7.15.

3.8. Synthesis of N-[(4-hydroxy-1-(4-methoxyphenyl)-2-oxo-1,2dihydro-3-quinolinyl)carbonyl] glycine (10).

Quinoline-Gly methyl ester derivative **8** (0.5 g, 1.31 mmol) was stirred at room temperature in aqueous ethanol with potassium hydroxide (0.2 g, 3.57 mmol) for 1 hr. Afterward, the mixture was poured onto water then acidified with HCl. The formed precipitate was filtered off, washed with water and dried.

Off white powder (0.3 g, 62.3%), m.p.248-250^o C R_f=0.66 (S_2). ^{1}H NMR ($CDCl_3$): δ 3.87 (3H, s,

OCH_3); 4.17 (2H, d, J=5.7 Hz, CH_2); 6.71 (1H, d, J=8.7 Hz, Ar-H); 7.07-7.27 (5H, m, Ar-H); 7.47 (1H, t, J=7.2 Hz , Ar-H); 8.21 (1H, d, J=8.1 Hz, Ar-H); 10.54 (1H, bs, NH); 11.95 (1H, s, COOH); 16.6 (1H, s, OH). IR spectrum, ν cm^{-1}: 3435 (OH), 3237 (NH), 1773 (C=O), 1630 (C=O), 1298 (C-O). Anal. Calcd. For $C_{19}H_{16}N_2O_6$ (Mol. wt. 368): C, 61.96; H, 4.35; N, 7.61; Found C, 62.26; H, 4.65; N, 7.3.

3.9. Anticancer activity

Evaluation of cytotoxicity against HCT-116 cell was achieved in The Regional Center for Mycology & Biotechnology – Al Azhar University using the MTT viability assay [21]. Dimethyl sulfoxide (DMSO), Fetal Bovine serum, MTT and trypan blue dye were purchased from Sigma (St. Louis, Mo., USA). RPMI-1640, HEPES buffer solution, L-glutamine, gentamycin and 0.25% Trypsin-EDTA were purchased from Lonza (Belgium). The relation between surviving cells and drug concentration is plotted to get the survival curve of each tumor cell line after treatment with the specified compound. The 50% inhibitory concentration (IC_{50}), the concentration required to cause toxic effects in 50% of intact cells, was estimated from graphic plots of the dose response curve for each conc.

3.10. H2O2 Scavenging activity

The In vitro H_2O_2 scavenging activity was performed in Botany and Microbiology Department in Suez Canal University- Ismailia. The absorbance was measured by T60 UV-Visible Spectrophotometer-PG INSTRUMENTS.

The hydrogen peroxide scavenging activities of synthesized compounds were carried out using iodometric titration method [22] with a modification.

To a solution of 10 μL of 0.01M hydrogen peroxide and10 μL of concentrations (10, 15 and 20 μg/mL) of the synthesized compounds, the following was added, in order, 2.0 mL of 0.05 M HC1, 0.2 mL of 1 M KI, 0.2 mL of 1 mM ammonium molybdate in 0.5 M H_2SO_4, and 0.2 mL (10%) of starch solution. Twenty minutes after adding the KI, the absorbance was measured (Ascorbic acid was applied as a reference compound) **vs** blank contains the previous mixture without H_2O_2 at 570 nm. The scavenging activity was calculated as follows:

% scavenged (H_2O_2) = [(Ac-At)/Ac] X100

Where **Ac** is the absorbance of control and **At** is the absorbance of the test.

3.11. Antimicrobial Activity

The in vitro antimicrobial activity was performed in Center for Environmental Studies and Consultation-Suez Canal University- Ismailia.

The antimicrobial activities of the synthesized compounds have been screened using two strains of bacteria (Staplylococcus aureus and Escherichia coli) and one strain fungi (Candida albicans). The disc diffusion method technique was adapted for antibacterial activity (Atlas et al., 1999) [23] while the well diffusion technique was used for antifungal activity (Taggand et al., 1971) [24]. Mean zone of the inhibition in mm. beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (20 μg/ disc) concentration of the tested samples for antibacterial evaluation test and (200-300 μM/ μL) concentration of the tested samples for antifungal evaluation test. Ampicillin (10 μg/ disc) was used as positive control while DMSO was used as negative control.

4. Results and discussions

4.1. Chemistry

Ethyl-4-hydroxy-N-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) was chosen as a key compound to start our synthetic rout. This key compound 4-hydroxy-quinoline-2-one derivative was aimed to perform reactions with its hydroxyl group in position 4 to produce chloro **2**, azido **3** and pyrolozo **4** derivatives moreover, carboxylate in position 3 underwent hydrazinolysis and nucleophilic substitution with glycine methyl ester hydrochloride to obtain the corresponding hydrazide **5** and glaycyl derivative **9** respectively. Heating of **1** with $POCl_3$ at 80^oC, resulted in formation of 4-chloro-quinoline-2-one derivative **2** which in turn underwent two different reactions as follows: the first was the reaction with sodium azide in DMF at 50-60^oC

to produce 4-azido-quinoline-2-one derivative **3**. The second was heating with hydrazine hydrate (5–7 equiv) in ethanol under reflux for 4 hours to give 5-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline-3,4(2H,5H)-dione (**4**). ^{1}H NMR spectra of compounds **2** and **3** showed the following signals at (ppm): protons of CH_3-ester appeared at 1.32-1.36 ppm respectively and quartet signal of CH_2 at 4.35-4.39 ppm respectively while protons of methoxy group appeared as singlet signal at 3.8 ppm as well as absence of singlet signal of hydroxyl group proton in the original quinoline whereas, mass spectra of compounds **2** and **3** showed molecular ion peak at m/z 357 and 364 corresponding to the molecular formula $C_{19}H_{16}ClNO_4$ and $C_{19}H_{16}N_4O_4$ respectively.^{1}H NMR spectrum of **4** shows disappearance of signals corresponding to aliphatic protons of ethyl ester group of the starting 4-chloroquinoline.

Hydrazide derivative **5** was obtained by stirring of 4-hydroxy-quinoline-2-one **1** with hydrazine hydrate in ethanol at room temperature. The hydrazide derivative is characterized not only by its higher melting point but also by increase of percentage of nitrogen when compared with the corresponding ester. ^{1}H NMR spectrum of compound **5** showed disappearance of ester protons and singlet peak at 10.81 ppm was attributed to the proton of NH while IR bands at 3249 cm^{-1}3073 were characterized for (NH_2) and (NH) respectively.

To prepare the sugar derivative **7**, Aldol condensation of the hydrazide **5** with D-arabinose **6** was performed in methanol in the presence of catalytic amount of acetic acid at 80^{o}C. Afterwards, the reaction of arabinose derivative **7** with acetic anhydride in pyridine resulted in production of the acetyl derivative **8.** ^{1}H NMR data of these derivatives displayed that multiplet signals between 3.82-2.91 ppm indicated aliphatic protons of the sugar moiety and singlet signals between 5.00-4.38 ppm for protons of OH groups were characterizing derivative **7** whereas a singlet signal at 2.19 ppm is attributed to protons of acetyl groups of derivative **8** in addition tolack of hydroxyl groups signals of parent D-arabinose derivative **7**. Since both derivatives **7** and **8** are basically hydrazones, it is well known that hydrazones may exist as geometrical isomers (E/Z) and as cis/trans rotamers due to the existence of imine functions (C=N) and amide bond (CO–NH) together [25–27]. In ^{1}H NMR spectra of aldehyde-derived compounds, one set of singlet belongs to N=CH and CO–NH protons, indicating the presence of a single isomer of the compounds more likely E isomer. ^{1}H-NMR spectra of these hydrazones showed the presence of signals belonging the proton of –CONH-N and –N=CH groups. The proton of –CONH-N appeared as singlet signal at 11.23 and11.74 ppm while the proton of –N=CH group appeared as singlet signal at 7.66 and 8.17 ppm respectively. Mass spectra compound **7** and **8** showed molecular ion peak at m/z 457 corresponding to the molecular formula $C_{22}H_{23}N_3O_8$ and at m/z 668 corresponding to the molecular formula $C_{32}H_{33}N_3O_{13}$ respectively. The molecular ion of these hydrazone may undergo fragmentation pattern as shown in fig 1 and 2.

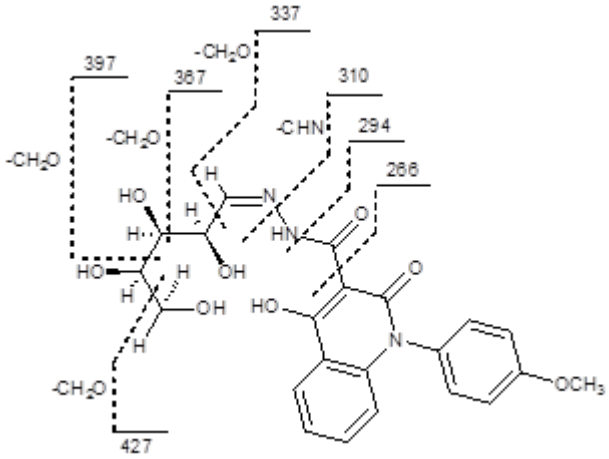


Figure 1: Predicted fragmentation pattern of arabinose derivative 7

Due to intramolecular hydrogen bonding between OH in position 4 and carbonyl group of ester in position 3, the key compound **1** could not couple with Gly-OMe by conventional coupling methods, instead **1** was heated directly in toluene with Gly-OMe in the presence of triethyl amine producing derivative **9.** To investigate the difference between forms of glycine derivative as an ester and free acid in terms of biological activity, N-[(4-hydroxy-1-(4-methoxyphenyl)-2-oxo-1,2dihydro-3-quinolinyl)carbonyl] glycine methyl ester (**9**) underwent saponification by stirring with

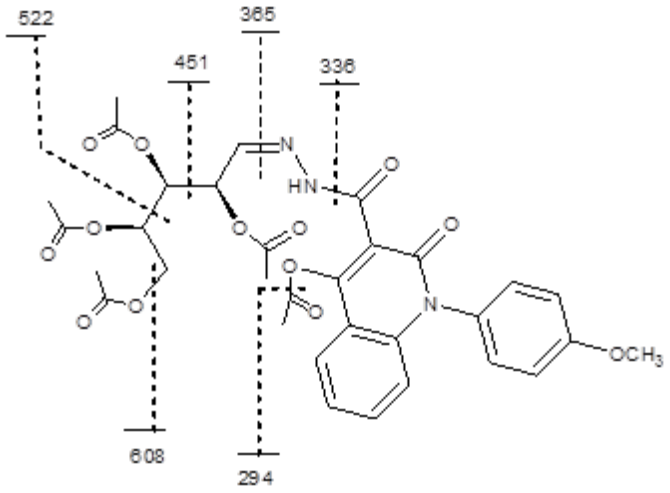


Figure 2: Predicted fragmentation pattern of acylated arabinose derivative 8

aqueous potassium hydroxide in ethanol to give the corresponding quinolinonyl-glycine derivative **10.** The ^{1}H NMR spectrum of this compound **10** revealed the absence of signal corresponding to the ester protons of the start derivative **9** as well as appearance of carboxylic acid proton as singlet signal at 11.95 ppm. The above reaction can be illustrated as the following scheme (1):

4.2. Biological Evaluation

4.2.1. Anticancer activity

All the synthesized derivatives were screened for their anticancer activity against HCT-116 cell line (human colon carcinoma) using MTT viability assay [21] and Cisplatin was used as a positive control. From the data of the test, it is obvious that that the start 4-hydroxy quinoline-2-one derivative **1** was practically inactive (IC_{50} 202.74 μg/mL) however; replacement of hydroxyl with chloro (derivative **2**) and azido (derivative **3**) groups improved the activity significantly with IC_{50} 53.02 μg/mL and IC_{50} 29.61 μg/mL, respectively. Pyrazolo derivative **4** exhibited lower activity than those of chloro and azido derivatives with IC_{50} 75.23μg/mL nevertheless, it is about 3 times more active than the key quinoline furthermore, conversion of ester to hydrazide **5** greatly enhanced the activity with IC_{50} 53.82 μg/mL (fig. 3). On the other hand, Gly-methyl ester derivative **9** did not effectively impacted the activity however, its corresponding free acid derivative **10** showed tangible activity with IC_{50} 69.15 μg/mL (fig. 4) accordingly, it may be concluded that presence of ester (in the key start **1** and its corresponding Gly derivative **9**) does not affect the activity against the HCT-116 cancer cells. When comparing hydrazide **5** with its corresponding sugar hadrazones, it is observed that both arabinose derivative **7** and its acylated derivative 8 have an opposite impact where **7** was dramatically reduced the activity of the original hydrazide while **8** considerably raised it with IC_{50} 23.5 μg/mL (fig. 5). Basing on the IC_{50} values (fig. 6), derivatives that have noticeable activity could be arranged in the following order according to the decrease in potency:

8> 3> 2≈5 > 10 > 4

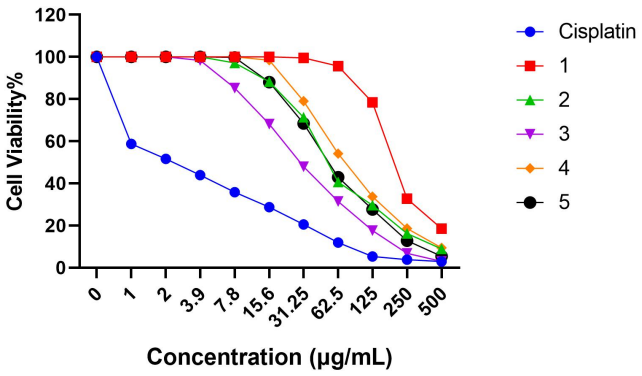


Figure 3: Cytotoxicity of 4-hydroxy-quinoline-2-one 1 and its corresponding substituents 2-5 against HCT-116 cell compared with the Cisplatin

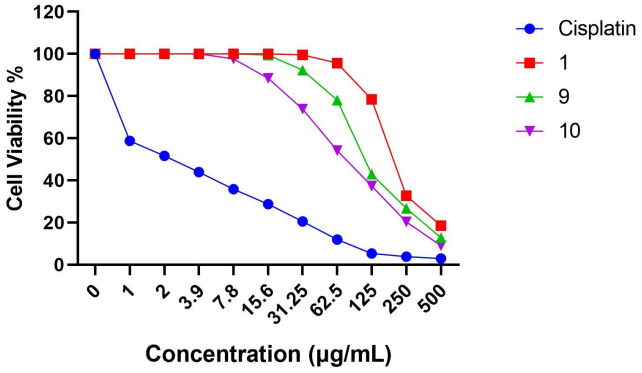
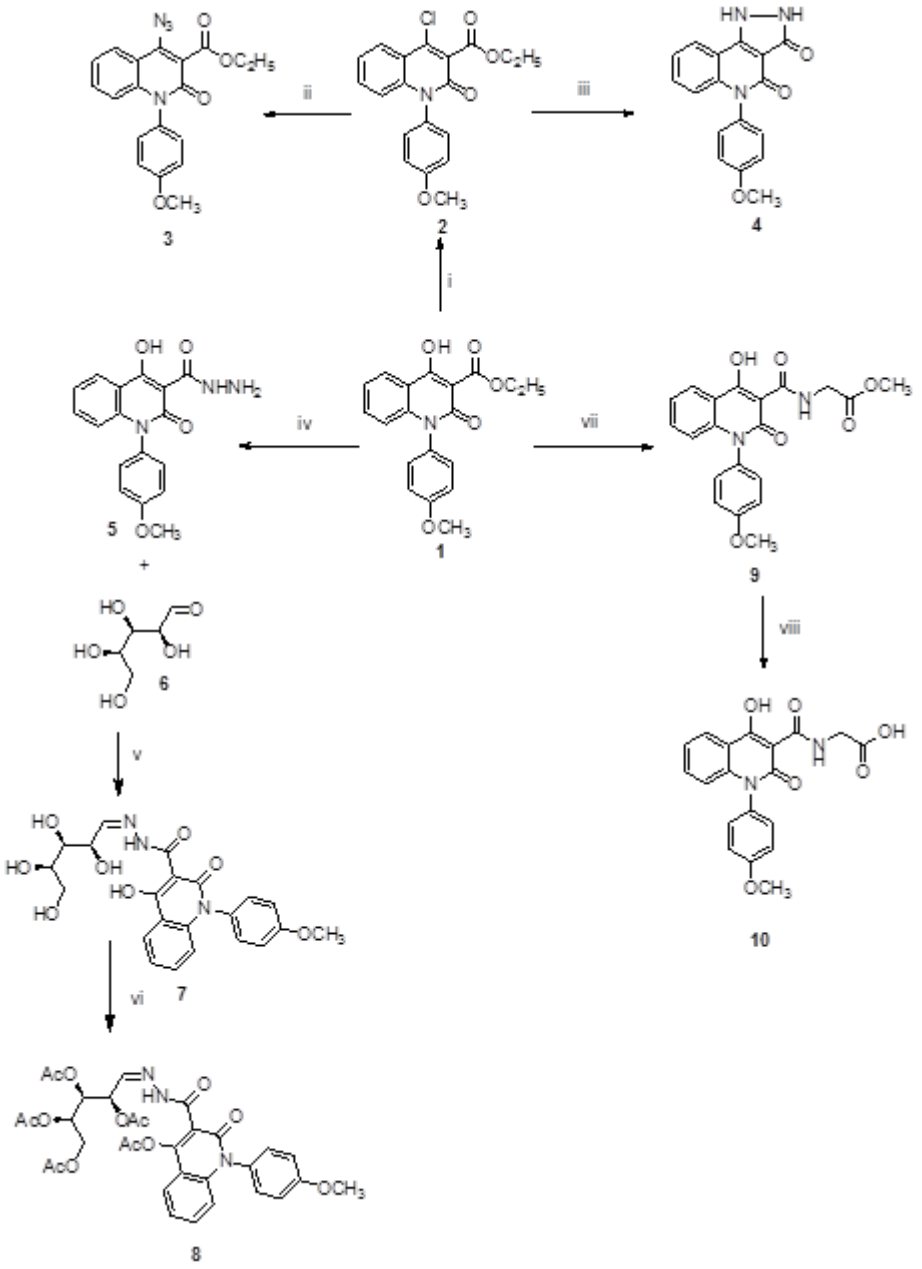


Figure 4: Cytotoxicity of 4-hydroxy-quinoline-2-one 1 and its corresponding Gly-derivatives 9,10 against HCT-116 cell compared with the Cisplatin



Scheme 1: Functionalized 2-quinolone amino acid derivatives. **Reagent and conditions: i)** $POCl_3$, 80^oC, 1h; **ii) NaN** $_3$, 50-60^oC, 24h; **iii)** $N_2H_4.H_2O$, EtOH, reflux; **iv)** $N_2H_4.H_2O$, EtOH, rt, stirring, 1h; **v)** AcOH, MeOH, 80^oC; **vi)** Ac_2O, pyridine; **vii)** Gly-methyl ester hydrochloride, Et_3N, toluene, heat; **vii)** KOH, aq. EtOH, rt, stirring, 1hr.

4.3. Anti-oxidant activity

Hydrogen peroxide scavenging activity was determined by iodometric titration method described in literature [22] which depends on the fact that hydrogen peroxide in the sample reacts with excess potassium iodide in the presence of an ammonium molybdate catalyst to produce iodine, which are subsequently titrated with a standard thiosulfate solution. The detection of the iodine can be enhanced by the addition of starch solution. Adding a fixed amount of sodium thiosulphate to the reaction mixture will react with a fixed amount of iodine therefore, the characteristic iodine/starch blue colour will disappear. A modification to the method was introduced as the titration against sodium thiosulphste was replaced by detecting

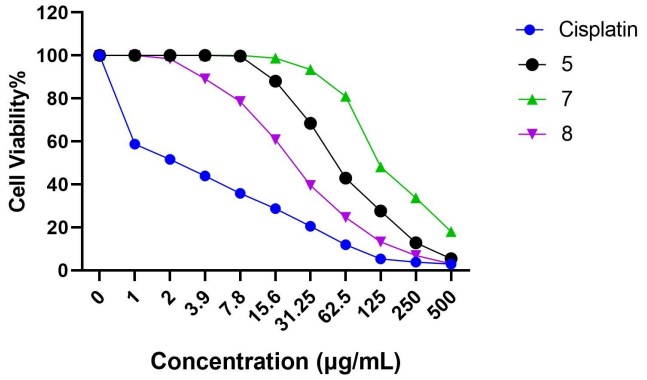


Figure 5: Cytotoxicity of 4-hydroxy-quinoline-2-one hydrazide 5 and its corresponding arabinose hydrazones 7,8 against HCT-116 cell compared with the Cisplatin

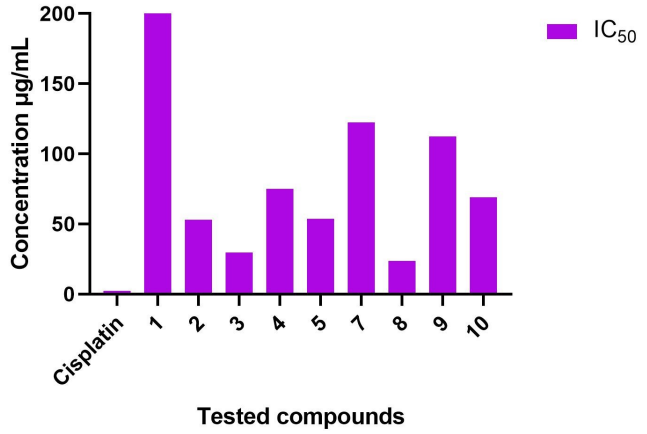


Figure 6: Anticancer activity against HCT-116 of the synthesized derivatives according to their IC50 values compared to Cisplatin

the absorbance of iodine/starch blue colour by UV spectrophotometer at 570 nm. The results of H_2O_2 scavenging activities of compounds were represented in (figs. 7 and 8). According to literature [28], the antioxidant activity related to the compound structure was found to be dependent on the number of the included active groups such as OH or NH_2 therefore, the scavenging activity of derivatives **10**, **1** and **7** that ranged from excellent to good (IC_{50} values 20.92, 37.5 and 47.5 μg/mL respectively) could be due to COOH and OH groups.

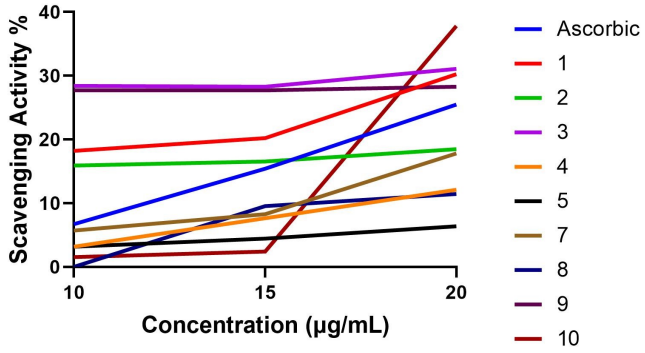


Figure 7: H_2O_2 Scavenging activity of the synthesized derivatives compared to Ascorbic acid

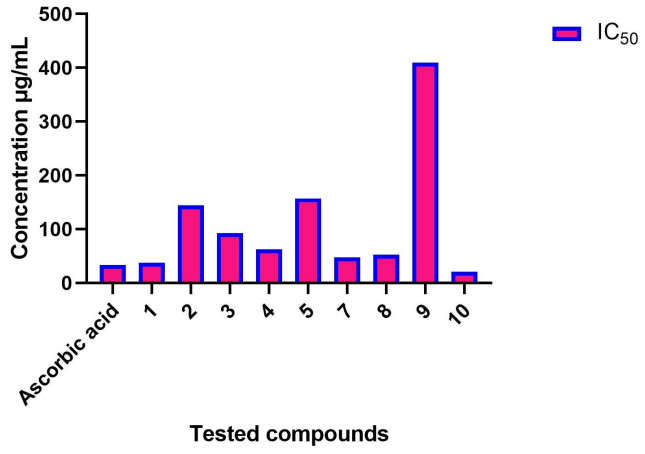


Figure 8: H_2O_2 scavenging activity of the synthesized derivatives according to their IC_{50} values

4.3.1. Antimicrobial activity

Antibacterial results (table 1) revealed that only acylated arabinose derivative **7** exhibited a good activity toward both Gram-negative bacteria Escherichia coli and Gram-positive bacteria Staphylococcus aureus compared to Ampicillin (fig.9). All the synthesized compounds up to 300 μM/μL were inactive against the strain of fungi.

5. Conclusion:

Quinolone acylated arabinose hydrazone derivative **8** showed noticeable activity as an anticancer (IC_{50} 23.5 μg/mL) and antibacterial against the two tested bacteria strains. Accordingly, it is strongly recommended in upcoming work to synthesize a series of acylated sugar hydrazones from

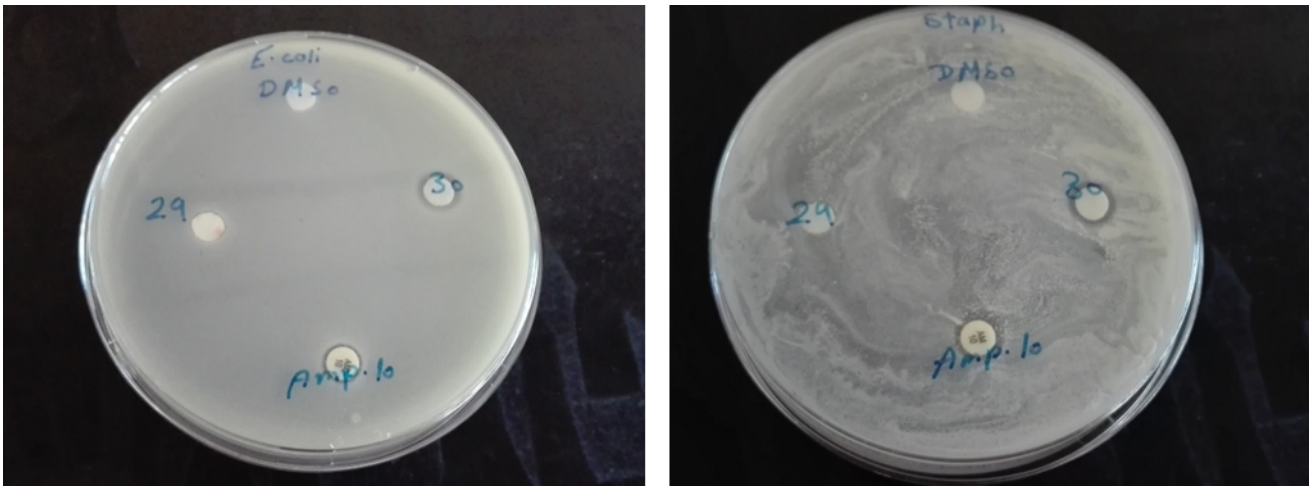


Figure 9: Inhibition zone of acetylated arabinose derivative 8 (coded 30 in the test) against bacteria strains (gram -ve) E. coli and (gram +ve) S. aureus

Table 1: The antibacterial activity of acetylated arabinose derivative 8 compared with Ampicillin

Compound No. 20 μg/ml	**Inhibition Zone (mm)**	
	Bacteria	
	Gram -positive bacteria (S. aureus)	**Gram -negative bacteria** (E. coli)
8	8	7
Ampicillin 10 μg	11	10

our started quinolone. Despite the start quinoline-2-one is practically inactive towards the human colon cancer cells with IC_{50}> 200 μg/mL, replacement of OH in position 4 by azido group (N_3) was considerably raise the activity with IC_{50} value of 29.61 μg/mL accordingly, it might be significant to choose the azido derivative as a promising scaffold. According to H_2O_2 scavenging activity results, derivatives **10** exhibited excellent activity compared to Ascorbic acid as a reference with IC_{50} 20.92 μg/mL.

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