

Novel Quinoline Derivatives as Antitumor Agents Against HepG2 Cells: Synthesis, Characterization, *In Silico*, *In Vitro* and Docking Studies

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ABSTRACT

New quinoline derivatives based on allyl and amino acid were prepared and characterized using elemental analysis (CHN%), ¹H NMR, ¹³C NMR spectra. The theoretical calculations which carried out using different computer programs permit proposing an optimized geometry for the formed complexes. The molecular modeling for some representative compounds were evaluated and discussed. The energy of the HOMO and LUMO was calculated and assessed. The most stable structure of the synthesized compounds was suggested and evaluated its energy. The most benefit properties, which play very important role in drug synthesis referred to the surface properties of the compounds, were evaluated and discussed. The application of the DFT, on the target compounds, gave promising properties required for antitumor drugs. Docking of the synthesized compounds with HepG2-code: 5EQG protein, as liver carcinoma cell, gave promising inhibition *in silico* level. The antitumor activity of the target compounds *in vitro* level gave activity with some compounds exceeded the market drug.

Key words: 5EQG, Antitumor, Docking, DFT, *In Silico*, *In vitro*, Quinoline.

INTRODUCTION

The synthesis of quinoline and its derivatives have attracted considerable attention of chemists in the field of organic and medicinal chemistry for many years (Kouznetsov *et al.*, 2005). The structural core of quinoline is frequently associated with medicinal and pharmaceutical applications (Bénard *et al.*, 2004; Borioni *et al.*, 2007; Desrivot *et al.*, 2007; Musiol *et al.*, 2006). The intensive efforts to find effective therapeutic agents with antiviral and antitumor activities have directed many researchers to synthesize a series of quinoline derivatives or their analogues.

The Pfitzinger reaction is a divergent approach to the synthesis of 2-substituted quinoline-4-carboxylic acids by the reaction of isatin with ketones in the presence of a strong nucleophile (such as hydroxide). Pfitzinger's own studies of the late nineteenth century indicate this reaction is generally efficient (Shvehkheimer, 2004). Zhu and coworkers (Zhu *et al.*, 2010), noting the dearth of methods to obtain quinoline-4-carboxylic acids unsubstituted in the 2-position, utilized the Pfitzinger reaction in combination with selective decarboxylation to obtain these analogs. Elghamry and Al-Faiyz (Elghamry and Al-Faiyz, 2016) investigated the use of enamines as the annulation partner in the Pfitzinger synthesis of 3-aryloketone quinoline-4-carboxylic acids.

Quinoline and its analogs represent privileged moieties in the field of synthetic and medicinal chemistry because of its diverse chemical and pharmacological properties. The broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows the generation of a large number of structurally diverse derivatives (Solomon and Lee, 2011).

Compounds containing the quinoline moieties were found to be the oldest chemicals for the treatment of various diseases (Solomon and Lee, 2011). The extremely drug resistant tuberculosis is a worldwide public health problem in recent years. The wide spread of this

disease is primarily due to the development of resistance to the existing drugs that has concerned researchers throughout the world. There is an urgent requirement of improvement in new drug molecules with newer targets and with an alternative mechanism of action (Koul *et al.*, 2011; Mandewale *et al.*, 2018).

According to the history of the important applications of the quinoline derivatives, this work introduces some new quinoline derivatives with new trend in the level of theoretical and experimental prospects. The new view of the synthesized compounds in the level of *in vitro* and *in silico* was attained to deep prospective view. Also, the anticancer activity of the target compounds was checked using the *in vitro* and *in silico* using the human liver carcinoma cell lines HepG2 (protein code: 5EQG).

MATERIAL AND METHODS

Materials

All chemicals used in this study were of analytical grade. The primitive chemicals (Koch-Light and Sigma-Aldrich) were used as received.

Apparatus

Thin layer chromatography (TLC) was carried out on silica gel type 60-F254 aluminum sheets (E. Merck, layer thickness = 0.2 mm) using the following solvent systems, S1: petroleum ether (40-60 °C)/ethyl acetate (5:1); S2: petroleum ether (40-60 °C)/ethyl acetate (2:1); S3: petroleum ether (40-60 °C)/ethyl acetate (1:1). The obtained spots were detected by UV lamp. Melting points were determined on 300 °C melting point apparatus and the values are used without extra correction. The infrared spectra were obtained in the 4000–400 cm⁻¹ region by using Bruker Alpha instrument with KBr disc technique. ¹H and ¹³C NMR spectra were recorded on Bruker spectrometer operating at 300 and 75.0 MHz uses CDCl₃ as solvent and TMS as internal standard. Elemental analysis was carried out by elementarvario instrument.

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In Vitro anti-tumor activity

The effect of the target compounds on the growth of HepG2 cell lines was evaluated according to the procedure adopted using Skehan method (Skehan *et al.*, 1990). Cisplatin was used as a standard to assess the cytotoxicity of compounds. The capabilities of the synthesized compounds to arrest the proliferation of tumor cells were evaluated after 48h of incubation. The results were analyzed by means of cell viability curves and expressed as IC₅₀ values. Cells were plated in 96-well plate (104 cells/well) for 24h by using RPMI-1640 media before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compound under investigation (1, 5, 10, 25 and 50 mM) were added to the cell monolayer which are then incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO₂.

Synthesis of the Target Quinoline derivatives*(A) Synthesis of 2-oxo-1, 2-dihydroquinoline-4-carboxylic acid (1)*

To a solution of isatin (a) (1g, 6.8 mmol) and malonic acid (b) (0.7 g, 6.7 mmol) in glacial acetic acid (6 ml), fused sodium acetate (0.1 g, 1.2 mmol) was added. The reaction mixture was refluxed for 3h. After cooling to room temperature, the obtained precipitate was filtered off, washed several times with methanol and dried at room temperature to give: 2-oxo-1,2-dihydroquinoline-4-carboxylic acid (1) (Scheme 1), brown powder (1.06 g, 83%), mp > 300 °C, Rf = 0.52 (S4). Anal. Calcd. for C₁₀H₇NO₃ (189.17): C, 63.49; H, 3.73; N, 7.40. Found: C, 63.22; H, 3.89; N, 7.73.

(B) Synthesis of methyl 2-oxo-1, 2-dihydroquinoline-4-carboxylate (2)

To a solution of 2-oxo-1, 2-dihydroquinoline-4-carboxylic acid (1) (0.97 g, 5.1 mmol) in absolute methanol (20 ml), concentrated Sulphuric acid (2 ml) was added dropwise. The reaction mixture was refluxed in a water bath for 13h. After cooling to room temperature, a solution of sodium carbonate was added. The formed precipitate was filtered off, washed with methanol several times, and then left at room temperature to dry, yielding: methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (2) (Scheme1): fainty pink powder (0.8 g, 76.9 %), mp 238 °C, Rf = 0.50 (S2). ¹HNMR (300.0 MHz, CDCl₃): δ = 12.10 (1H, br, NH), 8.02 (1H, d, J = 9.0 Hz, ArH), 7.56 (1H, t, J = 9.0, Hz, ArH), 7.38 (1H, d, J = 9.0 Hz, ArH), 7.23 (1H, t, J = 9.0 Hz, ArH), 6.90 (1H, s, ArH), 3.92 (3H, s, CH₃). ¹³CNMR (75.0 MHz, CDCl₃): δ = 166.0 (CO), 161.2 (ArCO), 140.3, 139.8, 131.4, 126.3, 124.5, 122.7, 116.3, 115.3 (Ar-C), 53.3 (OCH₃). Anal. Calcd. for C₁₁H₉NO₃ (203.20): C, 65.02; H, 4.46; N, 6.89; Found: C, 64.93; H, 4.77; N, 7.08.

(C) Synthesis of methyl 2-(allyloxy) quinoline-4-carboxylate (3), methyl 1-allyl-2-oxo-1, 2-dihydroquinoline-4-carboxylate (4)

To a solution of methyl 2-oxo-1, 2-dihydroquinoline-4-carboxylate (2) (5 g, 24.61 mmol) in dry dimethylformamide (30 ml), sodium hydride 60% (1.5 g, 62.50 mmol) was added dropwise. The reaction mixture was

refluxed for 1h then cooled to room temperature. An allyl bromide (5 ml, 41.32 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured on water (100 ml) in a beaker. The resultant mixture was extracted with chloroform (100 ml) and washed with water, dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated at room temperature. The residue was treated by column chromatography using petroleum ether (40-60 °C)/ethyl acetate (20:1, 15:1, 10:1) as eluent. The solvent was evaporated at room temperature. The products were chromatographed by petroleum ether (40-60 °C)/ethyl acetate (5:1) to give a mixture from methyl 2-(allyloxy) quinoline-4-carboxylate (3), and methyl 1-allyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (4) (S-scheme 1).

(C1) Synthesis of methyl 2-(allyloxy) quinoline-4-carboxylate (3)

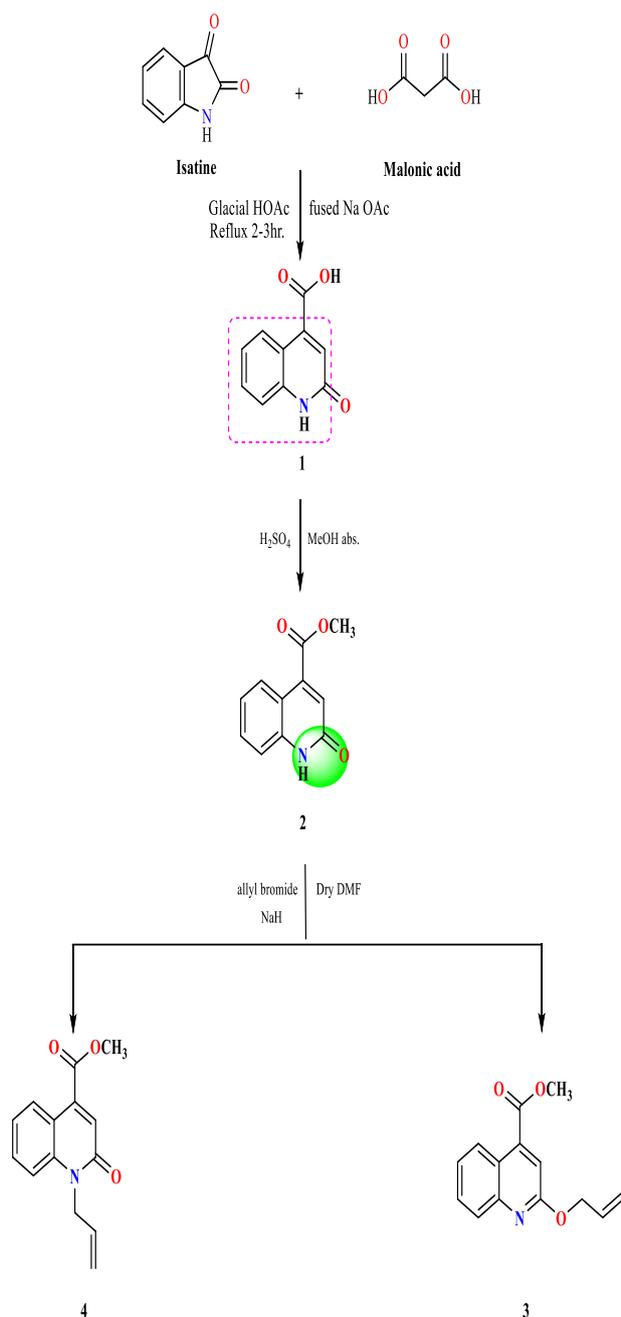
Yellow crystal (3.0 g, 50%), Rf = 0.70 (S2). ¹HNMR (300.0 MHz, CDCl₃) δ = 8.62 (1H, d, J = 9.0 Hz, ArH), 7.90 (1H, d, J = 9.0 Hz, ArH), 7.68 (1H, t, J = 9 Hz, ArH), 7.52-7.46 (1H, m, ArH), 7.28 (1H, s, ArH), 6.25-6.11 (1H, m, CH=), 5.49, 5.32 (2H, d, J = 18.0, 12.0 Hz, =CH₂), 5.06 (2H, d, J = 6.0 Hz, OCH₂), 4.03 (3H, s, OCH₃). ¹³CNMR (75.0 MHz, CDCl₃) δ = 166.2 (CO ester), 160.9 (Ar-CO), 147.5, 137.9 (Ar-C), 133.2 (=CH), 129.8, 127.7, 125.5, 125.2, 122.0 (Ar-C), 117.8 (=CH₂), 115.4 (Ar-C), 66.8 (OCH₂), 52.6 (OCH₃). Anal. Calcd. for C₁₄H₁₃NO₃ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.44; H, 5.58; N, 5.80.

(C2) methyl 1-allyl-2-oxo-1, 2-dihydroquinoline-4-carboxylate (4)

Yellow oil, Rf = 0.60 (S2). ¹HNMR (300.0 MHz, CDCl₃) δ = 8.21 (1H, d, J = 9.0 Hz, ArH), 7.45 (1H, t, J = 9.0 Hz, ArH), 7.26 (1H, d, J = 9.0 Hz, ArH), 7.15 (1H, t, J = 9.0 Hz, ArH), 7.10 (1H, s, ArH), 5.92-5.79 (1H, m, CH=), 5.13, 5.01 (2H, 2d, J = 12.0 Hz, J = 15.0 Hz, =CH₂), 4.86 (2H, d, J = 6.0 Hz, CH₂-N), 3.90 (3H, s, OCH₃). ¹³CNMR (75.0 MHz, CDCl₃) δ = 165.6 (CO ester), 160.7 (Ar-CO), 139.5, 138.7 (Ar-C), 131.3 (CH=), 131.0, 127.0, 124.0, 122.5, 117.4 (Ar-C), 117.2 (=CH₂), 115.1 (Ar-C), 52.7 (OCH₃), 44.7 (NCH₂). Anal. Calcd. for C₁₄H₁₃NO₃ (243.26): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.87; H, 5.64; N, 5.62.

(D) Synthesis of 2-(allyloxy) quinoline-4-carbohydrazide (5)

To a solution of ester (3) (1.6 g, 6.5 mmol) in methanol (30ml), hydrazine hydrate (2 ml, 41.11 mmol) was added. The reaction mixture was refluxed for 6h. After cooling to room temperature, the precipitated hydrazide was filtered off, washed with water and methanol followed by crystallization from aqueous methanol to yield: 2-(allyloxy)quinoline-4-carbohydrazide (5) (Scheme 2), white powder (1.2 g, 75.0%), m.p 168 °C, Rf = 0.67 (S₂). ¹HNMR (300.0 MHz, CDCl₃) δ = 9.88 (1H, br, NH), 8.05 (1H, d, J = 9.0 Hz, ArH), 7.80 (1H, d, J = 9.0 Hz, ArH), 7.72-7.67 (1H, m, ArH), 7.48-7.43 (1H, m, ArH), 6.97 (1H, s, ArH), 6.25-6.12 (1H, m, CH=), 5.52, 5.34 (br, NH₂). ¹³CNMR (75.0 MHz, CDCl₃) δ = 165.8 (CO), 161.5



Scheme (1): Synthesis of quinoline-allyl derivatives.

(Ar-CO), 146.8, 144.6 (Ar-C), 133.3 (CH=), 130.5, 127.5, 125.9, 124.9, 122.1 (Ar-C), 117.8 (=CH₂), 111.7. (Ar-C), 67.7 (OCH₂). Anal. Calcd. For C₁₃H₁₃N₃O₂ (243.27): C, 64.19; H, 5.39; N, 17.27 Found: C, 64.02; H, 5.69; N, 17.

(E) General procedure for the synthesis of *(E)*-2-(allyloxy)-*N'*-(benzylidene) quinoline-4-carbohydrazone derivatives (6a-c)

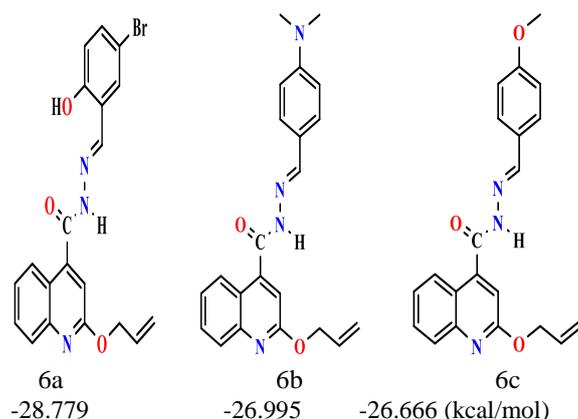
A mixture of hydrazide (5) (0.34 g, 1.4 mmol), aromatic aldehyde (1.4 mmol) and drops of acetic acid were refluxed in ethanol (30 ml) for 4-6 h. After cooling to room temperature, the resulting solid was filtered off, washed with ethanol and crystallized from aqueous ethanol to afford the corresponding hydrazone derivatives (6a-c) (Scheme 2).

(F) Synthesis of 2-(allyloxy)-quinoline-4-carboxamide (7a-e)

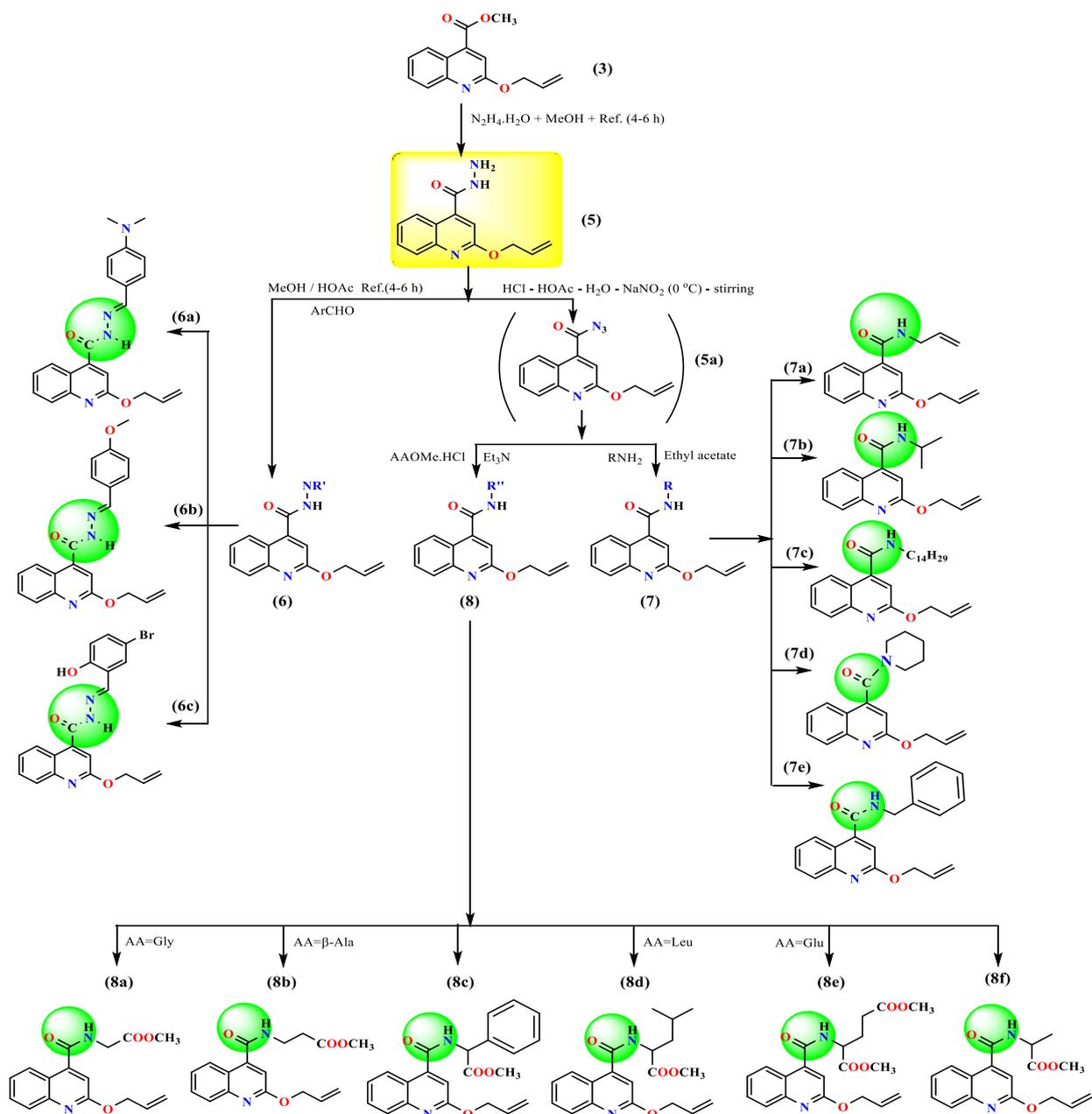
Azide coupling method: To a cold solution (-5 °C) of hydrazide (5) (0.48 g, 1.97 mmol) in acetic acid (10 ml), conc. hydrochloric acid (10 ml) and water (20 ml) was added a solution of sodium nitrite (2 g, 29 mmol) in cold water (20 ml). After stirring at the same temperature for 15 minutes, the faintly yellow syrup was formed. The azide was extracted with cold ethylacetate, washed with cold 5% Na₂CO₃, and then dried over anhydrous sodium sulphate. The obtained azide was used directly without further purification in the next step (5a). The previously prepared cold dried solution of azide was added to the target amines (a-e) (9.3 mmol) in ethylacetate (20 ml) for each one. Afterwards the reaction mixture was kept 24 h in refrigerator and then at room temperature for another 24 h. Then treated by washing with 5% HCl, 5% Na₂CO₃ and water. Dried over anhydrous Na₂SO₄. The solvent was evaporated, and the residue was precipitated in petroleum ether (40%-60%). Afterwards crystallized from PE to give 2-(allyloxy) quinoline-4-carboxamide (7a-e) (Scheme 2).

(G) Synthesis of methyl (2-(allyloxy) quinoline-4-carbonyl)glycinate (8a-f)

To a cold solution (-5 °C) of hydrazide (5) (0.75 g, 3.0 mmol) in HOAc (10 ml), conc. HCl (10 ml), and water (50 ml) was added a solution of NaNO₂ (2g, 29 mmol) in cold water (50 ml). After stirring at -5 °C for 15 min., the faint yellow syrup was formed. The azide was extracted with cold ethylacetate, washed with cold Na₂CO₃ (5%) then dried over anhydrous sodium sulphate, the azide was then used directly without further purification in the next step (5a). Amino acid methyl ester hydrochloride (AAOMe, HCl, 5.5 mmol), was stirred in ethylacetate (30 ml) with triethyl amine (1 ml) at 0 °C for 20 minutes. The formed triethyl amine hydrochloride was filtered off and the filtrate was added to the previously prepared cold dried solution of azide (5a).



Afterwards the reaction mixture was kept 24h in refrigerator and then at room temperature for another 24h. The reaction mixture was washed with 5% HCl, 5% Na₂CO₃ and water, then dried over anhydrous Na₂SO₄. The solvent was evaporated, and the residue was precipitated in petroleum ether (40%-60%) (Scheme 2).



Scheme (2): Synthesis of 2-(allyloxy)quinoline-4-carbohydrazone derivatives.

RESULTS AND DISCUSSION

Chemistry

The obtained quinoline derivatives were in pure form and gave the characteristic signals in the ^1H NMR and ^{13}C NMR analysis.

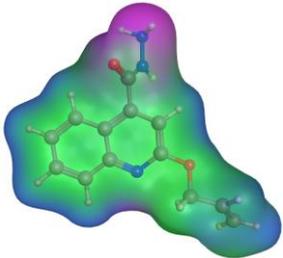
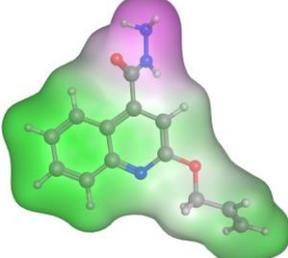
Molecular Modeling and DFT

The most benefit properties which play very important role in drug synthesis were referred to the surface properties of the compounds. The interaction of the drug with the living cells referred to the presence of active lone pair and the lipophilic character. Table 1 showed the active lone pair and lipophilic maps of the most abundant conformations of the compound 5 (as one

demonstrative examples) using molecular operating environment (MOE) 2008.10 molecular modelling (Chemical Group Inc., 2008). The active lone pair map was denoted by three colors: violet = H-bonding, green = Hydrophobic and blue = Mild polar. The H-bonding ability was concentrated in one site. The hydrophobic properties go well with the H-bonding ability.

The lipophilic map was represented using different colors, where violet = Hydrophilic, white = Neutral and green = Lipophilic. Compound 5 gave wide green area, which indicates the large lipophilic behavior of this compound. The obtained data gave some hints about the ability of the compound 5 to be act as active compounds towards the living cells (drug) (Hisaindee *et al.*, 2015; Musiol *et al.*, 2006; Shahzad *et al.*, 2015; Wang 2012).

Table (1): The surface properties of the synthesized compound 5.

Compound	Active lone pair map	Lipophilic and hydrophilic map
5	 <p>Violet = H-bonding Green = Hydrophobic Blue = Mild polar</p>	 <p>Violet = Hydrophilic White = Neutral Green = Lipophilic</p>

In Silico Docking studies

All molecular modeling studies were performed on a Hewlett-Packard Pentium Dual-Core T4300 2.10 GHz running Windows 7 Ultimate using molecular operating environment (MOE) 2008.10 molecular modeling software (Chemical Group Inc., 2008). HepG2 was downloaded in PDB format from the Protein Data Bank (PDB) web site and used in the docking studies "(PDB; protein data bank, <http://www.rcsb.org/pdb>," 2011). The docking studies were performed after deleting the co-crystallized inhibitors from the active site. Target compounds were then docked within the active site of the crystallized structures using the MOE dock tool in MOE, performed with the default values. The active site was defined by all the amino acid residues involved in the interaction with the co-crystallized inhibitors.

The docking work of the synthesized compounds with HepG2 (code: 5EQG protein) as human liver carcinoma was listed in Table 2 and shown in Figure 1. The obtained data could be discussed generally as the following:

1. Generally, the substituted hydrazide compounds gave binding energy larger than the free hydrazide compounds.
2. The increasing of the aliphatic side chain strongly enhanced the binding affinity.
3. The allyl derivatives gave largest binding energy when comparing with compounds free from the allyl chain.
4. The variation of R' on compound 6, gave nearly comparable binding affinity.
5. The binding affinity order for the synthesized compounds could be generally arranged as the following: O-allyl > N-allyl > un-allyl compound.

In vitro Anti-Tumor Activity

The IC₅₀ of the target compounds (Table 3) are almost close with the reference drug Doxorubicin (DOX). Generally, the obtained data reveal the very promising compounds as anticancer agents and it suitable to applied deep studies *in vivo* level.

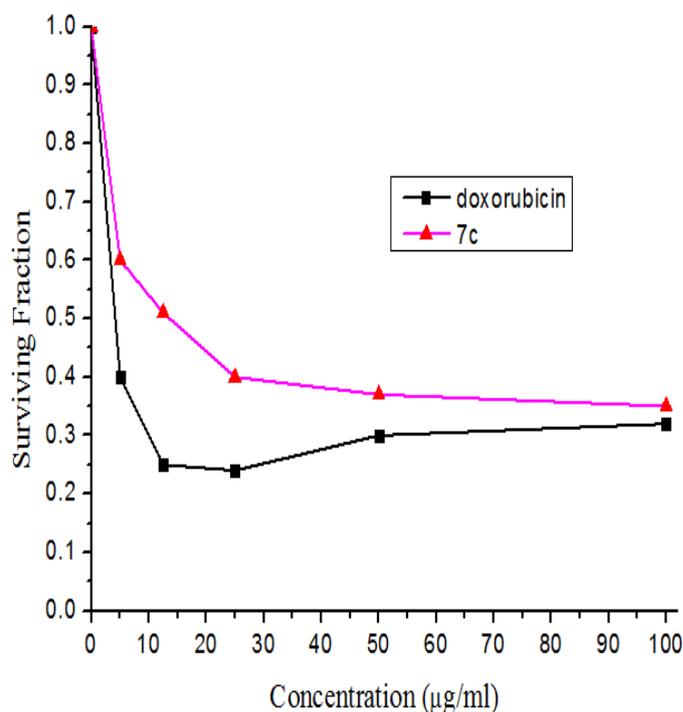


Figure (1): The variation of the tumor cell viability of Human liver carcinoma cell line (HepG2) with the target compound at different concentrations.

Table (2): The binding energy of some target compounds with HepG2 (5EQG protein).

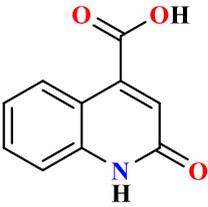
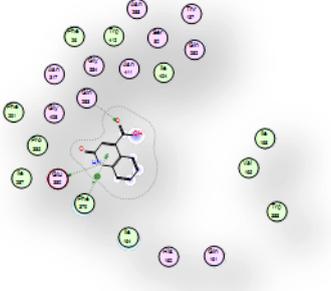
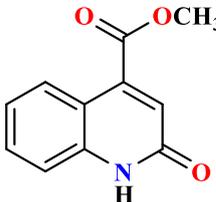
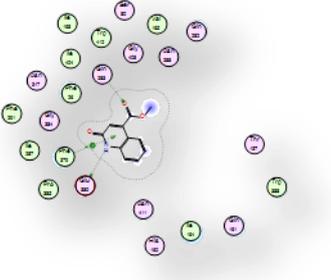
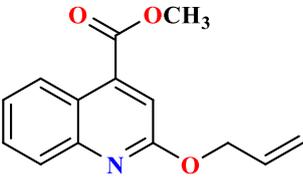
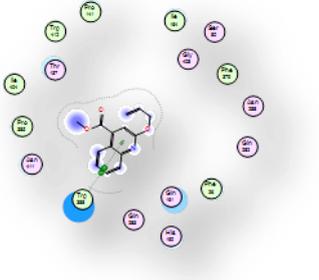
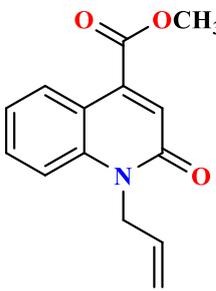
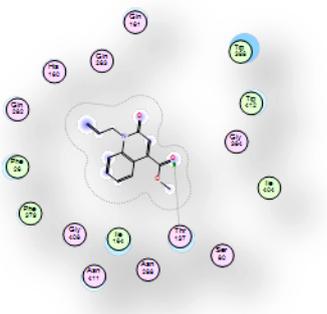
Compound number	Compound Structure	2D view of the docking result	Number of bonds	Binding Energy (kcal/mol)
1			3	-16.2087
2			3	-16.1979
3			1	-19.4590
4			1	-18.2852

Table (3): *In vitro* cytotoxic activity of the target compounds with HepG2 (5EQG protein).

Compound	Concentration (ug/ml)	Mean \pm SD	IC50 (ug/ml)
7c	0	1.00 \pm 0.033	13.456
	5	0.6 \pm 0.056	
	12.5	0.51 \pm 0.077	
	25	0.4 \pm 0.043	
	50	0.37 \pm 0.055	
	100	0.35 \pm 0.062	
Doxorubicin	0	1.00 \pm 0.033	4.059
	5	0.4 \pm 0.043	
	12.5	0.25 \pm 0.023	
	25	0.24 \pm 0.044	
	50	0.3 \pm 0.056	
	100	0.32 \pm 0.044	

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مشتقات الكينولين الجديدة كعوامل مضادة للسرطان للخلايا HepG2 : تحضير و توصيف والطرق الحسابية والطرق المعملية ودراسة عملية الإدخال

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الملخص العربي

مشتقات الكينولين الجديدة والتي تحتوى على الأحماض الأمينية ومجموعة الأليل قد تم تحضيرها وتوصيفها باستخدام التحاليل العنصرية والرنين النووى المغناطيسى. التراكيب الفراغية المستقرة قد تم حسابها باستخدام بعض برامج الكمبيوتر الحديثة. النمذجة الجزيئية قد تم حسابها والتعبير عنها وكذلك مناقشتها فى ضوء الأسس العلمية المختصة. تم حساب قيمة HOMO وكذلك LUMO للمركبات وكذلك مناقشتها. تم عمل Docking للمركبات المحضرة مع بروتين خلايا الكبد السرطانية وتم مناقشتها فى ضوء المستوى الحسابى.