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Design, synthesis and characterization of a new series of 2,3-dihydroquinazolin-4(1H)-one (DHQZ-1) derivatives and evaluation of antitumor resistant (by Molecule Docking)

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Abstract

The objective of this work is to use multicomponent reactions (MCRs) to produce a novel series of quinazoline derivatives with high yield. This occurs in one-pot condensation among Pyridine-3-carbaldehyde with 1*H*-3,1-benzoxazine-2,4-dione (Isatoic anhydride) and primary amines (**3-7**). The mixture refluxed into tetrahydrofuran (THF, aprotic solvent). It is carried out with sodium hydrogen sulfate ($NaHSO_4$) that is catalytically present, to afford a high yield of the 2,3-dihydroquinazolin-4(1H)-one derivative. The best yield has been obtained at 68°C. In general, all the products in the series (**8-12**) show a great ability as potent anticancer of the breast using a molecular docking study of the derivatives, point towards compound **11**, it shows the greatest investigated as an anticancer of the breast activity than the other prepared compounds. The evaluation of molecular docking studies of derivatives is carried out via using Auto Dock 4.2 drug design software (PDB, protein code 1M17).

Keywords: Antitumor resistant (protein 1M17), 2,3-Dihydroquinazolin4(1*H*)-one (**DHQZ-1**), Isatoic anhydride, Multi-component reactions (MCRs), Molecular Docking, Pyridine-3-carbaldehyde.

Introduction

Tumour can be defined as a kind of disease that has widespread unusual cell growth and attack of cells and tissues [1]. Examination of new cancer-treatment agents is a significant area in chemistry for the synthesis of new medicinal compounds. Fused-heterocyclic components containing nitrogen are essential for intercalating cancer agents as small molecule medications or synthetic compounds [1-4] as well as physiologically active natural items, could act as an anti-inflammatory, antimicrobial, anticancer, and anticonvulsant properties [5-8], analgesic, antihypertonic diuretic, antihistamine, antidepressant and vasodilation activities [9-11]. (DHQZ-1) is a large family that attracts extraordinary attention because of its biological activity. (DHQZ-1) is a compound containing two fused rings, a phenyl ring, and a heterocyclic (six-membered ring) containing two nitrogen atoms in both positions 1 and 3, and a

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carbonyl group on a C4 position (as a lactam) Fig. 1. The (DHQZ-1) derivative is frequently replaced at the chiral centre, which is position 2 (C2), due to their important and attractive properties, as these derivatives are a common synthetic medium for organic chemists. There are several different methods for preparing them as racemic mixtures, which have been published in numerous literature [12].

Generally, achievements have been in the presence of different types of catalysts, such as: 3-butyl-1-methylimidazollium bromide ([BMIM]Br) [13], $Au(III)Cl_3$ [14], IL@MNP (ionic liquid) [15], Amberlite-15 [16], Bismuth- catalysed (BiX_3) [17], or under thermal condition with solvent-free conditions [18]. Nevertheless, the majority of these procedures have some drawbacks, such as expensive catalysts (reagents), low yields, a high reaction time and so on [19].

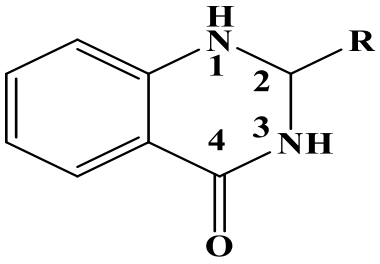

Figure 1. Show the structure of the DHQZ-1.

Several methods for synthesizing these compounds via multicomponent condensation reactions have been reported [20-23]. Due to their productivity, convergence, straightforward procedures, simplicity of execution, and use in the synthesis of physiologically active heterocyclic compounds, multicomponent reactions (MCRs) have been recognized as crucial techniques [24]. The one-pot synthesis of various useful heterocyclic compounds using MCRs is of outstanding interest in the most recent research papers [25-32]. Multicomponent reactions (MCR) is a term coined for chemical reactions in which at least three molecules combine to generate a single product that maintains all or most of the atoms of the starting components [33]. MCRs have numerous obvious advantages over multistep processes, including: low cost, high efficiency, decreased waste formation, and a short reaction time [34]. The computerized technique used to examine molecular behaviour (as an anticancer agent) in target protein binding is called molecular docking. It is broadly utilized in the drug development process. One of the best docking software programs is AutoDock, Vina, MOE-Dock, FLexX, and GOLD, in that order. GOLD and LeDock are employed for predicting the appropriate binding poses [35].

Our study focuses on the derivatization of a new series of MCRs from Isatoic anhydride **1**, Pyridine-3-carbaldehyde **2**, and primary amines (aliphatic and aromatic) **3-7** was mixed with tetrahydrofuran (THF, as an aprotic solvent), furthermore, sodium bisulphate ($NaHSO_4$) used as a catalytic at different temperatures (50, 60, and 68°C) to produce BDHQZ-1 derivatives **8-12**. Subsequently, the produced compounds were estimated by Molecular docking for their anticancer activity (breast cancer protein 1M17) to theoretically identify them as anticancer agents, the schematic diagram for this investigation is shown in Fig. 2.

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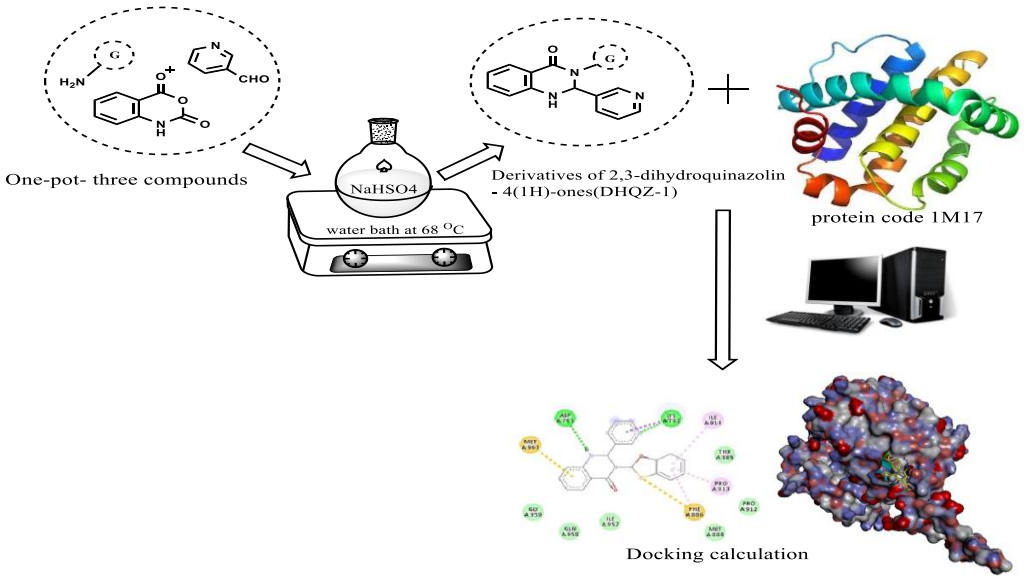

Figure 2. Schematic diagram of this study.

Experimental section

Chemical materials and Instruments

Sigma-Aldrich and Merck were the sources for all reagent-grade chemicals and solvents (Isatoic anhydride, Pyridine-3-carbaldehyde, pyridin-3-amine, 4-aminobenzenesulfonic acid, 4-amino-2-hydroxynaphthalene-1-sulfonic acid, 7,7a-dihydrobenzo[d][1,3]oxathiol-2-amine, 4-aminobenzoic acid , ethanol (99%), tetrahydrofuran (THF)(99%), sodium bisulfate ($NaHSO_4$) . We didn't purify any of the reagents further; we just used them all. The synthesized compounds were subjected to thin layer chromatography (TLC) analysis to ensure the completion of the reaction. The products have been purified by crystallization. Melting points (m.p.) were recorded on a binocular microscope XT-4 (Beijing Tech Instrument 55, China). Infrared spectra were recorded with a Fourier infrared (FT-IR) spectrometer from Bruker, Germany, In the frequency range (4000-400) cm^{-1}, ^{1}H-NMR spectra were recorded on a 400 MHz NMR spectrometer, Broker Biosoin GmbH 400 MHz, Germany, using DMSO-d6 as a solvent and using tetramethylsilane (TMS) as an internal standard. All chemical changes were represented in parts per million (ppm).

Method of one-pot three-component condensation

Synthesis of 2,3-Dihydroquinazolin4(1*H*)-ones derivatives (8-12)

Isatoic anhydride (1 mmol), Pyridine-3-carbaldehyde (1 mmol), and primary amines (1 mmol) (see Scheme 1) were mixed in 50 ml of water, ethanol, tetrahydrofuran (THF), separately, in the presence of catalytic sodium bisulfate ($NaHSO_4$) (3.6 mmol). Each mixture was stirred and refluxed by using a water bath at the appropriate temperature (see Table 1) for 3 h. TLC is used to monitor the reaction's development and confirm it (dichloromethane (DCM): ethyl acetate, 8:2). After the reaction is completed, the mixture is left to cool to the ambient temperature**.** The crud compound was recrystallized with ethanol to obtain pure products (**8-12**). The physical and chemical properties of the new products have been studied by using some spectroscopic methods, such as FT-IR and ^{1}H-NMR, see Supplementary Information S3-12, spectrum to complete the diagnosis of these prepared compounds, as shown in Tables 1 and 2.

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Table 1. Physical-chemical and analytical data for compounds.

Compd. No	Name of Product	Solvent			Yield % at temp.			m.p. °C	Mol. formula (Mol. Wt.)	Colour
		H_2O	EtOH	THF	50° C	60° C	68° C			
8	3-(pyridin-2-yl)-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one	×	×	√	30	37	**66**	205 - 207	$C_{18}H_{14}N_4O$ (302.34)	Dark yellow
9	4-(4-oxo-2-(pyridin-3-yl)-1,4-dihydroquinazolin-3(2H)-yl)benzenesulfonic acid	×	×	√	24	34	**63**	198 - 200	$C_{19}H_{15}N_3O_4S$ (381.41)	White
10	2-hydroxy-4-(4-oxo-2-(pyridin-3-yl)-1,4-dihydroquinazolin-3(2H)-yl)naphthalene-1-sulfonic acid	×	×	√	×	39	**68**	201 - 203	$C_{23}H_{17}N_3O_5S$ (447.47)	Yellow
11	3-(7,7a-dihydrobenzo[d][1,3]oxathiol-2-yl)-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one	×	×	√	×	26	**59**	197 - 199	$C_{20}H_{17}N_3O_2S$ (363.44)	Yellow
12	4-(4-oxo-2-(pyridin-3-yl)-1,4-dihydroquinazolin-3(2H)-yl)benzoic acid	×	×	√	29	33	**72**	195 - 197	$C_{20}H_{15}N_3O_3$ (345.36)	White

X = no reaction has been observed, √ = the reaction has been observed

Table 2. Spectral data for compounds, see Supplementary Information S3-12.

Compound No	Type	Data (δ (ppm))
8	FT-IR (cm^{-1})	1630($C=O_{amide}$), (2977,2874) ($C-H_{alph.}$) , 3115($C-H_{Arom.}$), 3219(NH), 1622($C=N_{pyridine}$)
	^{1}H-NMR (DMSO-d6)	6.49 (1H, s, NH), 6.04 (1H, s, CH 2), 8.72–7.12 (11H, m, 3Ar-H)
9	FT-IR (cm^{-1})	1640($C=O_{amide}$),(2987,2844)($C-H_{alph.}$), 3155($C-H_{Arom.}$) 3420 ($OH_{phenolic}$), 3235 (NH), 1644($C=N_{pyridine}$)
	^{1}H-NMR (DMSO-d6)	6.39 (1H, s, NH), 6.06 (1H, s, CH 2), 8.67–6.95 (12H, m, 3Ar-H), 8.51 (1H, s, OH sulfonic acid)
10	FT-IR (cm^{-1})	1650($C=O_{amide}$) , (2992,2845) ($C-H_{alph.}$) , 3167($C-H_{Arom.}$) 3420(OH) ,3233(NH), 1630 ($C=N_{pyridine}$)
	^{1}H-NMR (DMSO-d6)	6.79 (1H, s, NH), 5.96 (1H, s, CH 2), 8.67–6.91 (12H, m, 4Ar-H), 10.65 (1H, s, OH phenol)
11	FT-IR (cm^{-1})	1655($C=O_{amide}$) , (2940,2856) ($C-H_{alph.}$), 3110($C-H_{Arom.}$),3235(NH),3434(OH) 1630($C=N_{pyridine}$)
	^{1}H-NMR (DMSO-d6)	6.38(1H, s, NH), 5.95 (1H, s, CH 2), 8.64–6.79 (11H, m, 3Ar-H), 5.77 (1H, s, CH 2 oxathiol)
12	FT-IR (cm^{-1})	1650($C=O_{amide}$), (2992,2830) ($C-H_{alph.}$) ,3175($C-H_{Arom.}$) 3450 ($OH_{carboxyl}$), 3235 (NH), 1620($C=N_{pyridine}$)
	^{1}H-NMR (DMSO-d6)	6.44(1H, s, NH), 5.97 (1H, s, CH 2), 8.67–6.95 (12H, m, 3Ar-H), 12.67 (1H, s, OH carboxyl)

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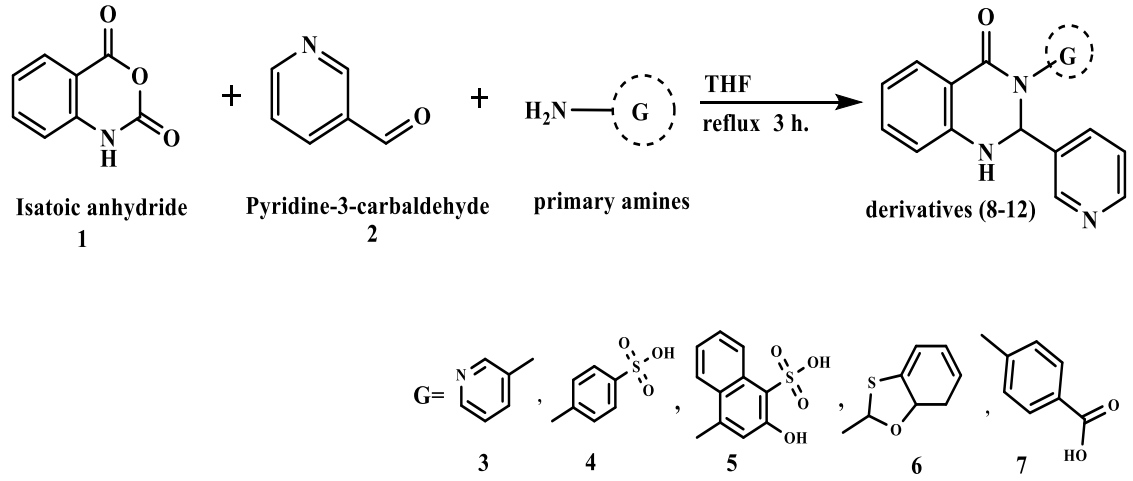
Molecular Docking Studies

The activity of the quinazoline derivatives series (1-5) as potent anticancer agents of the breast was evaluated using a molecular docking study of the derivatives using Auto Dock 4.2 drug design software (PDB, http://www.rcsb.org, code 1M17).

Results and Discussion

One-pot synthesis is a fairly unique and different technique from chemical synthesis. The term "one-pot synthesis" refers to a multi-step process that occurs in a single vessel. It offers several advantages in terms of time savings, less chemical waste, reduction of purification stages, synthetic alterations, and bond-forming procedures in a single pot. Because of these advantages, this synthesis is considered greener and comes under green chemistry. Currently, one-pot multicomponent reactions (MCRs) are widely employed in synthetic organic processes. In consideration of our interest in creating heterocyclic compounds, in order to produce 2,3-dihydroquinazolin-4(1H)-one derivative, we utilize a three-component one-pot condensation of isatoic anhydride, pyridine-3-carbaldehyde, and primary amines with $NaHSO_4$ as catalysts, under reflux on a water bath. The compounds (**8-12**) were synthesized using the generic route given in Scheme 1. Table 1 shows that in both solvents (H_2O and ethanol), no reaction has been observed, but the temperatures have changed (50, 60, and 68°C). THF solvent shows a great yield to obtain the products. Thus, the temperature has been changed to increase the reaction yield, and the reactions have demonstrated the highest yield obtained at 68 °C. However, some reactions did not react at 50 °C.



Scheme 1. Show the general reaction with different amines.

A mechanism for producing the 2,3-dihydroquinazolin-4(1H)-one derivative has been proposed as below: The first step was the condensation of isatoic anhydride with aromatic primary amines; decarboxylation was then performed to produce the appropriate anthranilamide. The second step is the condensation reaction of the pyridine-3-carbaldehyde with the amino group of anthranilamide to afford an imine intermediate. The cyclization that results from anthranilamide nitrogen's intramolecular nucleophilic assault on imine carbon. Then the expected result is 2,3-dihydroquinazolin-4(1H). We believe that the reaction occurs as a result of the synthesis of anthranilamide intermediates [40], as shown in Scheme 2.

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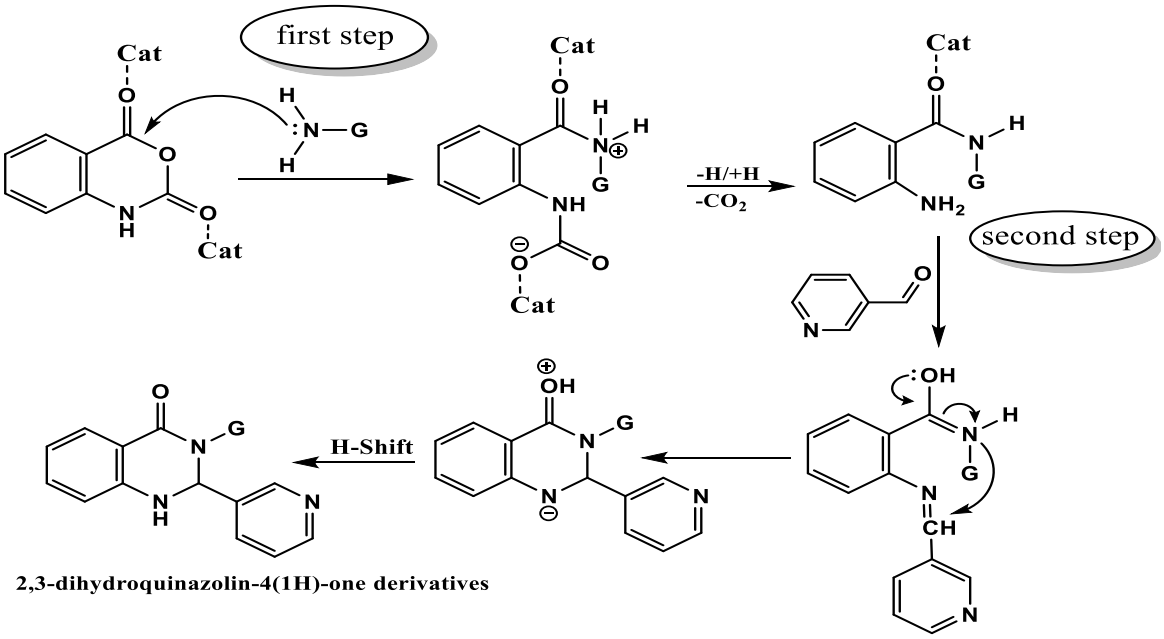

Scheme 2. Mechanism for producing 2,3-dihydroquinazolin-4(1H)-one derivatives[42].

In the case of Docking results, the results that were reached through molecular fusion between the prepared compounds and the target protein responsible for breast cancer (protein 1M17) were as shown in Table 3, which gave results for compound **8**.

Table 3. Results of molecular fusion with the protein responsible for breast cancer (1M17)

Compound	Lowest Binding Energy	Run
8	- 7.30	47
9	- 6.78	40
10	- 6.60	21
11	-7.39	2
12	- 6.91	14

As shown in Fig. 3, compound **11** contained two hydrogen bonds with amino acids (LYS782A and ASP783A) with a value of ΔG = - 7.3.9 kcal/mol. Its insistence lengths were 2.15 A and 2.55 A, respectively.

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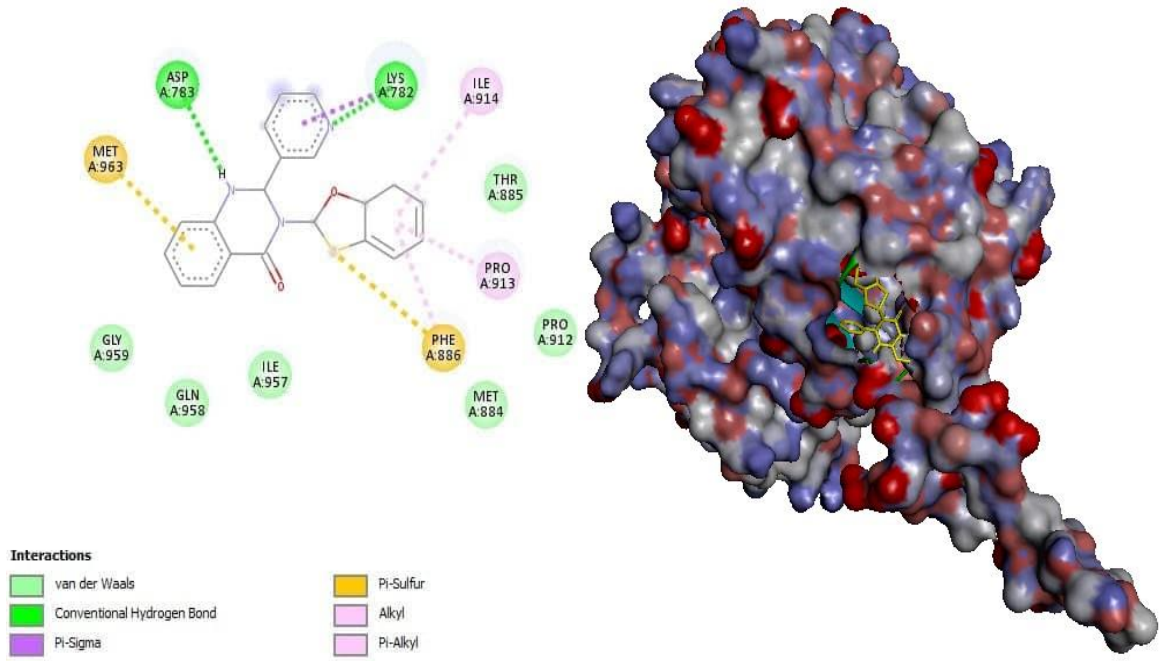

Figure 3. Shows Figure 2D and 3D of the binding of compound 11 with the target protein.

Compound **8**, which is shown in Fig. 4, has a G value of -7.30 Kcal/mol, is connected to amino acids by two hydrogen bonds (GLN 958A and MET 963A), and its insistence length is 2.52 A and 3.14 A, respectively.

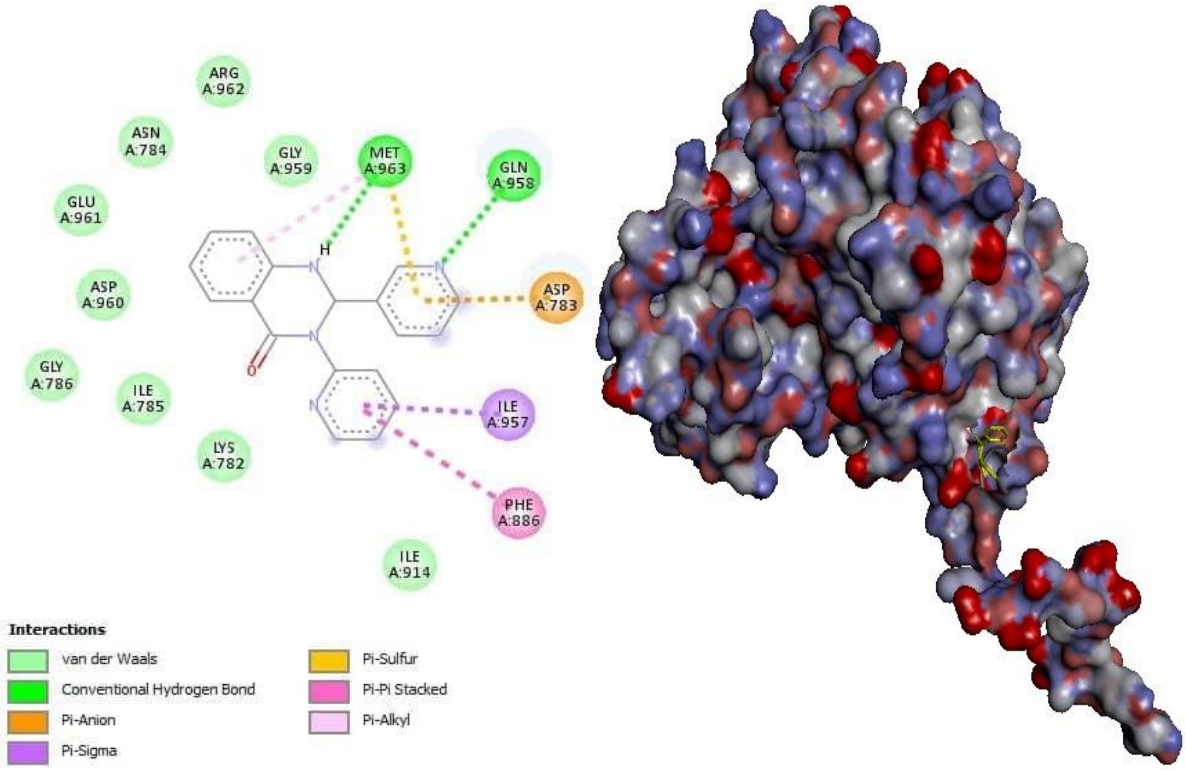

Figure 4. Shows Figure 2D and 3D of the binding of compound 8 with the target protein.

Additionally, compound **9** is shown in Fig. 5 with a ΔG value of -6.60 Kcal/mol and two hydrogen bonds with amino acids (HIS 749A, GLN 796A), with insistence lengths of 2.30 A and 2.17 A, respectively.

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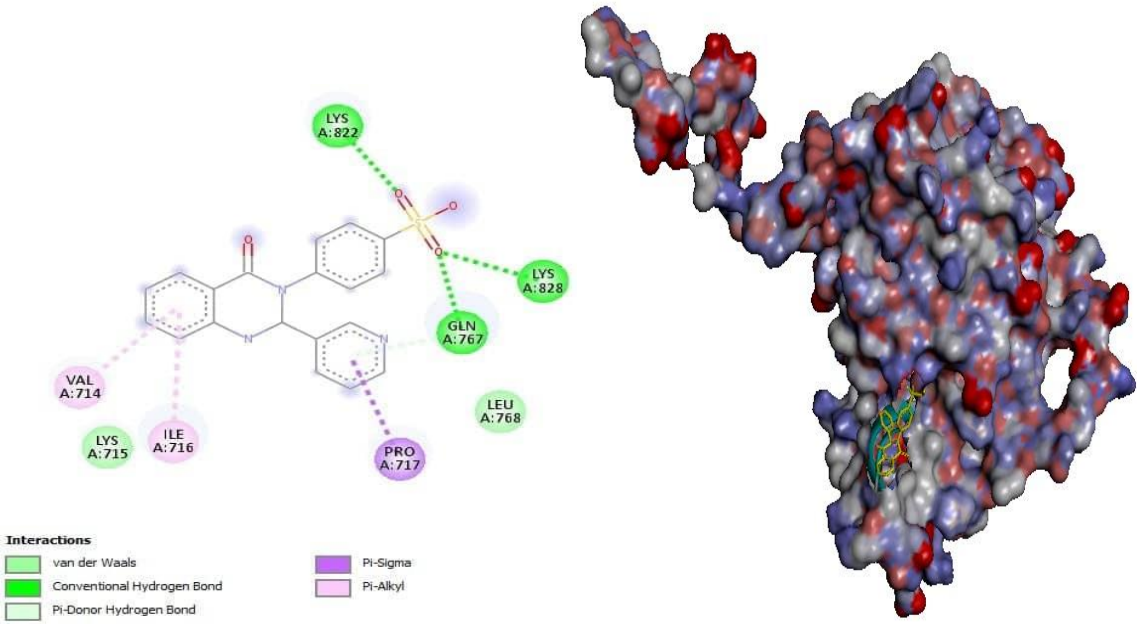

Figure 5. Shows Figure 2D and 3D of the binding of compound 9 with the target protein.

As shown in Fig. 6, compound **10** has a ΔG value of -6.78 Kcal/mol, three hydrogen bonds with amino acids (GLN 767A, LYS 822A, and LYS 828A), and their insistence lengths of 1.84 A, 3.14 A, and 3.53 A, respectively.

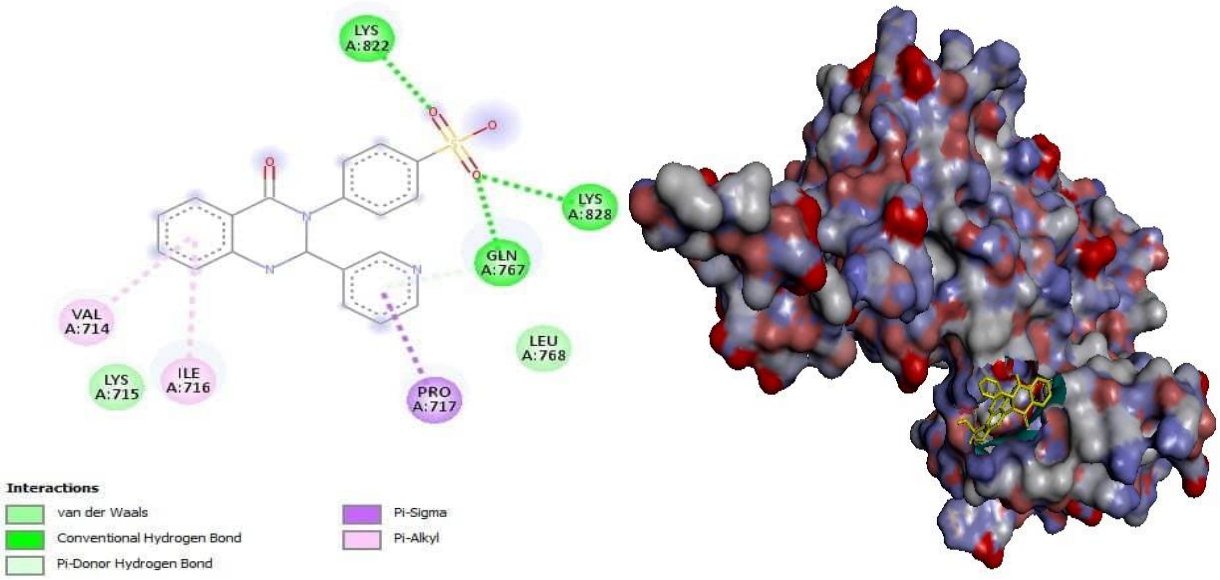

Figure 6. Shows Figure 2D and 3D of the binding of compound 10 with the target protein.

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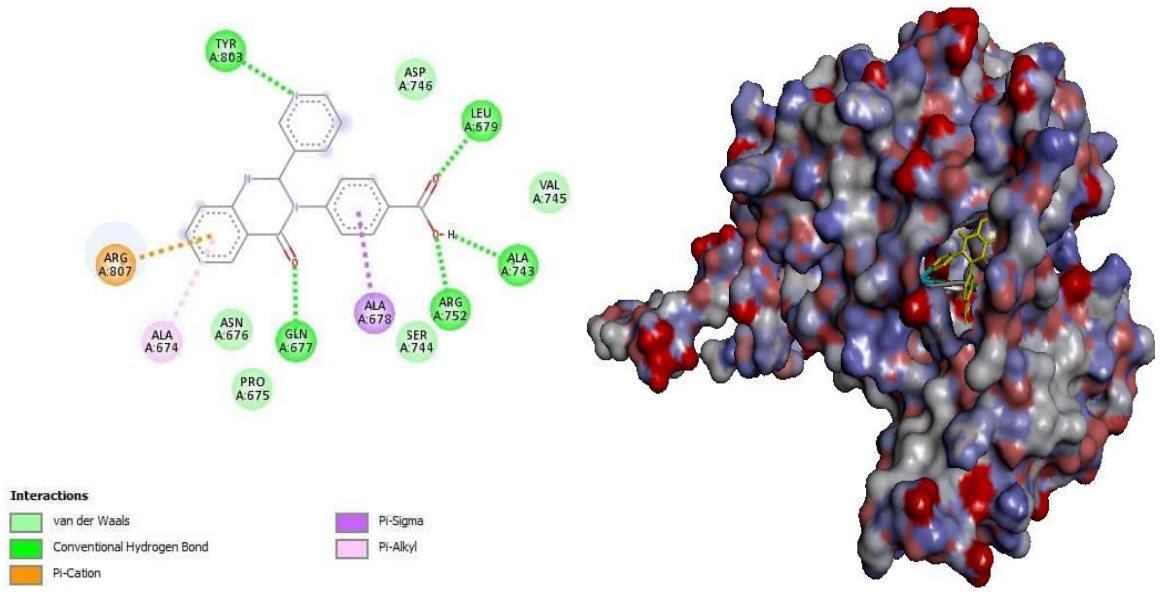

Figure 7. Shows Figure 2D and 3D of the binding of compound 12 with the target protein.

Finally, compound **12** has a ΔG value of -6.91 Kcal/mol and is linked to amino acids by five hydrogen bonds (GLN 677A, LEU 679A, ALA 743A, TYR 803A, and ARG 752A), with the corresponding insistence lengths of 1.97 A, 2.59 A, 1.81 A, 2.09 A, and 3.73 A (see Fig. 7).

Conclusion

In conclusion, we have constructed the derivatives of (2,3-dihydroquinazolin-4(1H)-one) were successfully synthesized using a simple and environmentally friendly one-pot, three-component method that included isatoic anhydride as a backbone, pyridine-3-carbaldehyde, and primary amines. We believe that the current methodology addresses the current push toward green chemistry as a result of high yields. To assess the activity of the new quinazoline derivative series as a potent breast cancer antagonist, we performed a molecular docking study of compounds using Auto Dock 4.2 drug design software. The structure elucidation of these novel series derivatives was done by FT-IR and NMR spectroscopy.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Anbar.

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Authors' Contribution Statement

MAK and EKZ are contributed to the design and implementation of the research, and performed the analysis of the results IR,1H-NMR. Furthermore, both of them drafted the manuscript and designed the figures. Manufactured the samples and characterized them with spectroscopy, performed the characterization, aided in interpreting the results, and worked on the manuscript. AHJ contributed to the design of the product and performed the analysis of the results by Molecule Docking.

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تصميم , تحضير , توصيف مجموعه جديدة من مشتقات ٢،٣- ثنائي هيدروكوينزولين -4 (*H*1) (DHQZ-1) وتقييم الفعالية المضادة للورم باستخدام الالتحام الجزيئي حاسوبيا

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الخلاصة

الهدف من هذا البحث هو استخدام التفاعلات متعددة المكونات لإنتاج سلسلة جديدة من مشتقات الكوينزولين والتي تعطي منتوج كثير.يحدث هذا التفاعل من خلال تكثيف بيريدين-3- كاربالديهايد مع 1,3-H1-بنزاوكزازين-2و4-ثنائي ون (أيساتويك انهيدرايد) والأمينات الأولية (7-3). وتمت اذابه المكونات باستخدام مذيب رباعي هيدروالفوران (THF ، مذيب غير بروتوني) (البروتوني). مع كبريتات الصوديوم الهيدروجينيه ($NaHSO_4$) على شكل عامل مساعد في التفاعل وذلك لتوفيرمنتوج عالي من مشتقات 3،2- ثنائي هيدروكوينزولين -4 (*H*1). تم الحصول على أفضل ناتج عند درجه حراره 68 درجة مئوية. بشكل عام ، تُظهر جميع المنتجات المتسلسلة (8-12) قدرة كبيرة كمضاد فعال لسرطان الثدي باستخدام دراسة الالتحام الجزيئي للمشتقات حيث اعطى المركب **11** ، اكثر فعالية مضادة من المركبات المحضرة الاخرى. تم تقييم دراسة الالتحام الجزيئي للمشتقات باستخدام برنامج تصميم الأدوية Auto Dock 4.2 (PDB)). ، كود البروتين 1M17).

الكلمات المفتاحية: مضاد للأورام(بروتين 1M17) , 3,2- ديهيدروكوينازولين-4 (1H) واحد(DHQZ-1) , أنهيدريد إيزاتويك , تفاعلات متعددة المكونات(MCRs) , الالتحام الجزيئي بيريدين -3 كاربالديهايد.