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Chemical synthesis and molecular Docking analysis for some novel heterocyclic compounds Derived from 1,2,3-benzotriazin-4-one

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A B S T R A C T

Our contribution entails a number of steps in the preparation of new heterocyclic compounds and some new Schiff bases : a) Ethyl 2-(4-oxobenzo[d]1,2,3-triazin-3 (4H)-yl) propanoate (2) was formed by converting the ester of anthranilate (1) into the diazonium salt, which then reacted with ethyl alaninate (newly prepared). b) The ester (2) was transformed into ethyl 2-(4-oxobenzo[d]1,2,3-triazine-3(4H)–yl) propanehydrazide (3) through a reaction with 85% of liquid hydrazine. c) The product hydrazide (3) was treated with several reagents and some of aldehydes to synthesize some new heterocyclic compounds, hydrazone and Schiff bases (4–9). In addition, theoretically molecular docking results showed that some of these compounds act as Vascular endothelial growth factor receptor 2 (3cjf) inhibitors and have biological activity as anticancer capabilities. The structure assignments of the newly synthesized heterocyclic compounds were based on physical properities, FT-IR, ^{13}C and $^{1}HNMR$ spectral data.

Introduction

Heterocyclic compounds are important in pharmaceutical chemistry, a large number of them have biological activity; 1,2,3-benzotriazin-4-one which has three nitrogen atoms is used as good anti-inflammatory [1], anticancer [2], exhibits noticeable anticancer activity [3], antidepressants, binding to (5-HT1A) receptors [4], anti-nematode disease cause of Meloidogyne incognita [5], antifungal agents [6] and used motif to prepare a variety of heterocyclic compounds. For example, Oxadiazole derivatives are important type of heterocyclic compounds with a spectrum of biological activity, like; anti-inflammatory activity [7], antibacterial [8] and treatment of Alzheimer's disease [9]. Also, thiadiazole compounds have shown anticancer evaluation [10] and hydrazone compounds are very utility as anti-inflammatory [11] and anticancer [12].

Schiff bases are important organic compounds containing C=N units, where the nitrogen atom is bonded to an aryl or alkyl moiety. They significant biological activity against various diseases [13]. Preparing Schiff bases from the reaction of 2-amino-1,3,4-thaidiazole with aromatic aldehydes increases their biological activity [14]. For instance, Schiff base and 1,3,4-thiadiazole moiety displayed an antiproliferative – antimicrobial activity [15], antituberculosis activity [16] and anticancer activity [17]. In this study, computational molecular docking investigation's were performed to measure the binding interactions of the synthesized molecules with target protein, the anti-cancer activity of the prepared Benzo-1,2,3-triazin-4-one derivatives was also determined, the results were contrasted with standard VEGFR2 (3cjf) and (3wzd) targets.

Methodology

Materials and Equipment

All chemical compounds and solvents were obtained from Fiuka, Sigma-Aldrich, and BDH without additional purification. Thin layer chromatography (TLC) was done using aluminium plates pre-coated with 60 F_{254} silica gel (Merck), (2:4) (Ethyl acetate: Petroleum ether) as an eluent, UV light and iodine fumes were used to differentiate the spots. A stuart (SPM30)– Melting point equipment was used to mark the melting points of materials and are uncorrected. The pye Unicom (sp 2000), has been used to record Infrared spectral data (FT-IR) at the Mosul's University (College of Sciences). Spectroscopy of nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were determined on Bruker spectrometer [400 MHz-100 MHz] in the Al-Basrah's University (College of Science) using (TMS) tetramethylsilaneas the internal standard and (DMSO) as a solvent.

Experimental methods:

Preparation of methyl anthranilate (1):

2-aminobenzoic acid (Anthranilic acid; AA) (6.2 g, 0.05 mole) was dissolved in (25 mL) absolute methanol (saturated with HCl gas). The reaction mixture was refluxed under a steam bath for 2 hours, the production mixture was cooled to the room temperature, then poured onto (100 g) from crushed ice and neutralized by using ammonium solution [18]. The organic layer was extracted with ether (4 * 20 ml), dried (with anhydrous Magnesium Sulfate), filtered off and evaporated the solvent under reduced pressure to give a yellow liquid product in (67%) yield, b.p. 254-255°C. FT-IR $\nu_{max.}$ cm^{-1}: 3478, 3370 (-NH_2), 3031 (-CH_{Ar}), 2951 (-CH), 1686 (C=O), 1614, 1586, 1487 (C=C), 1434 (-CH bend. -CH_3).

Preparation of L-alanine ester (ethyl hydrochloride):

L-alanine (14.5 g, 0.1 mole) was dissolved in (25 mL) absolute ethanol (saturated with HCl gas). The mixture of reaction was refluxed for (3 hours), then the unreacted ethanol was evaporated under reduced vacuum pressure. Followed by the addition of 50 mL toluene until the solution became completely miscible at a temperature of (70 ℃), the mixture was cooled down to 20 ℃ for 2 hours in a cool and dark place. It was then filtered to obtain a white precipitate (crystalline) with a melting point (78-80 ℃) and a (98.8%) yield [19,20]. FT-IR spectra of $\nu_{max.}$ cm^{-1}: 3480, 3402 (-NH_2), 2874 (-CH), 1744 (C=O), 1385 (-CH bending, -CH_3), 1113 (C-O) was obtained.

Preparation of ethyl 2-(4-oxobenzo[d] 1, 2, 3- triazin-3(4H)–yl) propanoate (2):

Methyl anthranilate (1) (6.04 g, 0.04 mole) was dissolved into a (35%) hydrochloric acid, cooled the solution at (0 - 5℃) and added the solution (4.25 g, 0.06 mole) of sodium nitrite ($NaNO_2$) in a (10 mL) of

water drop by drop, then added ethyl alaninate hydrochloric (6.12 g, 0.04 mole) to the reacting mixture on an ice path with stirring, for one hour. The reaction examined *via* TLC by using (1) Ethyl acetate : (2) Petroleum ether as the mobile phase [21]. After that neutralized the mixture of reaction with sodium carbonate (saturated solution), thereafter extracted the product with ether, then evaporated the solvent under reduced vacuum pressure to produce an orange liquid in (87%) yield and boiling point of (133 - 134℃). FT-IR $\nu_{max.}$ cm^{-1} : 3075 ($-CH_{Ar}$), 2984 (-CH), 1259 (N=N), 1720 (C=O, ester) 1668 (C=O, amid)), 1601, 1568, 1479 (C=C), 1436, 1371 (-CH bending CH_3) 1130 (C-N), 1084 (C-O). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 1.12 (3H, t, $-CH_2CH_3$), 1.49 (3H, d, $-CHCH_3$), 3.65 (2H, q, $-CH_2$), 4.08 (H, q, -CH), 6.49-8.15 (4H, m, $-CH_{Ar}$). ^{13}C-NMR (100 MHz; DMSO (d_6)) δppm: 15.7, 18.5 ($-CH_3$), 40 ($-CH_2$), 60 (C-N) 109.06 - 150 (C_{Ar}), 168 and 173 (2 C=O).

Prepare of ethyl 2- (4- oxobenzo [d]1,2,3- triazine-3(4H)–yl) propanehydrazide (3):

The ester (2) (2.47 g, 0.01 mole) was dissolved in (50 mL) absolute ethanol; (2 g, 0.04 mole) of freshly distilled hydrazine hydrate (in the existence of sodium hydroxide) was added and refluxed the solution of the reaction for (3) hours [22]. Then, filtered the producing precipitate and purified by recrystallization from 95% ethanol to obtain the hydrazide (3) as yellow precipitate in (80%) yield and (m.p. 193-194 ℃). FT-IR $\nu_{max.}$ cm^{-1}: 3474 (-NH), 3344, 3258 ($-NH_2$), 3109 ($-CH_{Ar}$), 2936, 2873, (-CH), 1297 (N=N), 1660 (C=O), 1575, 1454 ($C=C_{Ar}$), 1385 (-CH bending CH_3), 1173 (C-N). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 1.73 (3H, d, $-CH_3$), 4.34 (1H, q, -CH), 5.51 (2H, s, $-NH_2$), 7.88 - 8.23 (4H, m, $-CH_{Ar}$), 9.42 (1H, s, -NH). ^{13}C-NMR (100 MHz; DMSO (d_6)) δppm: 17.01 ($-CH_3$), 57.30 (C-N) 119.21-143.89 (C_{Ar}), 155.26 and 170.04 (2 C=O).

Prepare of N'-(3-nitrobenzylidene)-2-(4-oxobenzo[d]1,2,3-triazin-3(4H)-yl) propane hydrazide (4):

A mixture of propanehydrazide (3) (0.93 g, 0.004 mole) and (0.60 g, 0.004 mole) 3-nitrobenzaldehyde was dissolved in (25 mL) absolute ethanol in a 50 mL round flask with a magnetic stirrer, refluxed the reaction mixture for 3 hours, cooled and filtered the precipitate. Then, dried the product and recrystallized from 95% ethanol to get the hydrazone (4) as a yellow precipitate with (m.p. 221-223℃), (92%) yield and (Rf = 0.53) [21]. FT-IR $\nu_{max.}$ cm^{-1}: 3184 (-NH), 3081 (-CHAr), 2894 (-CH), 1697 (C=O), 1603 (C=N), 1531asym., 1355sym. (NO_2), 1258 (N=N). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 1.3 (3H, d, $-CH_3$), 3.5 (1H, q, -CH), 7.36 - 8.5 (8H, m, $-CH_{Ar}$), 8.87 (1H, s, =CH), 9.54 (1H, s, -NH).

Prepare of 3-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)ethyl)benzo[d]-1,2,3-triazin-4(3H)-one (5):

Hydrazide (3) (0.23 g, 0.001 mole) in (50 mL) ethanol was added to a solution of (0.84 g, 0.015 mole) KOH in (10 mL) ethanol and (10 mL) CS_2. The mixture was heated at 80℃ for 9 hours until the color of the mixture became yellowish orange. The reaction was followed up with a TLC test. After that, evaporated the excess of ethanol under vacuum, then acidified the remainder of the mixture to (PH = 5) by using (10% HCl). Filtered the resulting precipitate, washed with cold water several times and left to dry at room temperature overnight, then recrystallized the product with ethanol to give a yellow-colored precipitate with (m.p. 293-295℃), (Rf: 0.44) and a yield of (99%) [23]. FT-IR $\nu_{max.}$ cm^{-1}: 3361 (-NH), 3164 ($-CH_{Ar}$), 2650 (SH), 1624 (C=O), 1504 (C=N arom.), 1143 (N=N). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 1.23 (3H, d, $-CH_3$), 4.15 (1H, q, -CH), 7.18 – 7.86 (4H, m, $-CH_{Ar}$), 12.97 (1H, s, SH). ^{13}C-NMR (100 MHz; DMSO (d_6)) δppm: 15.58 (CH_3), 56.49 (CH), 120.27 - 123.11 (C_{Ar}), 129.52, 131.04 (2C=N), 160 (C=O).

Prepare of N-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-(4-oxobenzo[d]-1,2,3-triazin-3 (4H)-yl) propanamide (6):

A mixture (0.25 g, 0.001 mole) of hydrazide (3) with (0.1 g, 0.001 mole) of succinic anhydride was refluxed in (25 mL) of absolute ethanol for (9 hours), the reaction followed by TLC examination, then cooled the solid product, filtered and washed with cold water, the product dried and recrystallized from 95% ethanol to give a white product with (m.p. 227-229℃), (90%) yield and (Rf: 0.39) [24]. FT-IR $\nu_{max.}$ cm^{-1}: 3192 (-NH), 3062 (-CHAr), 2949 (-CH), 1736 (C=O anhydride), 1698 (C=O amide), 1610 (C=C), 1165 (N=N). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 1.78 (3H, d, $-CH_3$), 3.36 (1H, q, -CH), 5.62 (1H, d, =CH), 7.93–8.26 (4H, m, $-CH_{Ar}$), 10.18 (1H, s, -NH). ^{13}C-NMR (100 MHz; DMSO (d_6)) δppm: 16.97 (CH_3), 56.00 (CH), 119.59 - 136.03 (C_{Ar}), 143.86, 155.22 (C=C), 168.82, 170.43 and 174.02 (C=O).

Prepare of 2-(2- (4-oxobenzo [d]-1,2,3-triazin-3 (4H)-yl) propanoyl) hydrazine -1-carbothioamide (7):

A mixture of (0.6 g, 0.002 mole) hydrazide (3) and (0.15 g, 0.0025 mole) of ammonium thiocyanate and 2 mL of concentrated hydrochloric acid was refluxed in 25 mL of absolute ethanol for 24 hours. The solvent was evaporated under reduced vacuum pressure, the precipitate was collected, washed with water, air-dried and recrystallized from 95% ethanol yielding a white precipitate with a melting point of 235–237 °C and a 97% yield and (Rf: 0.37) [25]. FT-IR $\nu_{max.}$ cm^{-1} detected the following peaks: 3300, 3264 (-NH), 3215, 3200 ($-NH_2$),

3032 (-CH_{Ar}), 2926 (-CH), 1681, 1661 (C=O), 1618 (C=N), 1173 (N=N). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 1.78 (3H, d, -CH_3), 5.50 (1H, q, -CH), 7.92 – 8.26 (4H, m, -CH_{Ar}), 9.39 (1H, s, -NH), 9.49 (1H, s, -NH), 9.94 (2H, s, -NH_2). ^{13}C-NMR (100 MHz; DMSO (d_6)) δppm: 16.55 (CH_3), 55.35 (CH), 124.64 - 135.61 (C_{Ar}), 154.84 (C=S), 168.82(C=O).

Preparation of 3-(1-(5-amino-1,3,4-thiadiazol-2-yl) ethyl) benzo[d]-1,2,3-triazin-4 (3H)-one (8):

A mixture of thiosemicarbazide (7) (0.24 g, 0.0012 mole), 8 mL of concentrated sulfuric acid, and 4 mL of distilled water was reflux for 5 hours. At the end of the reaction, TLC examination was conducted. The solution was cooled down, then the ammonia solution was added with stirring and cooling until the medium became neutral (pH = 7), the precipitate was filtered, air- dried and recrystallized from 95% ethanol to obtain a brown precipitate with a melting point of 150-152 ℃, yielding a 90% yield and (Rf: 0.43) [26]. FT-IR $\nu_{max.}$ cm^{-1} detected the following peaks: 3472, 3371 (-NH_2), 3030 (-CH_{Ar}), 2926 (-CH),1667 (C=O), 1615 (C=N arom.), 1240 (N=N), 750 (C-S). ^{1}H-NMR (400 MHz; DMSO (d_6)) δppm: 2.86 (3H, d, -CH_3), 6.47 (1H, q, -CH), 6.51 – 7.69 (4H, m, -CH_{Ar}), 10.70 (2H, s, -NH_2).

Preparation of Schiff Bases (9a-c):

The mixture (0.2 g, 0.0005 mole) of the prepared thiadiazole (8) was mixed with 0.0005 mole of one aldehyde in 10 ml of absolute ethanol was refluxed for 5 hours, then cooled down. The product filtered and recrystallized with 95% ethanol to obtain compounds 9a-c [27].

Compound 9a: 3-(1-(5-((benzo[d][1,3]dioxol-4-ylmethylene)amino)-1,3,4-thiadiazol-2-yl)ethyl) benzo[d]-1,2,3-triazin-4(3H)-one: Yellow color, 79% yield, (m.p. 161-163℃) and (Rf: 0.62). FT-IR $\nu_{max.}$ cm^{-1}: 3079 (-CH_{Ar}), 2916, 2850 (-CH), 1673 (C=O), 1622 (C=N), 1599, 1486 (C=C_{Ar}), 1357 (-CH bending -CH_3), 1250 (N=N), 1032 (C-O). ^{1}HNMR (400 MHz; DMSO (d_6)) δppm: 1.23 (3H, d, CH_3), 6.12 (1H, q, CH), 6.18 (2H, s, CH_2), 7.11 - 7.88 (8H, m, CH_{Ar}), 9.87 (1H, s, =CH).

Compound 9b: 3-(1-(5-((4-methoxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)ethyl) benzo[d]-1,2,3triazin-4(3H)-one: Brown color, 69% yield, (m.p. 186-188℃) and (Rf: 0.56). FT-IR $\nu_{max.}$ cm^{-1}: 3008 (-CH_{Ar}), 2934, 2839 (-CH), 1680 (C=O), 1595 (C=N), 1576, 1460 (C=C_{Ar}), 1392 (CH bending -CH_3), 1253 (N=N), 1156 (C-O). ^{1}HNMR (400 MHz; DMSO (d_6)) δppm: 1.23 (3H, d, CH_3), 3.60 (1H, q, CH), 3.86 (3H, s, OCH_3), 7.14 - 7.56 (7H, m, CH_{Ar}), 9.81 (1H, s, =CH).

Compound 9c: 3-(1-(5-((4-(dimethylamino)benzylidene)amino)-1,3,4-thiadiazol-2-yl)ethyl) benzo[d]-1,2,3-triazin-4(3H)-one: Orange color, 81% yield, (m.p. 129-133℃) and (Rf: 0.68). FT-IR $\nu_{max.}$ cm^{-1}: 3063 (-CH_{Ar}), 2902, 2795 (-CH), 1659 (C=O), 1589 (C=N), 1547, 1463 (C=C Ar),1366 (-CH bending -CH_3), 1230 (N=N), 810 (C-S).

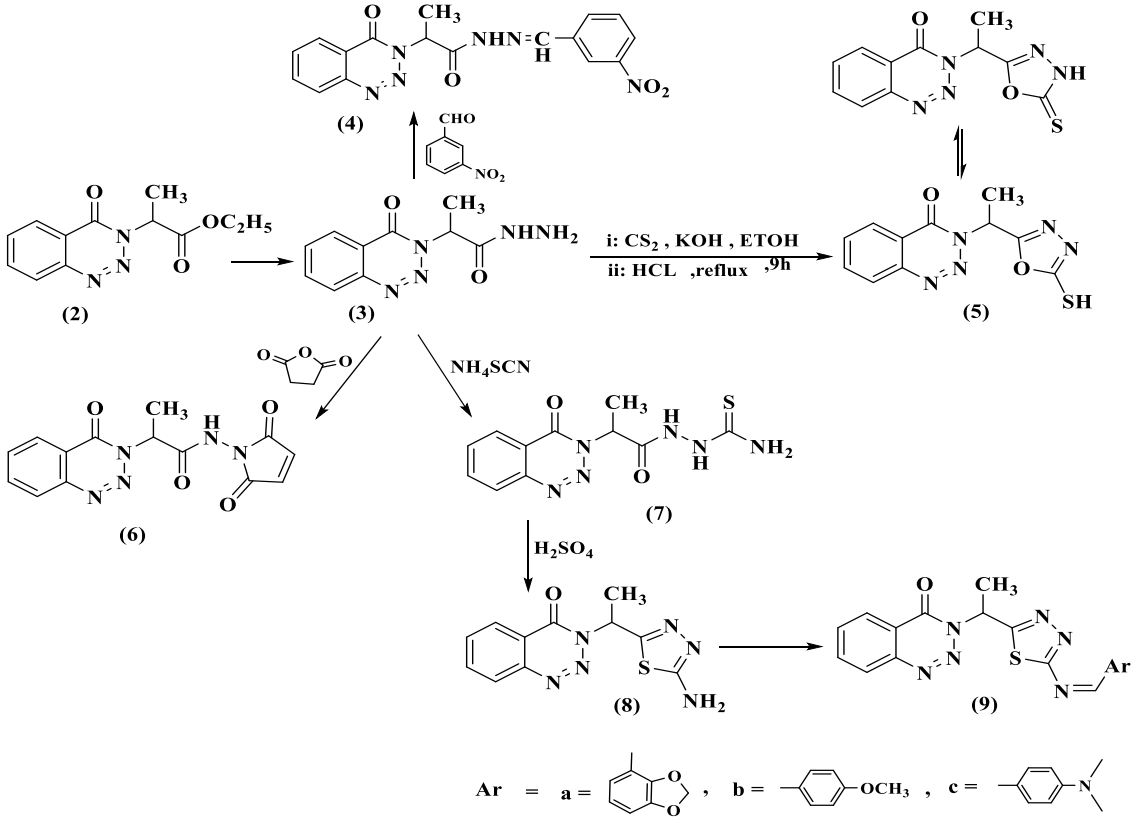
Molecular Docking

The biological activity of 1,2,3-benzotriazines compounds was studied as VEGFR-2 (vascular endothelial growth factor) inhibitors [28,29]. Therefore, we compared the previous study with our compounds to study the inhibition ability of these compounds by docking simulations for ligands 2-9a-c compounds, that were performed using Molecular Operating Environment (MOE-Dock) software version 2014.0901 [30].

The interactions of the synthesized ligands (2-9a-c), illustrating the highest VEGFR-2 inhibitory activities, were examined and docked within the active sites of the target enzymes to study their binding modes and orientations using PDB: 3CJF. The 2D structures of the newly synthesized 1,2,3-benzotriazine were drawn using Chem. Draw software. The protonated 3D structure was employed using standard bond lengths and angles. Then, geometry optimization and energy minimization were applied to obtain the Conf Search module in MOE, and the MOE file was then saved for the subsequent docking process. The co-crystallized structures of 3CJF with their potent inhibitor, were downloaded (PDB code: 3CJF) from the Protein Data Bank. All minimizations were performed using MOE with an MMFF94x force field, and the partial charges were automatically calculated. The preparation of the enzyme structure was performed for molecular docking using the protonated 3D protocol with the default options in MOE. The London dG scoring function and Triangle Matcher placement method were used in the docking protocol. First, validation of the docking processes was established by docking the newly compounds followed by docking native ligands, Lenvatinib drug and previous study compounds.

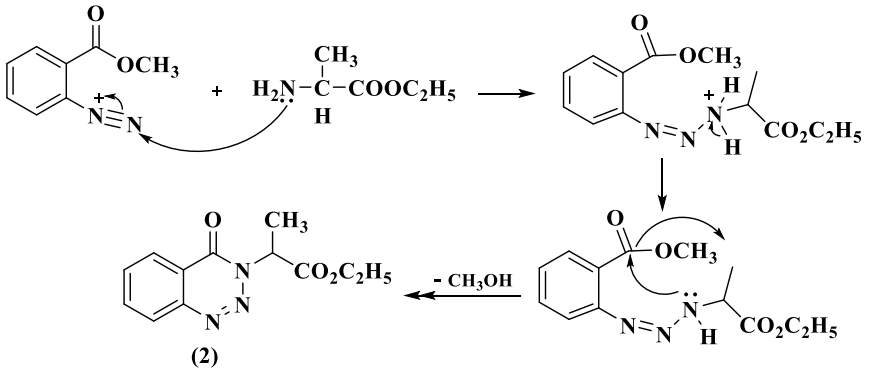
Results and Discussion

1,2,3-benzotriazin-4(3H)-one was used as moiety to synthesize some new heterocyclic compounds through the reaction of the hydrazide (3) with many reagents (Scheme 1 illustrates the prepared heterocyclic compounds).



Scheme 1. Diagram of synthesized heterocyclic compounds 1 - 9a-c

The mechanism of hydrazone and Schiff bases forming happened by the addition -elimination mechanism [30]. In the first step, ester anthranilate (1) was converted into diazonium salt, which reacted with ethyl alaninate to produce 1,2,3-benzotriazine, through the following suggested mechanism:



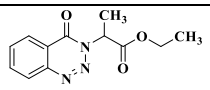
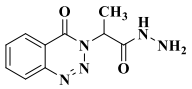
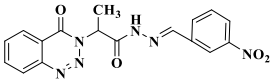
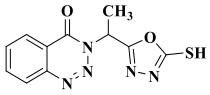
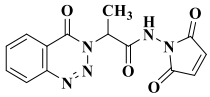
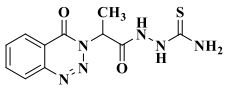
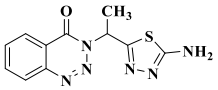
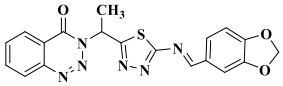
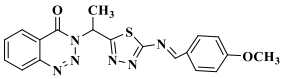
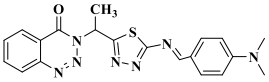
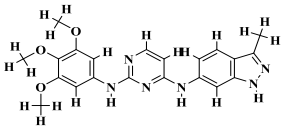
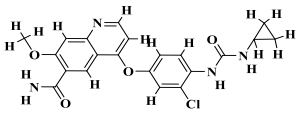
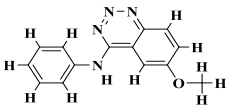
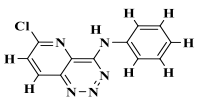
The FT-IR spectrum of compound (2) presented stretching bands to the carbonyl group (C=O) at 1720 cm^{-1}, 1668 cm^{-1} and the NH_2 bands disappeared. The hydrazide (3) was produced by a reaction of the ester (2) with 95% hydrazine hydrate, which was utilized to prepare some new heterocyclic compounds, hydrazone (4) and 5-amino-1,3,4-thiadiazol (8) which converted to some novel Schiff bases by reaction with some aldehydes.

The 1H-NMR spectrum of hydrazine (4) and Schiff bases (9a-c) showed the resonance of protons, where signals at 8.87 - 9.87 ppm referred to (-N=CH) proton, the SH proton of compound (5) showed the singlet band at 12.97 ppm, while compound (6) showed the singlet peak at 10.18 ppm attributed to NH proton, the compound (8) showed a singlet peak to the NH_2 protons in a region at 10.70 ppm. These peaks are absent in the observed spectra of compounds (9a-c) which indicates the production of Schiff bases.

Molecular docking investigations on a series of benzo-1,2,3- triazin-4-one derivatives are tested as Vascular endothelial growth factor receptor-2 (3cjf) inhibitors. The synthesized compounds showed good binding energy score and some of them (4, 9a-c) were given the highest score compared with previous studies (12,13) afforded energy scores of −6.35, −6.72, -6.69 and −6.94 kcal/mol with root-mean-square deviation (RMDS) values of 0.74, 1.24, 2.21 and 2.00 Å, respectively as shown in Table 1. The potent inhibitor of the 3cjf enzyme

(compound 10) and Lenvatinib drug (compound 11) show slightly higher energy scores (-7.37 and -7.32) than our compounds. All tested compounds are compatible with Lipinski rules.

Table 1. Binding energies and Lip-druglike criterion of the Benzo-1,2,3-triazin-4-one derivatives against VEGFR2 (3cjf).

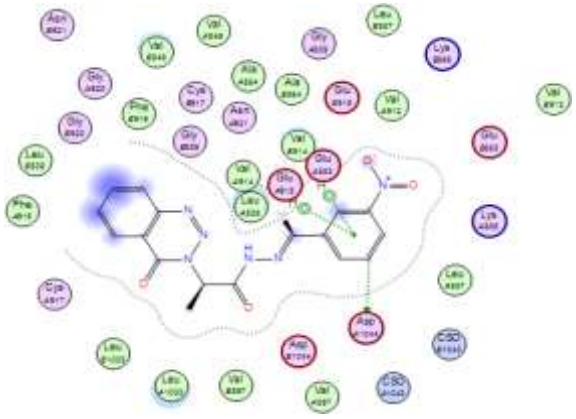
No.	Str. of database	S score (kcal/mol)	rmsd	Lip-druglike
2		**-5.55195**	**1.193142**	**1.0000**
3		**-5.61592**	**1.137873**	**1.0000**
4		**-6.35522**	**0.746212**	**1.0000**
5		**-5.6547**	**1.615172**	**1.0000**
6		**-5.9083**	**1.382878**	**1.0000**
7		**-5.7224**	**1.004927**	**1.0000**
8		**-5.64068**	**2.353328**	**1.0000**
9a		**-6.7238**	**1.243648**	**1.0000**
9b		**-6.6967**	**2.212174**	**1.0000**
9c		**-6.94716**	**2.005133**	**1.0000**
10		**-7.37022**	**1.275881**	**1.0000**
11		**-7.32952**	**1.740178**	**1.0000**
12		**-5.94712**	**0.692057**	**1.0000**
13		**-5.27171**	**1.248586**	**1.0000**

Two-dimensional views of compounds 4, 9a-c, respectively, docked in the active binding site of VEGFR-2 (PDB ID: 3CJF) using MOE software Table 2. To understand their binding modes within the VEGFR-2 site and

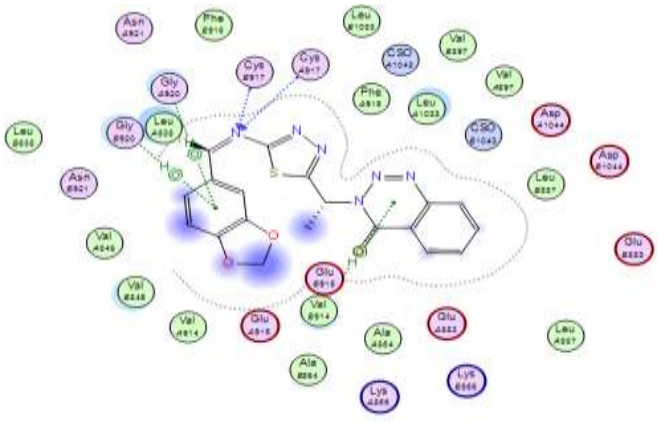
to interpret their promising in vitro inhibitory activities. Table 2 illustrates the amino acid interaction with ligand inside the active site and explains the atoms or rings and the type of interaction with distances and energy.

Table 2: Representing types of interactions of newly synthesized compounds (4,9a-c) inside the active site of VEGFR-2 (3cjf).

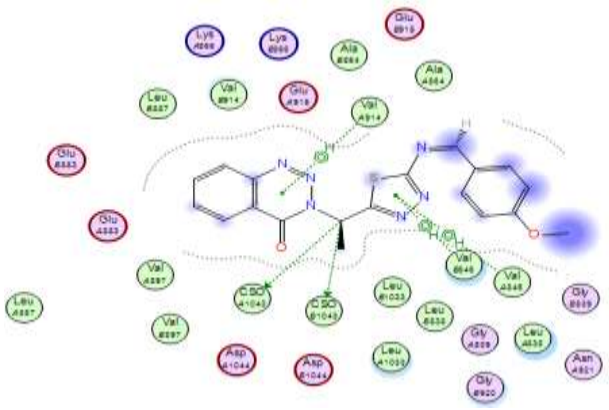
compds	Ligand	Receptor	Interaction	Distance A	E (kcal/mol)
	C 35	ASP 1044	H-donor	3.45	-0.6
4	6-ring	VAL 914 VAL	pi-H	4.34	-0.8
	6-ring	914	pi-H	4.23	-0.9
	N 27	CYS 917	H-acceptor	3.52	-0.6
	N 27	CYS 917	H-acceptor	3.99	-0.6
9a	6-ring	GLY 920	pi-H	3.99	-0.6
	6-ring	VAL 914	pi-H	3.93	-0.7
	6-ring	GLY 920	pi-H	3.52	-0.7
	C 16	CSO 1043	H-donor	4.17	-0.8
	C 16	CSO 1043	H-donor	4.18	-0.8
9b	5-ring	VAL 846	pi-H	3.72	-1.1
	6-ring	VAL 846	pi-H	3.63	-0.9
	5-ring	VAL 914	pi-H	3.77	-0.6
	N 27	CYS 917	H-acceptor	3.41	-1.1
	N 27	CYS 917	H-acceptor	3.41	-1.1
9c	6-ring	VAL 914	pi-H	3.72	-0.6
	6-ring	GLY 920	pi-H	3.92	-0.7
	6-ring	GLY 920	pi-H	3.92	-0.7



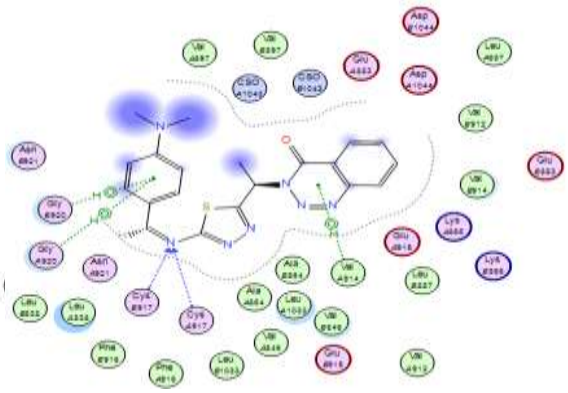
Compound (4)



Compound (9a)



Compound (9b)



Compound (9c)

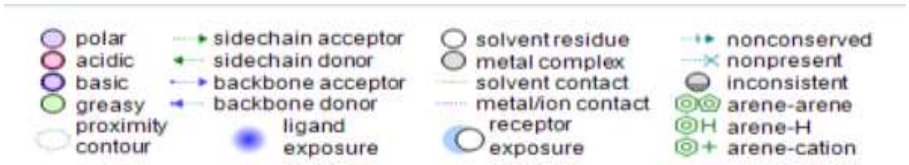


Figure1. 2D Interactions of selected compounds (4,9a-c) with amino acid residues of VEGFR-2 (3cjf).

Conclusion

Benzo-1,2,3-triazin has been successfully used to synthesize some novel hydrazone, heterocyclic compounds and Schiff bases with expected biological activity, further, the new hydrazone and Schiff bases could be used to synthesize many organic compounds and these compounds are subjected to evaluation in silico docking studies against the target VEGFR-2 (3cjf), to ascertain their potential as anti-cancer.

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