Egypt. J. Chem. Vol. 67, No. 11, pp. 411- 423 (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis, Anticancer Properties, and Molecular Modeling of Novel Thiazolyl-Pyrazolone Derivatives Conjugated With Tetrahydronaphthalene as Anticancer Agents with Potential VEGFR-2 Inhibition Activity

Eman Kh. Hamza[1], Eman S. Zarie[2], Issa M. I. Fakhr[1], Hanem M. Awad [3], Sameh A. Rizk [4] , and Nehal A. Hamdy [1]

[1] *Applied Organic Chemistry Department, National Research Centre, Dokki, Giza, 12622, Egypt*
[2] *Department of Therapeutic Chemistry, National Research Centre, Dokki, Giza, 12622, Egypt*
[3] *Department of Tanning Materials and Leather Technology, National Research Centre, Dokki, Giza, 12622, Egypt*
[4] *Department of Chemistry, Faculty of Science, Ain Shamas University, Cairo, Egypt*

Abstract

The synthesis of 4-arylidene-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones was described as a successful multi-component condensation reaction. Thiazole and pyrazolone are simultaneously formed during the synthesis process, and an active methylene group is condensed with an aryl aldehyde using the Knoevenagel reaction. Some of the remarkable characteristics of this technique are quick reaction times, gentle environmental conditions, straightforward operation, streamlined purification, and acceptable yields. The newly synthesized compounds were assessed as anticancer agents on HCT-116, HepG-2, and MCF-7 human cancer cells and one human healthy cell line (BJ-1) using the LDH assay. The most active compounds were examined as VEGFR inhibitors. Moreover, a molecular docking study was conducted to identify the binding interactions of the most potent candidates (**6e**, **6g,** and **6i**), within the active sites of the Vascular Endothelial Growth Factor Receptor (VEGFR-2/KDR) kinase. Compounds **6e**, **6g** and **6i** exhibited the most favorable binding interaction scores with the targeted enzyme. Furthermore, the bioassay results demonstrated that the three selected compounds (**6e**, **6g, and 6i**) displayed highly promising activities by significantly inhibiting VEGFR-2 kinase at very low IC_{50} values compared to their cytotoxicity IC_{50} outcomes.

Keywords: Thiazolyl-pyrazolone**;** Tetrahydronaphthalene; Multi-component condensation, Anticancer; VEGFR-2, Molecular docking.

1. Introduction

Cancer is a complex disease that results from a combination of environmental and hereditary variables. According to the World Health Organization (WHO), it is one of the major causes of death worldwide for millions of people under the age of 70 [1,2]. Four basic processes are involved in the development of cancer: angiogenesis, unchecked cell division, apoptosis avoidance, and metastasis [3,4]. The majority of cancer treatment programs are based on traditional chemotherapy used either as a curative measure after surgery, to lessen symptoms, or as a means of extending life after the procedure in conjunction with radiation therapy. Even though many chemotherapeutics have been successful in treating cancer, researchers continue to face a difficult task in developing new, safe, and effective chemotherapeutics to address issues such as drug resistance, high toxicity, and the increased risk of side effects from combination therapy protocols [5,6].

Designing, synthesizing, and developing compounds with the potential to be used as medicines for humans is one of the main goals of organic and medicinal chemistry. It therefore supports the urgent need for innovative chemotherapy drugs with stronger anticancer activity. Recently, it has been demonstrated in the literature that pyrazole and thiazole derivatives have a wide range of biological characteristics, primarily being ACE inhibitors [7,8], anticancer [9-13], anti-inflammatory, analgesic [14-16], antioxidant [17],

*Corresponding author e-mail: drnehalhamdy63@hotmail.com (Nehal A. Hamdy).
Receive Date: 30 January 2024, Revise Date: 20 February 2024, Accept Date: 25 March 2024
DOI: 10.21608/EJCHEM.2024.265915.9267

antihyperglycemic [18], anti-histaminic [19], and anti-viral [20].

Furthermore, certain compounds such as pyrazoles and thiazoles demonstrated broad-spectrum antibacterial action [21,22]. They exhibit strong therapeutic actions including powerful anti-HIV drugs, and anticancer [7,8,21-27].

Several pyrazole-containing moieties have previously found their therapeutic application in clinical settings, as NSAIDs like phenylbutazone (for rheumatoid arthritis and osteoarthritis), antipyrine (for analgesic and antipyretic effects), novalgin, Tartrazine, Ramifenazone and many others are already present in the market [8,28].

Numerous common medications with a thiazole core are used in chemotherapy, including dasatinib (treats some cases of chronic myelogenous leukemia and acute lymphoblastic leukemia) and tiazofurin (has potential clinical use in cancer treatment as it is a potential inhibitor of Inosine- 5'-monophosphate (IMP) dehydrogenase 1) [7,27,28]. More than 18 FDA-approved medications have been found to include the thiazole scaffold. Recently, the FDA approved the drug alpelisib for the treatment of specific forms of breast cancer [29].

Compounds **1** and **2** are thought to have exceptional anti-inflammatory and analgesic profiles with a rapid onset of action along with a super GI safety profile and safety margin for compounds containing the thiazole ring system. Several drugs and active natural molecules such as epothilones (cancer drugs), vitamin thiamine, dasatinib (used for treatment of leukemia), sulfathiazole (antimicrobial drug), cefdaloxime (cephalosporin antibiotic), Sodelglitazar and tiazofurin (antineoplastic drug) have thiazole moiety **(Figure 1)**.

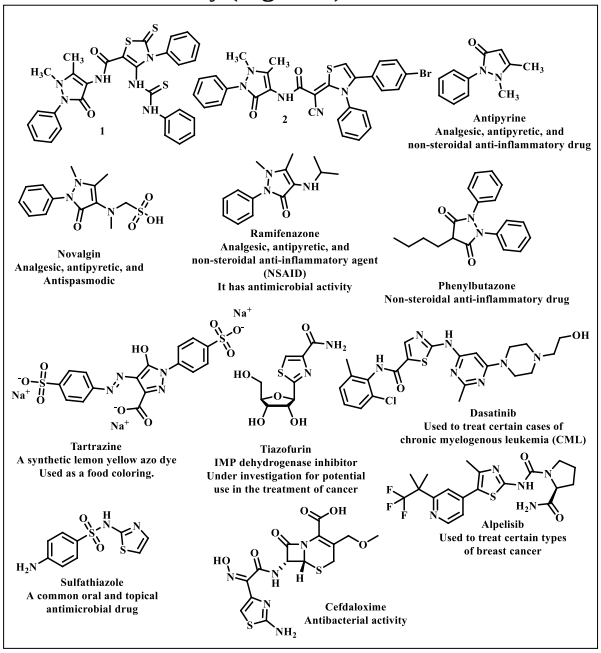


Fig. 1: The chemical structures of different pyrazole and thiazole- based drugs

We have reported here the practical method for the synthesis of novel derivatives based on thiazolyl-pyrazolone scaffold conjugated with 5,6,7,8-tetrahydronaphthalene as new hybrid molecules in the light of the aforementioned factors and in continuation of our investigations into the synthesis of biologically active heterocyclic compounds for finding new potent anticancer agents [30-37]. Using the LDH test, the newly synthesized compounds were evaluated as anticancer agents against the human cancer cell lines HCT-116, HepG-2 and MCF-7 as well as one healthy cell line (BJ-1) to study the safety profile of the new compounds.

The primary tyrosine kinase class responsible for endothelial cell proliferation, migration, survival, and angiogenic stimulation is called vascular endothelial growth factor receptor, or VEGFR [38,39].

Out of the three VEGF receptors, VEGFR-2 is the main receptor that causes the body's VEGF-stimulated angiogenesis and cell proliferation [38, 40]. Numerous malignancies have been shown to develop and spread through the upregulation of the VEGFR-2 signaling pathway [41,42]. Elevated levels of circulating VEGF have been reported in some metastatic tumors [43,44], and may be predictive of future outcomes for some malignancies.

Accordingly, the most active anticancer agents were evaluated as VEGFR inhibitors.

2. Experimental:

2.1. General

All newly synthesized compounds were measured their melting points using electric apparatus melting point (Weiss-Gallenkamp, London). Elemental analyses were determined in the Microanalytical unit, National Research Centre (NRC). FTIR spectra were recorded on a Bruker spectrometer (Bruker Tensor 27, Tokyo). The ^{1}H- and ^{13}C-NMR spectra were measured by NMR spectrometer a JEOL E.C.A-(500 MHz) for ^{1}H NMR using an internal standard TMS with deuterated DMSO solvent and 125 MHz for ^{13}C NMR in NRC, using. Chemical shifts (δ) were reported in parts per million (ppm) relative to an internal reference TMS and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu EIMS spectrometer (GCMS-QP 1000 EX, 70 Ev). Monitor the reactions follow and check the compounds purity via TLC (Type 60, F 254, Merck, Darmstadt, Germany) and were identified spots by UV light at 254 nm. Compound (**1**), was prepared as previously reported [36].

2.1.1. 2-bromo-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (1)

It was prepared by the reaction of acetyl tetralin with bromine according to the previously reported methodology [36].

2.1.2. General procedure for the synthesis of 6a-j

A reaction mixture of 1 mmol of 2- acetyl -1- (5, 6, 7, 8- tetrahydronaphthalen- 2- yl) bromide (**1**), 1 mmol of thiosemicarbazide and 1 mmol of ethyl acetoacetate was heated under reflux at 55^{o}C, 2 h in 10 ml of acetic acid, cooled; 2 mmol sodium acetate and 1.2 mmol aryl aldehyde were added and heated at 85^{o}C about 2 h. The gained precipitate that formed after cooling was filtered off washed with 3 × 10 ml water and 10 ml ethanol, respectively, dried in air and recrystallized from Ethanol/DMF mixture (2:1) to give **6** in good yield.

2.1.2.1. 4-benzylidene-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6a)

Yield: 78 %; brown powder; m.p.: 238-240^{o}C; IR (KBr, cm^{-1}): υ 2925 (CH, alicyclic), 1658 (C=O, pyrazolone), 1602 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.63-1.88 (m, 7H, 2CH$_2$ of tetrahydronaphthalene and CH$_3$ of pyrazolone), 2.61-2.70 (m, 4H, 2CH$_2$ of tetrahydronaphthalene), 6.85-7.61 (m, 9H, 8H- Ar-H and 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole); ^{13}C NMR (126 MHz, DMSO-d_6, δ ppm): 17.02 (CH$_3$), 23.15, 23.19 (2CH$_2$), 29.10, 29.28 (2CH$_2$), 108.53, 128.44, 128.92, 129.3, 129.36, 130.46, 131.88, 137.13, 137.37, 147.57, 149.84 and 162.83 (C=O); MS: m/z (%) 400.41 (M^{+}+1, 18); Analysis for $C_{24}H_{21}N_3OS$ (399.51), calcd.: C, 72.15; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.25; N, 10.49.

2.1.2.2. 3-methyl-4-(4-methylbenzylidene)-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6b)

Yield: 79%; black crystals; m.p.: 230-232^{o}C; IR (KBr, cm^{-1}): υ 2921 (CH, alicyclic), 1657 (C=O, pyrazolone), 1610 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.66-1.88 (m, 7H, 2CH$_2$ of tetrahydronaphthalene and CH$_3$ of pyrazolone), 2.27 (s, 3H, CH$_3$), 2.63-2.70 (m, 4H, 2CH$_2$ of tetrahydronaphthalene), 6.98-7.50 (m, 8H, 7H- Ar-H and 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 16.02 (CH$_3$), 21.12 (CH$_3$), 23.2, 23.25 (2CH$_2$), 29.09, 29.26 (2CH$_2$), 107.9, 122.39, 125.69, 128.06, 129.25, 130.08, 134.60, 136.88, 137.06, 143.82, 147.63, 150.7 and 162.82 (C=O); MS: m/z (%) 413.00 (M^{+}, 23), 411.50 (M^{+}-2, 21); Analysis for $C_{25}H_{23}N_3OS$ (413.54), calcd.: C, 72.61; H, 5.61; N, 10.16. Found: C, 72.57; H, 5.59; N, 10.17.

2.1.2.3. 4-(4-methoxybenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6c)

Yield: 77%; light brown crystals; m.p.: 248-250^{o}C; IR (KBr, cm^{-1}): υ 2926 (CH, alicyclic), 1668 (C=O, pyrazolone), 1607 (C=N), 1583 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.63-1.88 (m, 7H, 2CH$_2$ of tetrahydronaphthalene and CH$_3$ of pyrazolone), 2.61-2.69 (m, 4H, 2CH$_2$ of tetrahydronaphthalene), 3.69 (s, 3H, OCH$_3$), 6.88-7.61 (m, 8H, 7H- Ar-H and 1H. Ar-CH=), 7.92 (s, 1H, CH of thiazole); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 17.43 (CH$_3$), 23.20, 23.89 (2CH$_2$), 29.09, 29.29 (2CH$_2$), 55.57 (OCH$_3$), 108.94, 114.93, 116.93, 124.71, 125.82, 129.18, 129.32, 136.34, 137.09, 140.43, 141.22, 146.31, 151.83, 158.9 and 162.82 (C=O) ppm; MS: m/z (%) 431.74 (M^{+} +2, 59), 429.93 (M^{+}, 62); Analysis for $C_{25}H_{23}N_3O_2S$ (429.53), calcd.: C, 69.91; H, 5.40; N, 9.78. Found: C, 69.87; H, 5.37; N, 9.76.

2.1.2.4. 4-(3,5-dimethoxybenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6d)

Yield: 78%; brick red crystals; m.p.:224-226^{o}C; IR (KBr, cm^{-1}): υ 2925 (CH, alicyclic), 1656 (C=O, pyrazolone), 1592 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.66-1.88 (m, 7H, 2CH$_2$ of tetrahydronaphthalene and CH$_3$ of pyrazolone), 2.7 (br s, 4H, 2CH$_2$ of tetrahydronaphthalene), 3.66 (s, 6H, 2OCH$_3$), 6.38-7.66 (m, 7H, 6H- Ar-H and 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 11.88 (CH$_3$), 21.57, 23.19 (2CH$_2$), 29.10, 29.29 (2CH$_2$), 55.69, 56.45 (2OCH$_3$), 99.30, 104..76, 106.61, 106.93, 122.79, 125.49, 125.86, 126.88, 129.27, 131.65, 132.22, 136.92, 145.13, 145.97, 150.91, 161.19, 161.47 (C=O) ppm; MS: m/z (%) 458.49 (M+, 7), 453.26 (61); Analysis for $C_{26}H_{25}N_3O_3S$ (459.56), calcd.: C, 67.95; H, 5.48; N, 9.14. Found: C, 67.92; H, 5.45; N, 9.15.

2.1.2.5. 4-(3-hydroxy-4-methoxybenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6e)

Yield: 82 %; dark brown powder; m.p.: 280-282^{o}C; IR (KBr, cm^{-1}): υ 3215 (OH), 2921 (CH, alicyclic), 1658 (C=O, pyrazolone), 1605 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.66-1.88 (m, 7H, 2CH$_2$ of tetrahydronaphthalene and CH$_3$ of pyrazolone), 2.64-2.69 (m, 4H, 2CH$_2$ of tetrahydronaphthalene), 3.64 (s, 3H, OCH$_3$), 6.76-7.06 (m, 6H, Ar-H), 7.63 (s, 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole), 9.16 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 15.76 (CH$_3$), 23.21, 23.23 (2CH$_2$), 29.06, 29.13 (2CH$_2$), 56.37 (OCH$_3$), 108.51, 111.62, 116.35, 123.07, 125.98, 128.23, 129.23, 130.19, 133.52, 136.23, 137.39, 142.9, 145.08, 147.53 (C-OH), 149.16, 150.1 and 162.69 (C=O); MS: m/z (%) 443.66 (M^{+}-2, 100); Analysis for $C_{25}H_{23}N_3O_3S$ (445.53), calcd.: C, 67.40; H, 5.20; N, 9.43. Found: C, 67.36; H, 5.18; N, 9.39.

2.1.2.6. 4-(2-hydroxybenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6f)

Yield: 69%; black crystals; m.p.: 254-256^{o}C; IR (KBr, cm^{-1}): υ 3109 (-OH), 2921 (CH, alicyclic),

1656 (C=O, pyrazolone), 1605 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.65-1.88 (m, 7H, $2CH_2$ of tetrahydronaphthalene and CH_3 of pyrazolone), 2.65-2.70 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 6.84-7.22 (m, 7H, Ar-H), 7.64 (s, 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole), 9.66 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 15.78 (CH_3), 22.76, 23.24 ($2CH_2$), 29.16, 29.43 ($2CH_2$), 108.63, 117.25, 123.68, 126.88, 128.13, 129.06, 129.15, 130.30, 131,71, 136.54, 138.12, 148.64, 151.22, 152.41, 154.85 and 162.82 (C=O); MS: m/z (%) 414.66 (M^+-1, 15); Analysis for $C_{24}H_{21}N_3O_2S$ (415.51), calcd.: C, 69.37; H, 5.09; N, 10.11. Found: C, 69.35; H, 5.07; N, 10.09.

2.1.2.7. 4-((3-methyl-5-oxo-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-4(5H)-ylidene)methyl)benzonitrile (6g)

Yield: 85 %; dark brown crystals; m.p.: 232-234 ^{o}C; IR (KBr, cm^{-1}): *υ* 2918 (CH, alicyclic), 2226 (CN), 1655 (C=O, pyrazolone), 1606 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.66-1.96 (m, 7H, $2CH_2$ of tetrahydronaphthalene and CH_3 of pyrazolone), 2.62-2.69 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 6.92-7.84 (m, 8H, 7H- Ar-H and 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole); ^{13}C NMR (125 MHz, DMSO-d_6, *δ* ppm) 15.08 (CH_3), 23.16, 23.2 ($2CH_2$), 29.08, 29.3 ($2CH_2$), 109.97, 111.14, 117.66 (CN), 122.84, 126.89, 127.93, 129.98, 130.84, 133, 137.24, 137.54, 143.07, 147.2, 150.25 and 162.84 (C=O); MS, m/z (%): 424.14 (M^+, 12); Analysis for $C_{25}H_{20}N_4OS$ (424.52), calcd.: C, 70.73; H, 4.75; N, 13.20. Found: C, 70.69; H, 4.72; N, 13.18.

2.1.2.8. 4-(4-fluorobenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6h)

Yield: 77%; brown powder; m.p.: 256-258^{o}C; IR (KBr, cm^{-1}): *υ* 2919 (CH, alicyclic), 1653 (C=O, pyrazolone), 1602 (C=N), 1224 (C-F); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.65-1.88 (m, 7H, $2CH_2$ of tetrahydronaphthalene and CH_3 of pyrazolone), 2.62-2.69 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 6.87-7.40 (m, 7H, Ar-H), 7.63 (s, 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 16.03 (CH_3), 23.11, 23.18 ($2CH_2$), 29.08, 29.27 ($2CH_2$), 109.28, 115.94, 116.45, 122.97, 127.11, 128.92, 129.48, 129.77, 130.31, 137.18, 137.34, 143.46, 146.03, 149.28, 151.29, 154.08, 162.84 (C-F) and 163.34 (C=O); MS, m/z (%): 416.47 (M^+ -1, 100); Analysis for $C_{24}H_{20}FN_3OS$ (417.50), calcd.: C, 69.04; H, 4.83; N, 10.06. Found: C, 69.08; H, 4.79; N, 10.09.

2.1.2.9. 4-(4-chlorobenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6i)

Yield: 67%; brown powder; m.p.: 272-274^{o}C; IR (KBr, cm^{-1}): *υ* 2928 (CH, alicyclic), 1654 (C=O, pyrazolone), 1599 (C=N), 813 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.65-1.88 (m, 7H, $2CH_2$ of tetrahydronaphthalene and CH_3 of pyrazolone), 2.61-2.69 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 6.83-7.54 (m, 8H, 7H- Ar-H and 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, *δ* ppm): 15.57 (CH_3), 23.19, 23.25 ($2CH_2$), 29.12, 29.51 ($2CH_2$), 108.41, 126. 87, 129.03, 129.23, 129.44, 130.28, 133.11, 134.13, 136.88, 137.69, 139.98, 143.14, 143.16, 147.27, 150.71 and 165.78 (C=O); MS, m/z (%): 433.54 (M^+, 5); Analysis for $C_{24}H_{20}ClN_3OS$ (433.95), calcd.: C, 66.43; H, 4.65; N, 9.68; Found: C, 66.39; H, 4.63; N, 9.69.

2.1.2.10. 4-(4-bromobenzylidene)-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-one (6j)

Yield: 74%; brown powder; m.p.: 230-232^{o}C; IR (KBr, cm^{-1}): *υ* 2924 (CH, alicyclic), 1653 (C=O, pyrazolone), 1590 (C=N), 660 (C-Br); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.63-1.91(m, 7H, $2CH_2$ of tetrahydronaphthalene and CH_3 of pyrazolone), 2.62-2.69 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 6.83-7.62 (m, 8H, 7H- Ar-H and 1H, Ar-CH=), 7.92 (s, 1H, CH of thiazole) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, *δ* ppm): 14.33 (CH_3), 23.18, 23.21 ($2CH_2$), 29.11, 29.15 ($2CH_2$), 108.12, 115.58, 122.78 (C-Br), 123.7, 127.81, 128.75, 129.25, 129.69, 130.61, 136.97, 137.31, 143.48, 145.82, 150.53 and 162.8 (C=O); MS: m/z (%) 478.05 (M^+, 3); Analysis for $C_{24}H_{20}BrN_3OS$ (478.40), calcd.: C, 60.25; H, 4.21; N, 8.78. Found: C, 60.23; H, 4.19; N, 8.75.

2.2. Biological activity

2.2.1. Anticancer potentiality against human cell lines

The cytotoxicity of the synthesized compounds was assessed using lactate dehydrogenase (LDH) release assay as described previously [45-49].

2.2.2. VEGFR2/(KDR) Kinase Assay

Vascular endothelial growth factor receptor 2 (VEGFR2) inhibition was carried out according to the manufacture supplied protocol (BPS Bioscience, San Diego, CA 92121, Cat. #40325) using Kinase-Glo® MAX as a detection reagent (Promega, Cat. #V6071) [45].

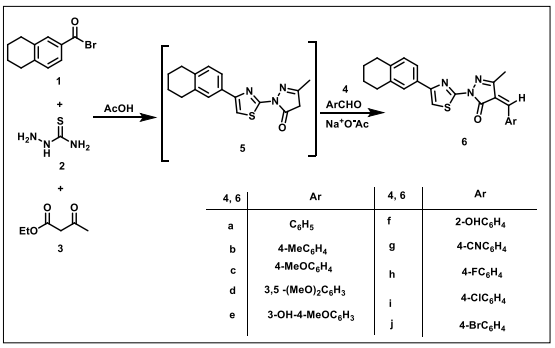
3. Results and discussion

3.1. Chemistry

In accordance with the previously outlined protocol, 2-acetyl-tetrahydronaphthalene was reacted with bromine to produce the crucial starting

compound, 2-acetyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)bromide **1** [36].

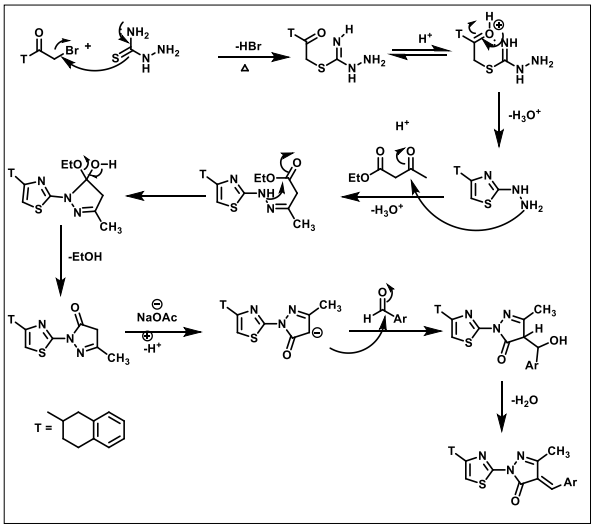
Equimolar amounts of 2-bromo acetyl tetralin **1**, thiosemicarbazide **2**, and ethyl acetate **3** were combined in heated CH_3COOH at 55°C to produce 3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1*H*-pyrazol-5(4*H*)-one **5** with an active CH_2 group. Aryl aldehyde **4** and sodium acetate as a base were added to the reaction mixture without isolating the intermediate **5**. The desired products, the thiazolyl-pyrazolone derivatives **6a–j**, are produced in good yields by undergoing a Knovenagel condensation reaction on the intermediate **5** and then an intramolecular dehydration [50] **(Scheme 1)**.



Scheme 1: Synthesis of 4-arylidene-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1*H*-pyrazol-5(4*H*)-one derivatives **6**

The mechanism of the reaction that led to the formation of products **6** was depicted in **Scheme 2** and is probably similar to those described in publications by Venkata *et al*. [51] and Aychiluhim *et al*. [52]. A 2-hydrazinyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazole was produced when the bromine atom of 2-acetyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)bromide **1** was swapped out for a sulfur atom from a thiosemicarbazide, resulting in the formation of an open chain-thio ketone, which underwent protonation and intermolecular condensation to furnish a Hantzsch-thiazole product (2-hydrazinyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazole). In order to capitulate the pyrazolone moiety 3-methyl-2-(4-(5,6,7,8-tetrahydronaphthalen-2-yl) pyrazol-5-on-1-yl) thiazole **5**, which has an active CH_2, the latter thiazolyl hydrazine underwent cyclocondensation reaction with ethylacetoacetate **(Scheme 2)**, which, in turn, underwent the Knoevenagel condensation reaction with different aromatic aldehydes on active methylene group without isolation of the intermediate **5 (Scheme 2)**.

Here, the base (sodium acetate) participated in the reaction by generating a carbanion, which then underwent nucleophilic addition and intramolecular dehydration of a water molecule to produce the desired products **6** in good yields [51,53].



Scheme 2: A plausible mechanism for the formation of compounds **6**

The obtained spectral analysis (FTIR, ^{1}HNMR, ^{13}CNMR), as well as elemental analysis, served as the foundation for the establishment of all the structures of the newly synthesized compounds **6a–6j**. The infrared spectrum (IR) of compound **6a** as a representative example of the corresponding derivatives of **6** exhibited an absorption band for (CO) at 1658 cm^{-1} of pyrazolone. Its ^{1}H-NMR spectrum in DMSO-d_6 displayed multiplet signals at δ1.63-1.88 ppm indicating that the CH_3 of pyrazolone ring overlapped with the signals $2CH_2$ of tetralin as well as multiplet signals at δ 6.85–7.61 ppm for the aromatic and the protons of vinylic group. In addition, a singlet signal was observed at δ 7.92 ppm indicating the proton of thiazole-C5. The ^{13}C NMR of **6a** showed a signal at δ 17.02 ppm for methyl group in the pyrazolone moiety and at δ 162.83 ppm for C=O of pyrazolone. The remaining carbons of the proposed structure of compound **6a** were observed in the expected regions which in agreement with the proposed structure.

Similarly ^{1}H NMR spectrum of **6g** displayed multiplet signals in the region δ 1.66-1.96 ppm indicating the $2CH_2$ of tetralin and the CH_3 of the pyrazolone ring and multiplet signals at δ 6.92–7.84 ppm for the vinylic and aromatic protons, and also a singlet at δ 7.92 ppm indicating the proton of thiazole-C5. The ^{13}C-NMR of compound **6g** exhibited the signals at δ 15.08 ppm for methyl in the pyrazolone ring, *δ* 117.66 for CN, and at δ 162.10 for C=O of pyrazolone ring. The IR spectrum of **6g** showed prominent bands at 2226 cm^{-1} for CN and 1655 for C=O of the pyrazolone ring. Elemental analysis is in good agreement with calculated values. All the spectral data clearly showed the formation of products **6a–j**.

In our work, the methodology is characterized by informal workup, mild conditions, short reaction time and clean reaction profile with wide range of substrate applicability

3.2. Biological activity

3.2.1. *In Vitro* Antiproliferative activity

The selected compounds were investigated *in vitro* on HCT-116, HepG-2 and MCF-7 human cancer cells as well as one human normal cell line (BJ-1) by the LDH assay. The dead cells % was evaluated relative to those of the control and compared to that of doxorubicin. These compounds suppressed all cells in a dose-dependent manner **(Figs. 2 - 4)**. Regarding of HCT-116 human colorectal carcinoma cells according to both **Fig. 2** and **Table 1** it is observed that five compounds (**6i**, **6e**, **6f**, **6c** and **6a**, respectively) have comparable cytotoxic activities; the rest of the compounds have moderate cytotoxic activity on HCT-116 comparative to that of doxorubicin. Regarding of MCF-7 human breast cancer cells: all compounds have comparable cytotoxic activities on MCF-7 related to the reference drug (**Fig. 3** &**Table 1**). Regarding of HepG-2 human liver cancer cells: all compounds have superior cytotoxic activities on HepG-2 related to that of doxorubicin (**Fig. 4** &**Table 1**). Regarding of the non-tumor fibroblast-derived cell line (BJ): both **Fig. 5** and **Table 1** show that all the compounds have less cytotoxic activities against the healthy cells relative to that of doxorubicin.

By comparing the cytotoxicity results on all cancer types relative to normal cell line, one can conclude that's: five compounds (**6a**, **6c**, **6e**, **6f** and **6i**) are having good cytotoxic activities on the three human cancer types; five compounds (**6b**, **6d**, **6g**, **6**h and **6j**) are having good cytotoxicity on both human liver and breast cancer types rather than on the human colon cancer type.

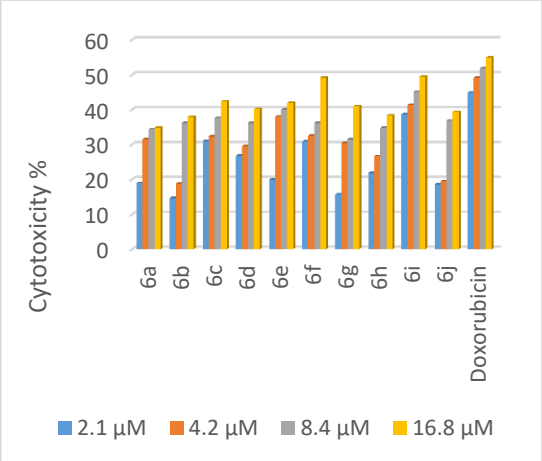


Fig. 2. Antiproliferative data of the selected compounds on HCT-116 cancer cells via LDH assay after 48 h of exposure.

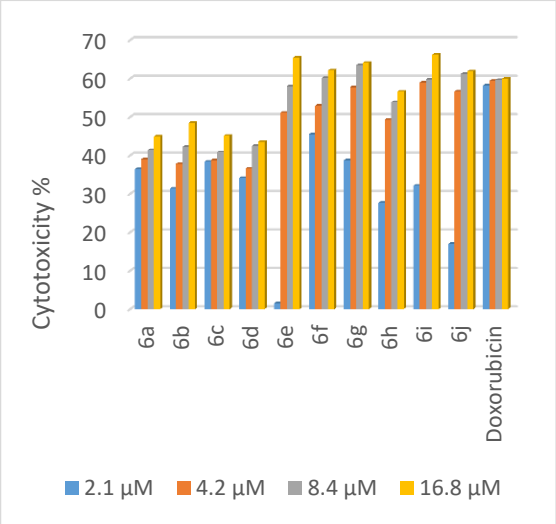


Fig. 3. Antiproliferative data of the selected compounds on MCF-7 cancer cells by LDH assay after 48 h of exposure.

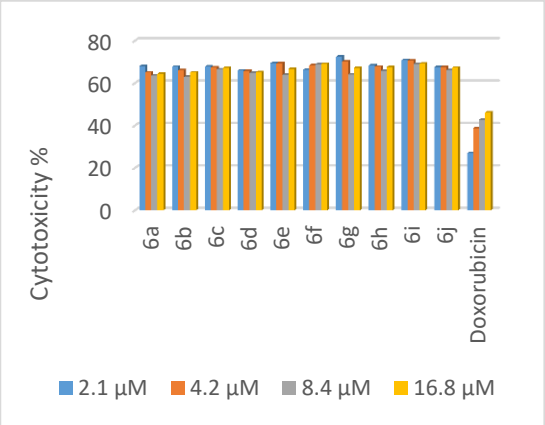


Fig. 4. Antiproliferative data of the selected compounds on HepG-2 cancer cells by LDH assay after 48 h of exposure.

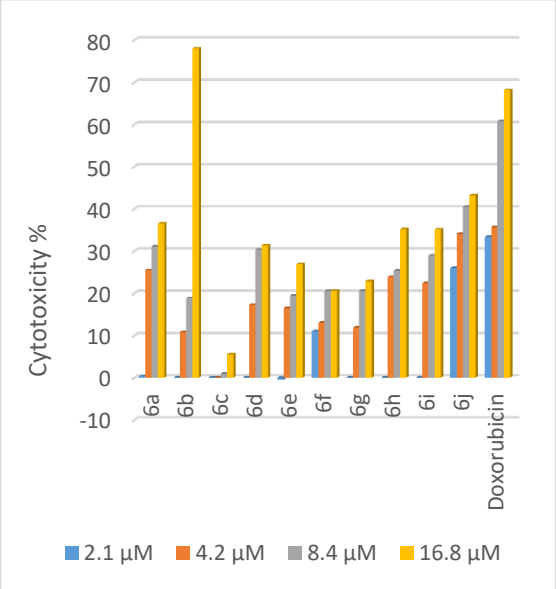


Fig. 5. Antiproliferative data of the selected compounds on BJ-1 normal cells by LDH assay after 48 h of exposure.

Table 1: The antiproliferative activities of compounds **6a-j** (IC_{50}; µM) against the four cell lines using LDH assay

Compound Code	IC_{50} (µM) ± SD			
	HCT-116	**HepG-2**	**MCF-7**	**BJ-1**
6a	6.7 ± 0.6	1.5 ± 0.1	5.3 ± 0.2	13.5 ± 1.5
6b	11.2 ± 1.2	1.6 ± 0.1	5.6 ± 0.3	22.2 ± 2.2
6c	6.5 ± 0.9	1.5 ± 0.1	5.4 ± 0.3	> 400
6d	7.1 ± 1.0	1.6 ± 0.1	5.7 ± 0.2	13.8 ± 1.9
6e	5.5 ± 0.4	1.5 ± 0.1	4.1 ± 0.2	21.5 ± 2.1
6f	6.5 ± 0.4	1.6 ± 0.2	4.0 ± 0.1	20.4 ± 2.3
6g	6.9 ± 0.6	1.4 ± 0.1	3.6 ± 0.2	20.3 ± 2.2
6h	7.9 ± 1.1	1.5 ± 0.1	4.3 ± 0.2	15.5 ± 1.4
6i	5.1 ± 0.3	1.5 ± 0.1	3.6 ± 0.2	14.5 ± 1.3
6j	10.8 ± 1.1	1.6 ± 0.1	3.7 ± 0.1	10.4 ± 1.1
Doxorubicin	4.3 ± 0.2	5.4 ± 0.3	1.8 ± 0.2	6.9 ± 0.3

3.2.2. VEGFR-2 (KDR) Kinase Assay

Since VEGFR-2, which is tyrosine kinase (TK) receptor for VEGFs, plays an important role in tumor angiogenesis. Therefore, its inhibition is a wise targeting therapeutic strategy for inhibiting tumor angiogenesis and growth [54,55]. Based on the cytotoxicity results and in order to find out the anticancer mechanism of the excellent derivatives, three compounds (**6e**, **6g**, **6i**) were selected for further assessment of their *in vitro* VEGFR-2 inhibitory activity. The results of this assay revealed that the three selected investigated compounds (**6e**, **6g**, **6i**) showed very promising activities as they all inhibited the VEGFR-2 at very low IC_{50} **(Table 2)** compared to their cytotoxicity IC_{50} results **(Table 1)**.

Table 2: The *in vitro* inhibitory IC_{50} values of compounds **6e**, **6g**, and **6i** against VEGFR-2 Kinase

Compound Code	IC_{50} (µg/ml) ± SD
6e	0.2142 ± 0.008
6g	0.1408 ± 0.005
6i	0.534 ± 0.021
Sorafenib	0.31 0.001

3.3. Molecular docking study

The simulation of molecular docking was carried out to evaluate the interaction between the synthesized pyrazolone based derivatives and binding site of active pocket of Vascular Endothelial Growth Factor Receptor (VEGFR-2/KDR) kinase. MOE (Molecular Operating Environment) software version 2008.10 was used for molecular docking [56], The co-crystal arrangement of sorafenib with VEGFR-2/KDR kinase was chosen as the docking model , which was verified by re-docking of Sorafenib as the native ligand in active binding site of the VEGFR-2. The docking score for sorafenib in the VEGFR-2/KDR active areas exhibited an energy (S) of -9.69 kcal/mol. Figure 9 illustrated the interactions between Sorafenib and with active site residues of VEGFR-2. The binding mechanism of sorafenib with VEGFR-2, which was derived from the crystallographic complex accessible in the Protein Data Bank (4ASD.pdb, https://www.rcsb.org/structure/4ASD) was used to construct the molecular design of the Pyrazolone based derivatives as VEGFR-2 inhibitor [57-59].

Binding ability of Sorafenib depends on the urea linker which clearly plays an important role for the enzyme's allosteric VEGFR-2 position to produce significant hydrogen bonds with necessary amino acids binding residues. Sorafenib exhibited two H-bond donations: one H-bond donations between NH of urea side chain with Glu885 and other one H-bond donation between hydrogen in -NHCO- side chain with CYS919. Sorafenib also showed two H-bond acceptors between nitrogen atom in pyridine ring with CYS919 and other one hydrogen acceptor between the oxygen of urea moiety and ASP1046 (incorporated in Figure 9 as a 2D and 3D visualization). Molecular docking investigation revealed that the Pyrazolones (**6e**, **6g**, and **6i**) (Fig.10) connect with the active site of VEGFR-2/KDR kinase enzyme in manner analogues to Sorafenib, with binding energies ranging from -9.57 to -10.30 kcal/mol and root mean standard deviation (RMSD) of 1 Å. Table 3 highlights the energy levels and receptor interactions of type II VEGFR-2 inhibitors in comparison to the native ligand (Sorafenib).

Eventually, compounds **6e**, **6g**, and **6i** showed successful fitting with VEGFR-2/KDR kinase with superior docking score (S= -9.83, -10.30, and -9.57 -kcal/mol respectively) to native ligand (Sorafenib). (S = −9.69 kcal/mol) as illustrated in Table3. The docking results revealed that the most powerful inhibitors were **6g** and **6e** (Figs. 7, 6). The binding affinity of compound 6g was -10.30 kcal/mol. Furthermore, as shown in Figure 7, compound **6g** was strongly linked to the important key amino acids ASP1046, ARG1027, and LYS868 via H bonding and arene-cation interactions. On the other hand, compound **6e**

demonstrated a high binding energy value of -9.83 kcal/mol. In addition , compound **6e** is similar to the reference compound sorafenib with the same H-bond between interaction with ASP1046, CYS919, and GLU917 through formation of H bonds in the active site of protein residues of VEGFR-2/ KDR (as described in Figure 6), on the other hand, compounds **6i** in type II VEGFR-2 inhibitor showed 2 H-bond acceptors between the nitrogen atoms in pyrazolone and thaizole rings with LYS868,and Arene-cation bond interactions with Lys868 and ARG 1027 as depicted in (Figure 8 as a 2 and 3D view). Molecular docking study shows that compound **6e**, as VEGFR-2/KDR inhibitor, exhibited two H-bonds: one H-bond donor between H in hydroxyl group based phenyl ring in tetralin skeleton with GLU917, and another H-bond acceptor between methoxy and hydroxyl groups based phenyl ring with CYS919 and H-bond acceptor between nitrogen of thiazole nucleus with Asp1046. Compound 6g forms two H-bond acceptors, one between the thiazole moiety's nitrogen atom and ASP1046 and the other with ARG1027. Furthermore, there is a -H bond interaction with LYS868. As seen in Fig. 7.

The docking results also provide us a new route to synthesize new VEGFR-2/KDR kinase inhibitors that can interact with main amino acids (CYS919 and ASP1046). The molecular docking study may give the rational design of more powerful VEGFR-2/KDR inhibitors.

Table 3: Molecular docking data of the newly synthesized compounds **6e**, **6g** and **6i** comparing with the native ligand Sorafenib into the active pocket of VEGFR-2 inhibitor (PDB code: 4ASD) utilizing MOE software version 2008.10

Compd. NO.	Docking Score (Kcal/mol)	Amino Acid Residues (Bond Length Å	Atoms of Compound	Type of Bond
6e	-9.83	GLU917 (1.51);CYS919(2.65, 3.00);ASP1046(2.76)	H(OH) $O(OCH_3)$ O(OH) N(Thiazole ring)	H-don H-acc H-acc H-acc
6g	-10,30	ARG 1027(2.92);ASP 1046(3.14);LYS 868	N(CN), N(thiazole rin	H-acc H-acc Arene-cation
6i	-9.57	LYS868 (2.94); LYS868 (3.00); ARG1027	N(Pyrazolone ring) N(thiazole ring)	H-acc H-acc Arene-cation
Sorafenib	-9.69	GLU885 (1.58); CYS919 (3.05, 1.94);ASP1046(2.51)	H(NH-CO-NH) N(pyridine ring) $H(CH_3$-NHCO) O(NH-CO-NH)	H-don H-acc H-don H-acc

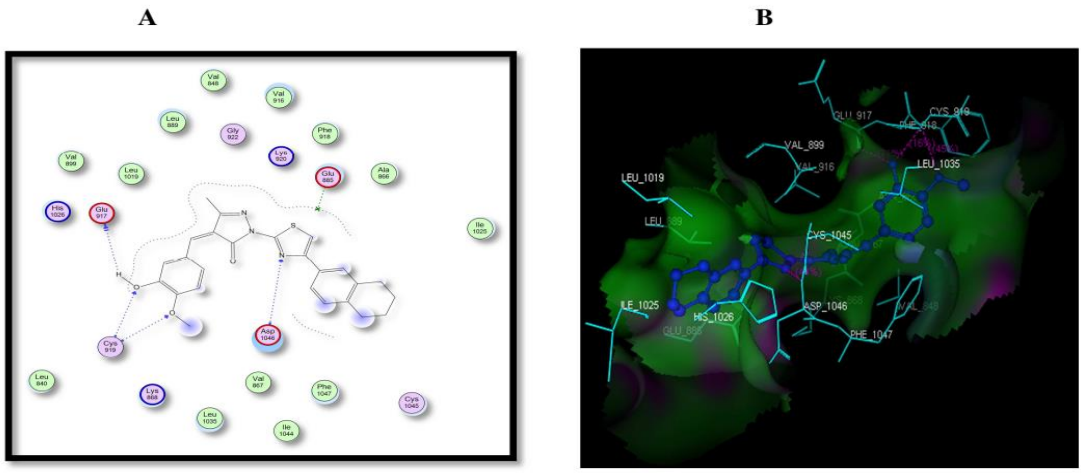


Fig. 6: 2D (A) and 3D (B) visualization images Illustrated the position of the targeted compound **6e** in the binding site of VEGFR-2 (PDB code:4ASD).

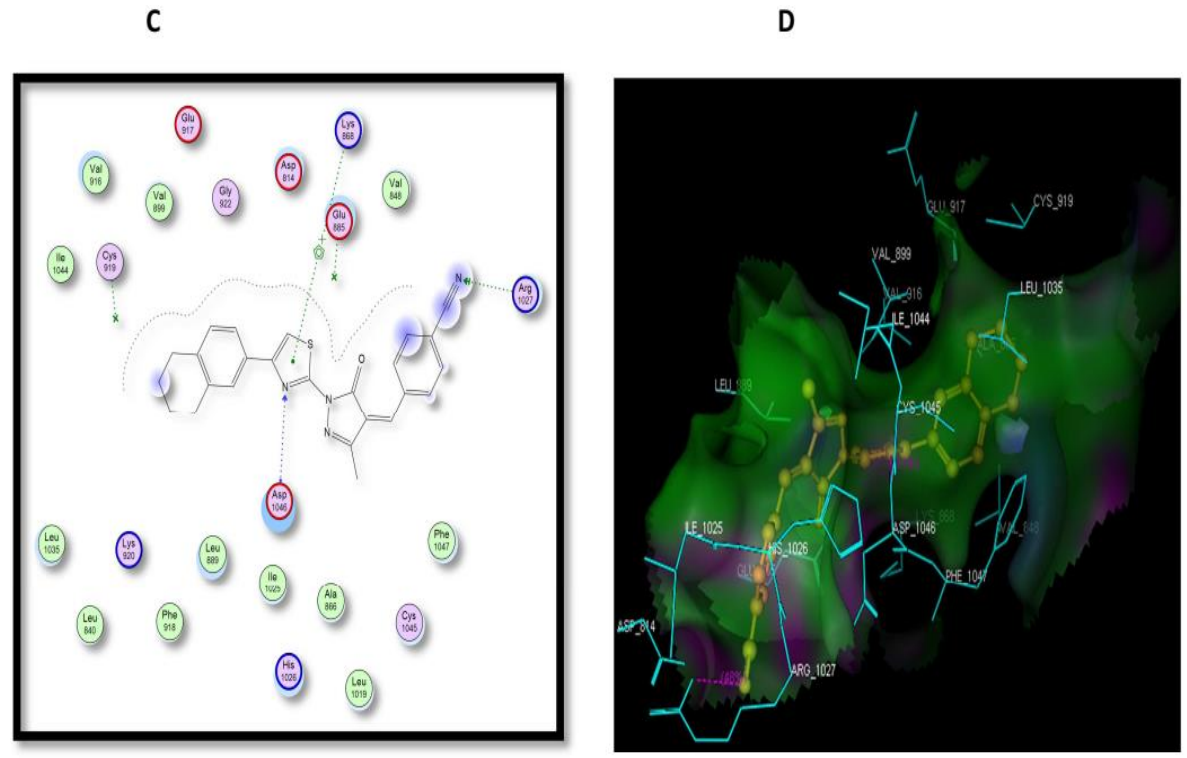


Fig. 7: 2D(C) and 3D(D) visualization images showed the interaction of compound **6g** in the active site of VEGFR-2 (PDB code:4ASD).

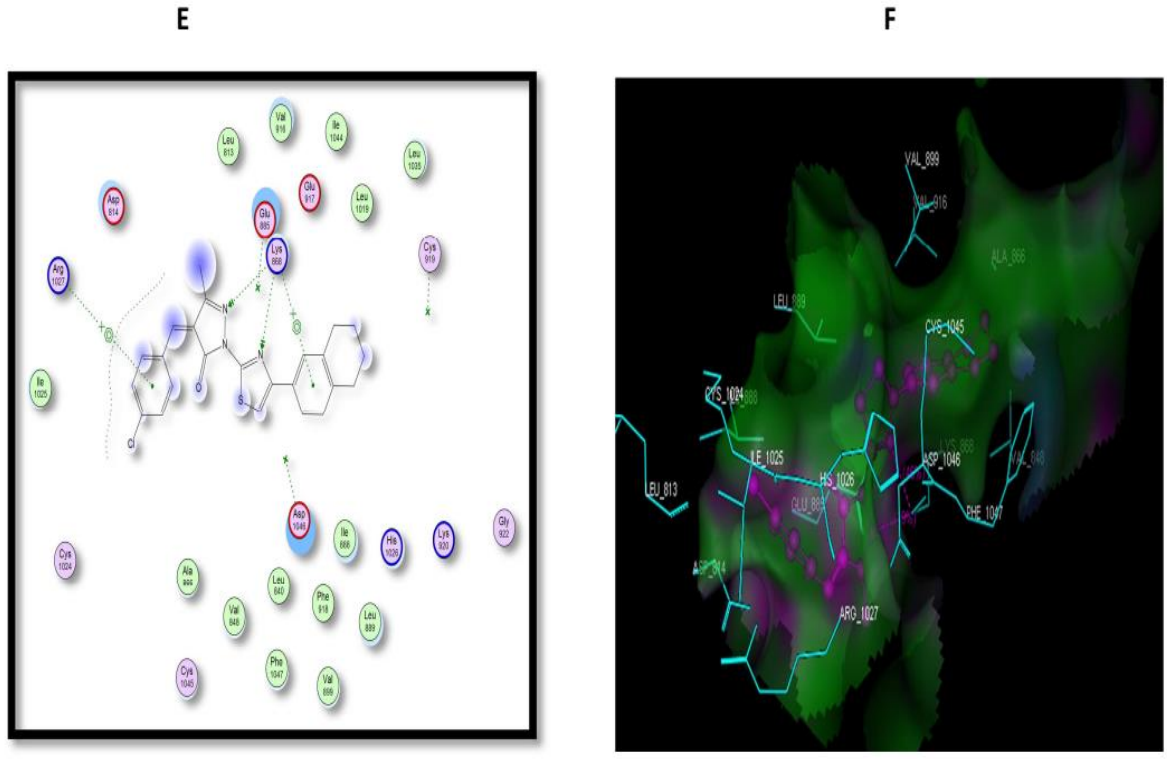


Fig. 8: 2D(E) and 3D(F) visualization images Illustrated the position of the original **6i** in the binding pocket site of VEGFR-2 (PDB code:4ASD).

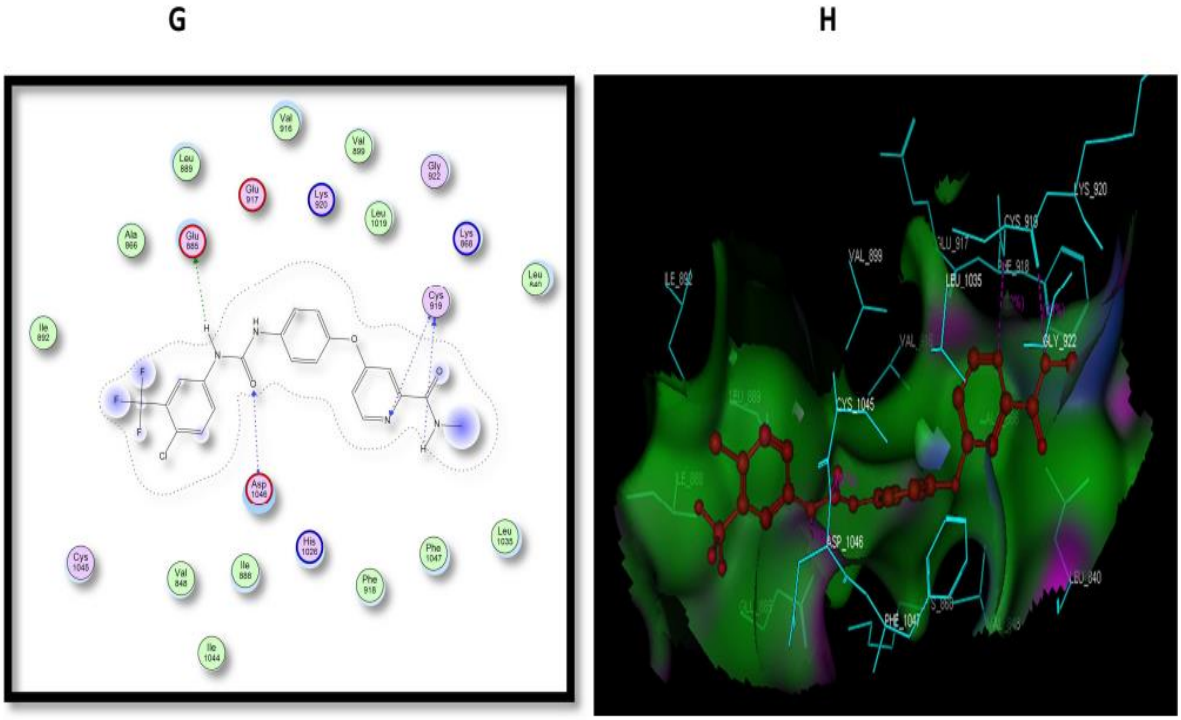


Fig.9: 2D(G) and 3D (H) visualization images of the co-crystallized ligand (sorafenib)inside the active site pocket of VEGFR-2 (4ASED).

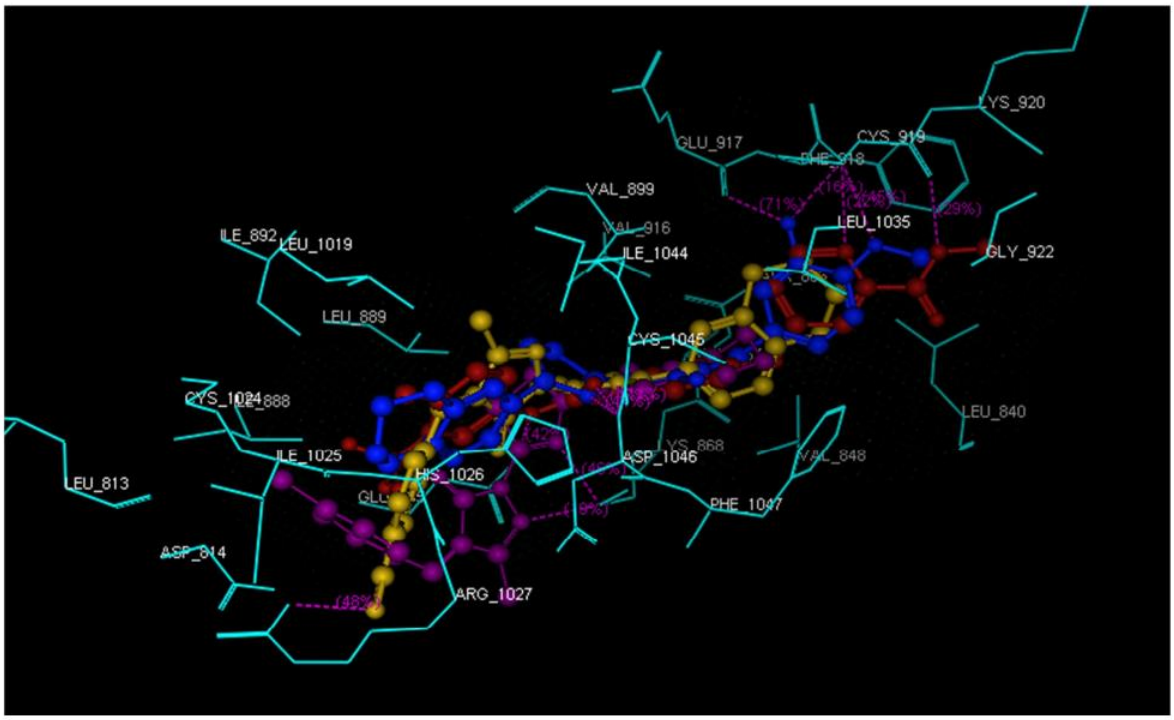


Fig. 10. 3D visualization images are presented to elucidate the superimposition of the novel chemical entities, namely **6e** (depicted in blue), **6g** in (yellow) and **6i** (in purple), in contrast to the reference drug sorafenib (represented in red) into the active pocket of VEGFR-2 (PDB code: 4ASD).

4. Conclusions

In conclusion, a novel and facile series of 4-arylidene-3-methyl-1-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)-1H-pyrazol-5(4H)-ones **6a-j** has been synthesized through one-pot reaction. Short reaction time, mild conditions, simple operation, simplified purification and good yields are some of the noteworthy features of this protocol. (IR, ^{1}H NMR and ^{13}C NMR confirmed their assumed structures). Additionally, a molecular docking analysis is performed to elucidate the binding interactions of majority effective derivatives (**6e**, **6g**, and **6i**) within the active sites of Vascular Endothelial Growth Factor Receptor (VEGFR-2) kinase. These compounds demonstrated highly profitable binding interaction scores with the targeted enzyme. Moreover, bioassay results showed the significant inhibition of VEGFR-2 by the three selected compounds (**6e**, **6g**, **and 6i**) at remarkably low IC_{50} values **(see Table 2)** in comparison to their cytotoxicity IC_{50} outcomes as shown in **Table 1**.

5. Conflict of interest

The authors declare that the article content has no conflict of interest.

6. Acknowledgement

The authors are thankful to National Research Centre, Dokki, Giza, 12622, Egypt for their financial support through the in-house fund for project number 13060101.

7. References

[1] K. Ibiş, E. Nalbat, B. Çalışkan, D.C. Kahraman, R. Cetin-Atalay, E. Banoglu, Synthesis and biological evaluation of novel isoxazole-piperazine hybrids as potential anti-cancer agents with inhibitory effect on liver cancer stem cells, *Eur. J. Med. Chem.* 221 (2021) 113489-113509. https://doi.org/10.1016/j.ejmech.2021.113489.

[2] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA: Cancer J. Clin.* 71 (2022) 209-249. https://doi.org/10.3322/caac.21660.

[3] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, *Cell.* 100 (2000) 57–70. https://doi.org/10.1016/S0092-8674(00)81683-9.

[4] T. Mikalsen, N.G. Gerits, U. Gerits, Inhibitors of signal transduction protein kinases as targets for cancer therapy, *Biotechnol. Annu. Rev.* 12 (2006) 153–223. https:// doi.org/10.1016/S1387-2656(06)12006-2.

[5] K. Bukowski, M. Kciuk, R. Kontek, Mechanisms of Multidrug Resistance in Cancer Chemotherapy, *Int. J. Mol. Sci.* 21 (2020) 3233-3256. https://doi.org/10.3390/ ijms21093233.

[6] P.A. Halim, S.M. Sharkawi, M.B. Labib, Novel pyrazole-based COX-2 inhibitors as potential anticancer agents: Design, synthesis, cytotoxic effect against resistant cancer cells, cell cycle arrest, apoptosis induction and dual EGFR/Topo-1 inhibition, *Bioog. Chem.* 131 (2023) 106273-106273. https://doi.org/10.1016/j.bioorg.2022.106273

[7] A.M. Katz, C.M. Pearsom, J.H. Kannedy, A.Clinical trial of indomethacin in rheumatoid arthritis, *Clin. Pharmacol. Ther.* 6 (1965) 25–30.

[8] Md. J. Alam, O. Alam, M. J. Naim, F. Nawaz, A. Manaithiya, Recent Advancement in Drug Design and Discovery of Pyrazole Biomolecules as Cancer and Inflammation Therapeutics, *Molecules* 27 (2022) 8708-8734.

[9] Z. Ratkovic, Z.D. Juranic, T. Stanojkovic, D. Manojlovic, R. D. Vukicevic, N. Radulovic, M. D. Joksović, Synthesis, characterization, electrochemical studies and antitumor activity of some new chalcone analogues containing ferrocenyl pyrazole moiety, *Bioorg. Chem.* 38 **(**2010) 26- 32.

[10] B. Rafia, O. Syed, Y. Shafiya, H. Hinna, M. S. Alam, S. Mohammad, S. Surender, J. Kalim, Synthesis of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulfonamide as anticancer and anti-inflammatory agents, *Bioorg. Med. Chem. Lett.* 21 (2011) 4301- 4305.

[11] I. Braulio, T. Alexis, O. Fabian, Q. Jairo, A. Rodrigo, N. Manuel, S. Adolfo, C. Justo, Synthesis of novel pyrazolic analogues of chalcones and their 3-aryl-4-(3-aryl-4,5-dihydro-1*H*-pyrazol-5- yl)- 1-phenyl-1*H*-pyrazole derivatives as potential antitumor agents, *Bioorg. Med. Chem.* 18 (2010) 4965-4974.

[12] X. Li, X. Lu, M. Xing, X. Yang, T. Zhao, H. Gong, H. Zhu, Synthesis, biological evaluation, and molecular docking studies of N,1,3-triphenyl-1H-pyrazole-4-carboxamide derivatives as anticancer agents, *Bioorg. Med. Chem. Lett.* 22 (2012) 3589- 3593.

[13] Y. Xia, Z.W. Dong, B.X. Zhao, X. Ge, N. Meng, D.S. Shin, J.Y. Miao, Synthesis and structure activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide derivatives as potential agents against A549 lung cancer cells, *Bioorg. Med. Chem.* 15(22) (2007) 6893- 6899.

[14] S. Bondock, W. Fadaly, M. A. Metwally, Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety, *Eur. J. Med. Chem.* 45 (2010) 3692- 3701.

[15] I. G. Rathish, J. Kalim, A. Shamim, B. Sameena, M. S. Alam, K. K. Pillai, S. Surender, B. Vivek, Synthesis and antiinflammatory activity of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulfonamide, *Bioorg. Med. Chem. Lett.* 19 (2009) 255- 258.

[16] S. Joshi, P. G. Mandhane, S. D. Diwakar, S. K. Dabhade, C. H. Gill, Synthesis, analgesic and anti-inflammatory activities of some novel pyrazolines derivatives. *Bioorg. Med. Chem. Lett.* 20 (2010) 3721- 3725.

[17] T. S. Jeong, K. S. Kim, J. R. Kim, K. Y. Cho, S. Lee, W. S. Lee, Novel 3,5-diaryl pyrazolines and

pyrazole as low-density lipoprotein (LDL) oxidation inhibitor, *Bioorg. Med. Chem. Lett.* 14 (2004) 2719- 2723.
[18] P. A. Datar, S. R. Jadhav, Design and synthesis of pyrazole-3-one derivatives as hypoglycaemic agents, *Inter. J. Med. Chem.* 2015 (2015) 1- 10.
[19] V.; Alagarsamy, V. R. Solomon, M. Murugan, Synthesis and pharmacological investigation of novel 4- benzyl- 1-substituted-4H-[1,2,4] triazolo[4,3-a]quinazolin-5-one as new class of H1-antihistaminic agents, *Bioorg. Med. Chem.* 15 (12) (2007) 4009- 4015.
[20] S. A. F. Rostom, M. A. Shalaby, M. A., El-Demellawy, Polysubstituted pyrazoles, part 5.1 Synthesis of new 1-(4- chlorophenyl)-4-hydroxy-1H-pyrazole- 3-carboxylic acid hydrazid analogs and some derived ring systems, A novel class of potential antitumor and anti-HCV agents, *Eur. J. Med. Chem.* 38 (2003), 959-974.
[21] S. A. F. Rostom, I. M. El-Ashmawy, H. A. Abd El Razik, M. H. Badr, H. M. A. Ashour, Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents, *Bioorg. Med. Chem.* 17 (2009) 882-895.
[22] N. Siddiqui, M. F. Arshad, W. Ahsan, M. Sh. Alam, Thiazoles: A Valuable Insight into the Recent Advances and Biological Activities, *Int. J. Pharm. Sci. Drug Res*, 1 (3) (2009) 136-143.
[23] A. Hassanabadi, M. Tabatabaei, Kh. Barani, J. Saffari, Synthesis of 4-arylidene-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-ones through a four-component condensation, *J. Chem. Res.* 39 (2015) 601-602.
[24] M. Propsavin, L. Torovic, S. Spaic, S. Stankov, A. Kapor, Z. Tomic, V. Popsavin, Synthesis and biological evaluation of new pyrazole- and tetrazole-related C-nucleosides with modified sugar moieties, *Tetrahedron* 58 (2002) 569- 580.
[25] P.D. Sauzem, P. Machado, M.A. Rubin, S. G. Da Sant'Anna, H.B. Faber, A.H. De Souza, C.F. Mello, P. Beck, R.A. Burrow, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, D. Patricia, Design and microwave-assisted synthesis of 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles: novel agents with analgesic and anti-inflammatory properties, *Eur. J. Med. Chem*. 43 (2008), 1237-1247.
[26] M.L. Barreca, J. Balzarini, A. Chimirri, D. De Clercq, L. De. Luca, H.D. Holtje, M. Holtje, A.M. Monforte, P. Monforte, C. Pannecouque, A. Rao, M. Zappala, Design, Synthesis, Structure−Activity Relationships, and Molecular Modeling Studies of 2,3-Diaryl-1,3-thiazolidin-4-ones as Potent Anti-HIV Agents, *J. Med. Chem.* 45 (2002) 5410-5413.
[27] H. Mansouri-Torshizi, E. Rezaei, F. Kamranfar, M. H. Majd, Investigating the Apoptosis Ability of Ethylenediamine 8-Hydroxyquinolinato Palladium (II) Complex, *Adv. Pharm. Bull.* 6 (3) (2016) 449-453.
[28] M. Moghaddam-manesh, H. Beyzaei, M. Heidari Majd, S. Hosseinzadegan, K. Ghazvini, Investigation and comparison of biological effects of regioselectively synthesized thiazole derivatives, *J. Heterocycl. Chem.* 58 (7) (2021) 1525-1530.
[29] A. Petrou, M. Fesatidou, A. Geronikaki, Thiazole Ring—A Biologically Active Scaffold. *Molecules* 26 (2021) 3166-3240. https://doi.org/ /10.3390/molecules26113166
[30] N.A. Hamdy, M.T. El Sayed, H.A. R. Hussein, M.M. Mounier, M.M. Anwar, Synthesis of novel heterocyclic compounds bearing tetralin moiety of potential anticancer activity targeting the intrinsic apoptotic pathway, *Synth. Commun*. 53 (4) (2023) 298-315. DOI: 10.1080/00397911.2023.2172348
[31] N. A., Hamdy, H. M. Awad, M. M. Tarek, H. A. Mohamed, Synthesis, Anticancer Activity, and Molecular Docking of New Furan-2-one and Pyrazole heterocycles Based on 5, 6, 7, 8-Tetrahydronaphthalene. *Egypt. J. Chem.* 66 (1) (2023) 15-29.
[32] E. K. Hamza, N. A. Hamdy, E. S. Zarie, I. M. Fakhr, A. H. Elwahy, H. M. Awad, Synthesis and In Vitro Evaluation of Novel Tetralin-Pyrazolo [3,4-b] Pyridine Hybrids as Potential Anticancer Agents, *J. Heterocycl. Chem.* 57 (1) (2020) 182–196. DOI: 10.1002/ jhet.3764.
[33] E. K. Hamza, N. A. Hamdy, E. S. Zarie, I. M. I. Fakhr, A. H. M. Elwahy, H. M. Awad, Synthesis and In Vitro Anticancer Evaluation of Novel Pyridine Derivatives Bearing Tetrahydronaphthalene Scaffold, *Arkivoc* vi (2019) 459–480.
[34] A.M. Gamal-Eldeen, N.A. Hamdy, H.A. Abdel-Aziz, E.A. El-Hussieny, I.M. Fakhr, Induction of intrinsic apoptosis pathway in colon cancer HCT-116 cells by novel 2-substituted-5, 6, 7, 8-tetrahydronaphthalene derivatives, *Eur. J. Med. Chem*. 77 (2014) 323-333.
[35] N. A. Hamdy, M. M. Anwar, K. M. Abu-Zied, H. M. Awad, Synthesis, Tumor Inhibitory and Antioxidant Activity of New Polyfunctionally 2-Substituted 5,6,7,8- Tetrahydronaphthalene Derivatives Containing Pyridine, Thioxopyridine and Pyrazolopyridine Moieties, *Acta Pol. Pharm. Drug Res.* 70 (2013) 987–1001.
[36] N. A. Hamdy, A. M. Gamal-Eldeen, H. A. Abdel-Aziz, I. M. Fakhr, Modulation of Carcinogen Metabolizing Enzymes by New Fused Heterocycles Pendant to 5,6,7,8-Tetrahydronaphthalene Derivatives, Eur. J. Med. Chem. 45 (2010) 463–470. DOI: 10.1016/j. ejmech.2009.10.027.
[37] F. Lefranc, G. Nuzzo, N. A. Hamdy, I. Fakhr, L.M.Y. Banuls, G. Van Goietsenoven, G. Villani, V. Mathieu, R. van Soest, R. Kiss, M. L. Ciavatta, In Vitro Pharmacological and Toxicological Effects of Norterpene Peroxides Isolated from the Red Sea Sponge Diacarnus erythraeanus on Normal and Cancer Cells, *J. Nat. Prod.* 76 (2013) 1541–1547. DOI: 10.1021/np400107t.
[38] N. Ferrara, Vascular endothelial growth factor, Arterioscler, *Thromb. Vasc. Biol.* 29 (6) (2009) 789–791.
[39] P.S. Sharma, R. Sharma, T. Tyagi, VEGF/VEGFR pathway inhibitors as anti-angiogenic agents: present and future, *Curr. Cancer Drug Targets* 11 (5) (2011) 624–653.
[40] R.A. Goodlad, A.J. Ryan, S.R. Wedge, I.T. Pyrah, D. Alferez, R. Poulsom, N. R. Smith, N. Mandir, A.J. Watkins, R.W. Wilkinson,

Inhibiting vascular endothelial growth factor receptor-2 signaling reduces tumor burden in the ApcMin/+ mouse model of early intestinal cancer, *Carcinogenesis* 27 (10) (2006) 2133–2139.

[41] P.K. Kopparapu, S.A. Boorjian, B.D. Robinson, M. Downes, L.J. Gudas, N. P. Mongan, J.L. Persson, Expression of VEGF and its receptors VEGFR1/VEGFR2 is associated with invasiveness of bladder cancer, *Anticancer Res.* 33 (6) (2013) 2381–2390.

[42] S. Weis, J. Cui, L. Barnes, D. Cheresh, Endothelial barrier disruption by VEGF-mediated Src activity potentiates tumor cell extravasation and metastasis, *J. Cell Biol.* 167 (2) (2004) 223–229.

[43] J.L. Duque, K.R. Loughlin, R.M. Adam, P.W. Kantoff, D. Zurakowski, M. R. Freeman, Plasma levels of vascular endothelial growth factor are increased in patients with metastatic prostate cancer, *Urology* 54 (3) (1999) 523–527.

[44] H.K. Kim, K.S. Song, Y.S. Park, Y.H. Kang, Y.J. Lee, K.R. Lee, H.K. Kim, K.W. Ryu M. Bae, S. Kim, Elevated levels of circulating platelet microparticles, VEGF, IL-6 and RANTES in patients with gastric cancer: possible role of a metastasis predictor, *Eur. J. Cancer* 39 (2) (2003) 184-191.

[45] H.A. Soliman, A.Y. Mubarak, A. El-Mekabaty, H.M. Awad, S.S. Elmorsy, Eco-friendly synthesis of amidochloroalkylnaphthols and its related oxazepinones with biological evaluation, *Monatsh. Chem.* 147 (2016) 809–816. https://doi.org/10.1007/s00706-015-1536-2

[46] A. Younis, U. Fathy, A. A El-kateb, H.M. Awad, Ultrasonic assisted synthesis of novel anticancer chalcones using water as green solvent. *Der Pharma Chemica*. 8 (17) (2016) 129-136.

[47] A.F. Kassem, I.F. Nassar, M.T. Abdel-Aal, H.M. Awad, W.A. El-Sayed, Synthesis and Anticancer Activity of New ((Furan-2-yl)-1,3,4-thiadiazolyl)-1,3,4-oxadiazole Acyclic Sugar Derivatives, *Chem. Pharm. bull.* 67 (8) (2019) 888-895. DOI: 10.1248/cpb.c19-00280 .

[48] E.M. Flefel, W.I. El-Sofany, H.M. Awad, M. El-Shahat, First Synthesis for Bis-Spirothiazolidine Derivatives as a Novel Heterocyclic Framework and Their Biological Activity**,** *Mini Rev. Med. Chem.* 20 (2) **(**2020) 152-160. DOI: 10.2174/1389557519666190920114852

[49] A.A.H. Abdel Rahman, I.F. Nassar, A.K.F. Shaban, D.S. EL-Kady, H.M. Awad. W.A. El Sayed, "Synthesis, docking studies into cdk-2 and anticancer activity of new derivatives based pyrimidine scaffold and their derived glycosides. *Mini Rev. Med. Chem.* 19 (13) (2019) 1093-1110. DOI: 10.2174/1389557519666190312165717

[50] A. Hassanabadi, M.R. Hosseini-Tabatabaei, K. Khandan-Barani, J. Saffari, Synthesis of 4-arylidene-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5 (4H)-ones through a four-component condensation, *J. Chem. Res.* 39 (10) (2015) 601-602.

[51] C.S. Venkata, V.R. Rao, A facile one-pot expeditious synthesis of thiazolyl-pyrazolones, *Phosphorus, Sulfur, Silicon Relat. Elem.* 186 (3) (2011) 489-495.

[52] T.B. Aychiluhim, S. Penta, V.R. Rao, One pot synthesis of 4-(arylidene)-2-[5-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-thiazol-2-yl]-5-methyl-2, 4-dihydro-pyrazol-3-ones via multi-component approach, *Ind. J. Chem.* 53 (B) (2014) 1242-1246.

[53] R.D. Kamble, R.J. Meshram, S.V. Hese, R.A. More, S.S. Kamble, R.N. Gacche, B.S. Dawane, Synthesis and in silico investigation of thiazoles bearing pyrazoles derivatives as anti-inflammatory agents, *Comput. biol. Chem*. 61 (2016) 86-96.

[54] E.A. Abd El-Meguid, A.M. Naglah, G.O. Moustafa, H.M. Awad, A.M. El Kerdawy, Novel benzothiazole-based dual VEGFR-2/EGFR inhibitors targeting breast and liver cancers: Synthesis, cytotoxic activity, QSAR and molecular docking studies, *Bioorg. Med. Chem. Lett.* 58 (2022) 128529-128537. https://doi.org/10.1016/j.bmcl.2022.128529.

[55] H.A. Abuelizz, M. Marzouk, A.H. Bakheit, H.M. Awad, M.M. Soltan, A.M. Naglah, R. Al-Salahi, Antiproliferative and Antiangiogenic Properties of New VEGFR-2-targeting 2-thioxobenzo[g]quinazoline Derivatives (In Vitro), *Molecules* 25(24) (2020) 5944-5968. https://doi.org/10.3390/molecules25245944

[56] A. M. Srour, H. H. Fahmy, M. A. Khater, E.S. Zarie, S. S. Mohamed, M.F. Abdelhameed, Synthesis, anti-inflammatory properties, molecular modelling and potential COX-2, TNF-α, PGE2 and IL1β inhibitors of pyrazole-based scaffolds, *J. Mol. Struct.* 1266 (2022) 133499-133513. https://doi.org/10.1016/j.molstruc.2022.133499

[57] T. Z. Abolibda, M. Fathalla, B. Farag, M. E. A. Zaki, S. M. Gomha, Synthesis and Molecular Docking of Some Novel 3-Thiazolyl-Coumarins as Inhibitors of VEGFR-2 Kinase, *Molecules* 28 (2) (2023) 689-706. **https://doi.org/10.3390/molecules28020689**

[58] C. Wu, M. Wang, O. Tang, R. Luo, L. Chen, P. Zheng, W. Zhu, Design, Synthesis, Activity and Docking Study of Sorafenib Analogs Bearing Sulfonylurea Unit, *Molecules* 20 (10) (2015) 19361–19371. https:// doi: 10.3390/molecules 201019361

[59] N. A. A. M. Aziz, R. F. George, K. El-Adl, W. R. Mahmoud, Design, synthesis, in silico docking, ADMET and anticancer evaluations of thiazolidine-2,4-diones bearing heterocyclic rings as dual VEGFR-2/EGFRT790M tyrosine kinase inhibitors, *RSC Adv.* 12 (20) (2022) 12913–12931. https://doi: 10.1039/d2ra01119k