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Synthesis, biological evaluation, ADME studies and molecular docking of 1-(3-substituted phenylisoxazol-5-yl) naphthalen-2-ol moiety with VEGFR-2 and Caspase-3 enzymes inhibitors

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In this investigation, a few isoxazole derivatives have been synthesized from the cyclization of chalcone derivative with hydroxylamine hydrochloride in a basic medium using ultrasonication. The synthesized compound has been confirmed based on ^{1}H NMR, mass spectroscopy and IR analysis. The titled compounds have been screened for their *in vivo* anti-microbial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. All compounds show excellent activity against *Escherichia coli* and *Staphylococcus aureus* bacteria. Each compound has a bioavailability score of 55%, a pain assay score of zero, complies with Lipinski's rule of five, and has high gastrointestinal (GI) absorption. Compounds **3b**, **3e**, **4b**, **4d**, and **4e** show the best docking scores with VEGFR-2 (PDB IDs: 4ASD, 4ASE) and Caspase-3 (PDB ID: 4QTX), ranging from –8.2 to –9.9 kcal/mol compared to standard curcumin and sorafenib. All the synthesized compounds have excellent docking scores. These compounds may thus be used as lead compounds in studies investigating VEGFR-2 and Caspase-3 inhibitors.

Keywords: Chalcone, Isoxazole, Antimicrobial activity, VEGFR-2, Caspase-3 enzymes

In medicinal chemistry, isoxazole, chalcone, and their derivatives are crucial for synthesizing novel compounds, a field that has grown significantly over the past few decades[1]. Understanding the significance of these chemicals is essential. Several methods have been developed for the preparation of chalcones, including Claisen reactions, Heck coupling, Suzuki coupling, and Wittig reaction[2-5]. Chalcone is extremely susceptible to α,β-unsaturated keto functions, which react with bidentate nucleophiles to produce five-membered heterocyclic compounds[6].

A multicomponent reaction (MCR) is a chemical reaction that combines three or more compounds to form a single product. New isoxazole derivatives were synthesized through the multi-component reaction of chalcone derivatives, hydroxylamine hydrochloride, NaOH/KOH, and ethanol, used as a deep eutectic solvent[7-10]. Isoxazole derivatives containing nitrogen and oxygen exhibit a broad range of biological effects, such as antiviral, anti-inflammatory, and anticancer properties[11-13].

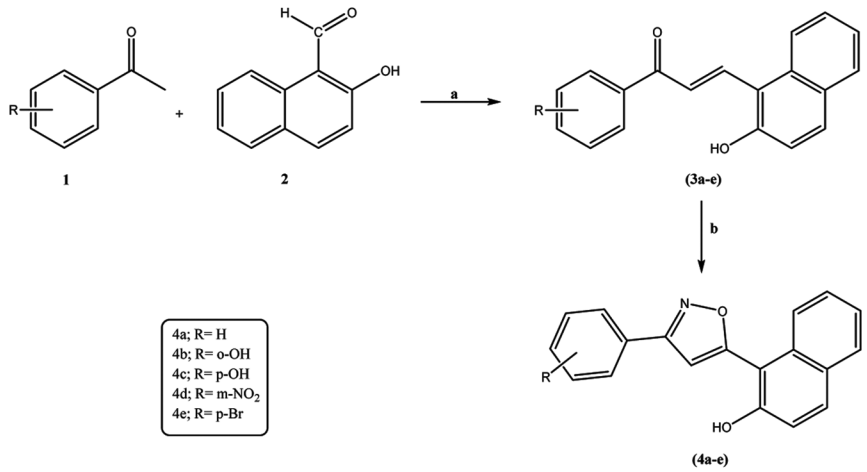
Different signaling pathways are used by protein kinases in cell processes such as development, survival, infiltration, and angiogenesis during the onset and progression of tumors[14]. Growth factors and various protein kinases control the angiogenesis process[15]. One potent angiogenic agent that governs angiogenesis and contributes to tumor development is the vascular endothelial growth factor (VEGF)[16]. Due to the hydrophobic nature of VEGFR-2, it exhibits a broad range of chemical interactions[17].

Experimental Section

^{1}H NMR spectra were recorded using a Bruker 400 MHz NMR spectrometer in DMSO-d_6 solution, with TMS as an internal standard. IR spectra were recorded using a Bruker Alpha FTIR spectrometer. Mass spectral data were obtained using a Shimadzu LC2010 mass analyzer, and CHN analysis was performed using a Perkin-Elmer PE 2400.

General procedure for synthesis of (E)-3-(2-hydroxynaphthalen-1-yl)-1-substituted phenylprop-2-en-1-one, 3a-e

In an ice bath, dissolve equimolar concentrations of the substituted acetophenone (0.01 mol), ethanol, and NaOH (3 pellets) and stir for 30 minutes until the solution clears. Then, slowly add 2-hydroxy-1-



Reagents and Conditions: (a) MeOH, NaOH, stirring for 48 h (b) NH_2OH HCl, KOH, MeOH, Acetic acid, reflux 4-6 h

Scheme 1 — Synthesis of chalcone and isoxazole compounds

naphthaldehyde (0.01 mol) over 15 minutes while maintaining the mixture in the ice bath. Continue stirring the mixture at RT for 48 hours. Monitor the reaction progress using TLC. Once the reaction is complete, evaporate the solvent and add a minimal amount of water. Filter the resulting solution using a Büchner funnel. Adjust the *p*H of the solid precipitate to acidic by adding 10% HCl. Filter the precipitate and recrystallize it using alcohol[18] (Scheme 1).

3-(2-Hydroxynaphthalen-1-yl)-1-phenylprop-2-en-1-one, 3a: Yield 69.24%. m.p.95-110℃. IR (KBr): 3074-3056 (O-H Str.), 2887 (C-H Str.), 1662 (C=O Str.), 1621 (C=C Str.), 1309 (C-H Bend), 1170 (C-O Str.) 770-735 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.56 (1H, s, OH), 9.05 (1H, d), 8.49 (2H, d), 7.86 (2H, m), 7.83 (2H, d), 7.53 (1H, t), 7.49 (1H, d), 7.34-7.38 (2H, t), 7.20 (2H, t); MS: *m/z* 275.36, $C_{19}H_{14}O_2$ requires: 274.32. Anal. Calcd for C, 83.19; H, 5.14. Found: C,83.25; H, 5.10%.

3-(2-Hydroxynaphthalen-1-yl)-1-(2-hydroxy phenyl) prop-2-en-1-one, 3b: Yield 75.56%. m.p.101-107℃. IR (KBr): 3043 (O-H Str.), 2804 (C-H Str.), 1610 (C=O Str.), 1535 (C=C Str.), 1422 (OH Bend), 1159 (C-O Str.), 831 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.95 (1H, s, OH), 10.50 (1H, s, OH), 8.94 (1H, d), 8.63 (1H, s), 8.24 (1H, d), 7.89 (1H, d), 7.83-7.86 (3H, m), 7.71 (2H, t), 7.67 (1H, d), 7.37 (1H, t), 6.97 (1H, d); MS: *m/z* 291.01; $C_{19}H_{14}O_3$ requires: 290.32. Anal. Calcd for: C, 78.61; H, 4.86. Found: C,78.64; H, 4.80%.

3-(2-Hydroxynaphthalen-1-yl)-1-(4-hydroxy phenyl) prop-2-en-1-one, 3c: Yield 85.79%. m.p.90-95℃. IR (KBr): 3001 (O-H str), 2804 (O-H Str), 1747 (C=O Str.), 1576 (C=C Str.), 1421(OH Bend), 1159 (C-O Str.), 971 (C-H Bend), 831, 744 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.32 (1H, s, OH), 9.59 (1H, s, OH), 8.56 (1H, d), 8.32 (2H, d), 8.01 (1H, dd), 7.92 (1H, d), 7.73 (1H,d), 7.43 (1H, d), 7.47 (1H, t), 7.46 (1H, s), 7.16 (1H, d), 6.96 (2H, d); MS: *m/z* 290.45; $C_{19}H_{14}O_3$ requires: 290.32. Anal. Calcd for C, 78.61; H, 4.86; N,4.39. Found: C, 78.66; H, 4.82; N,4.42%.

(E)-3-(2-Hydroxynaphthalen-1-yl)-1-(3-nitro phenyl) prop-2-en-1-one, 3d: Yield 65.47%. m.p.80-90℃. IR (KBr): 3004 (O-H Str.), 2803(C-H Str.) 1698 (C=O Bend), 1682(N=O Str.), 1537 (C=C Str), 1421(OH Bend), 1355(C-N Str.), 1158(C-O Str.), 1081, 971 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.73 (1H, s, OH), 8.79 (1H, d), 8.63 (1H, t), 8.59 (1H, d), 8.49 (1H, d), 8.14 (1H, m), 8.12 (1H, m), 8.03 (1H, s), 7.90 (2H, d), 7.83 (1H, m), 7.74 (1H,m), 7.55 (1H, d); MS: *m/z* 320.04; $C_{19}H_{13}NO_4$ requires: 319.32. Anal. Calcd for C, 71.47; H, 4.10; N, 4.39. Found: C, 71.86; H, 4.04; N, 4.25%.

1-(4-Bromophenyl)-3-(2-hydroxynaphthalen-1-yl) prop-2-en-1-one, 3e: Yield 61.21%. m.p.85-90□. IR (KBr): 3500-3200 (O-H Str.), 1581.19 (C=C Str), 1388.18 (C=O Bend), 1069.70 (C-H Bend), 862.39 (C-H Bend), 684.56 cm^{-1} (C-Br Str.); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.02 (1H, s, OH), 8.22 (1H, d), 8.05 (2H, d), 7.97 (1H, dd), 7.95 (1H, dd), 7.83

(2H, d), 7.65 (1H, m), 7.51 (1H, t), 7.42 (1H, s), 7.40 (1H, m), 6.99 (1H, d); MS: *m/z* 354.23; $C_{19}H_{13}BrO_2$ requires: 353.22. Anal. Calcd for C, 64.61; H, 3.71. Found: C, 64.67; H, 3.69%.

General procedure for synthesis of 1-(3-substituted phenylisoxazol-5-yl) naphthalen-2-ol, 4a-e

Substituted chalcone (0.01 mol), hydroxylamine hydrochloride (0.02 mol), and potassium hydroxide (0.002 mol) were dissolved in methanol (10 mL). The solution was sonicated for about 30 minutes and then refluxed for 4-6 hours. The reaction mixture was cooled, and acetic acid[64] was added to acidify it, resulting in the precipitation of a solid product. The solid was filtered using Buchner funnels, washed with water, dried, and recrystallized using ethanol (Scheme 1).

1-(3-Phenylisoxazol-5-yl) naphthalen-2-ol, 4a: Yield 81.36%. m.p.105-110℃. IR (KBr): 3329.51 (OH Str.), 1631.97(C=N stretch), 1590.69(C=C str.),1463.72(C-H Bend), 1413.94 (C-H Bend), 1162.42 (C-O Str.), 934.82 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.26 (1H, s, OH), 9.06 (1H, d), 7.42 (1H, m), 7.33 (2H, m), 7.17 (1H, m), 6.89 (2H, m), 6.88 (2H, m), 6.86 (1H, m), 6.46 (1H, d), 6.26 (1H, s); MS: *m/z* 288.88; $C_{19}H_{13}NO_2$ requires: 287.32. Anal. Calcd for: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.53; H, 4.87; N, 4.68%.

1-(3-(2-Hydroxyphenyl) isoxazol-5-yl) naphthalen-2-ol, 4b: Yield 79.67%. m.p.110-120□. IR (KBr): 3321.92(O-H Str.), 1631.64 (C=N Str.), 1589.85 (C=C str.), 1463.48 (C-H Bend), 1413.52 (C-H Bend), 1150-1000 (C-O Str.), 770-735 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.64 (1H, s, OH), 8.94 (1H, d), 8.33 (1H, d), 8.14 (1H, dd), 8.05 (1H, d), 7.88 (2H, m), 7.40 (2H, m), 7.31 (1H, d), 7.14 (1H, dd), 7.10 (1H, s), 6.98 (1H, s); MS: *m/z* 305.10 $C_{19}H_{13}NO_3$ requires: 303.32 Anal. Calcd for C, 75.24; H, 4.32; N, 4.62. Found: C, 75.74; H, 4.22; N, 4.72%.

1-(3-(4-Hydroxyphenyl) isoxazol-5-yl) naphthalen-2-ol, 4c: Yield 77.41%. m.p.85-95□. IR (KBr): 3026 (O-H Str.), 1636.43 (C=N Str.), 1150.19 (C-O Str), 1483.51 (C=C Bend), 1225-1000 (C-H Bend), 1225-960 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.12 (1H, s, OH), 9.88 (1H, s, OH), 8.97 (1H, dd), 8.18 (1H, dd), 8.01 (1H, d), 7.58 (2H, m), 7.49 (2H, d), 7.31 (1H, d), 7.01(2H, d), 6.89 (1H, s); MS: *m/z* 305.10; $C_{19}H_{13}NO_3$ requires: 303.32. Anal. Calcd for C, 75.24; H, 4.32; N, 4.62. Found: C, 75.74; H, 4.47; N, 4.89%.

1-(3-(3-Nitrophenyl) isoxazol-5-yl) naphthalen-2-ol, 4d: Yield 61.26%. m.p.95-100□. IR (KBr): 3326.94 (O-H Str), 3080-3030 (C-H Str), 1690-1640 (C=C Str), 1570-1550 (N-O Str), 1600-1400 (C=N Str), 1225-1000 (C-H Bend),770-735 cm^{-1} (C-H Bend); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.89 (1H, s, OH), 8.99 (1H, m), 8.50 (1H, s), 8.39 (2H, dd), 8.18 (1H, m), 8.02 (1H, d), 7.92 (1H, t), 7.52 (1H, m), 7.12 (1H, d), 6.91(1H, s); MS: *m/z* 334.09; $C_{19}H_{12}N_2O_4$ requires: 332.32. Anal. Calcd for C, 68.67; H, 3.64; N, 8.43. Found: C, 68.47; H, 3.64; N, 8.73%.

1-(3-(4-Bromophenyl) isoxazol-5-yl) naphthalen-2-ol, 4e: Yield 66.56%. m.p.100-110℃. IR (KBr):3026.00 (O-H Str), 1692.70 (C=N Str), 1569.64 (C=C Bend), 1200.22 (C-H Bend), 1019.44 (C-O Str), 770-735 (C-H Bend), 600-500 cm^{-1} (C-Br Str); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.87 (1H, s, OH), 8.14 (1H, t), 8.12 (1H, t), 7.87 (1H, m), 7.83 (1H, m), 7.74 (1H, d), 7.70 (1H, d), 7.55 (2H, d), 7.03 (2H, d), 6.30 (1H, s); MS: *m/z* 367.01; $C_{19}H_{12}BrNO_2$ requires: 366.21. Anal. Calcd for: C, 62.32; H, 3.30; N, 3.82. Found: C, 62.68; H, 3.39; N, 3.78%.

Biological evaluation

***In vitro* antibacterial activity**

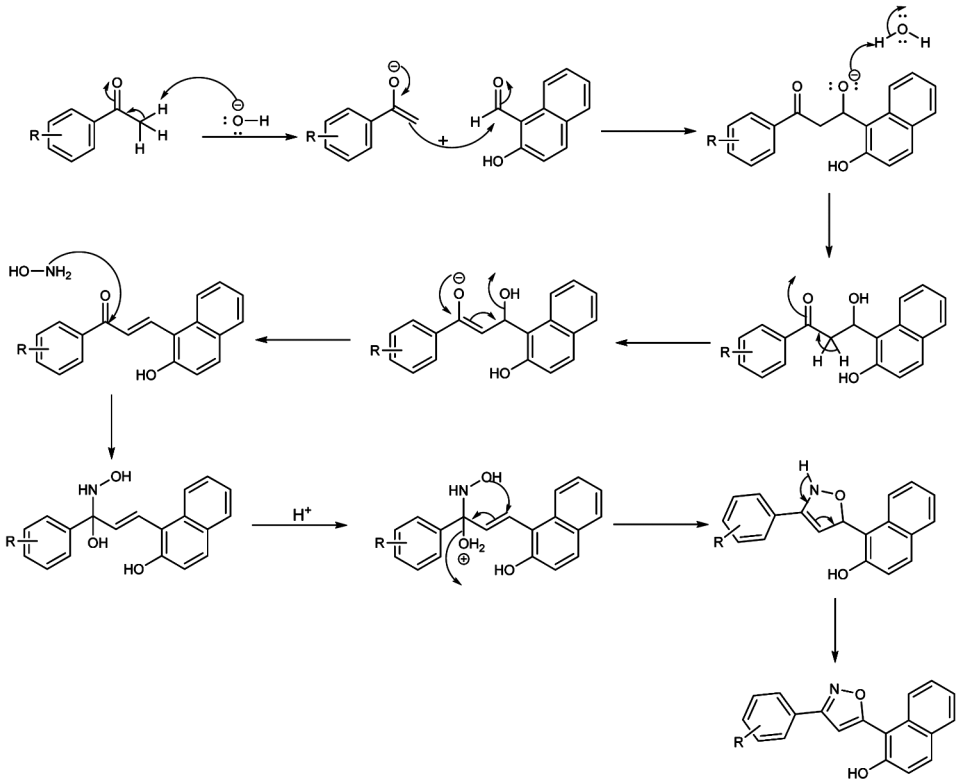
The antibacterial activity of derived derivatives (**3a-e** and **4a-e**) was viewed for four bacterial strains by protocol. The compound that was obtained was tested for its antibacterial effectiveness against *Pseudomonas aeruginosa* (gm –ve), *Escherichia. Coli* (gm –ve), *Bacillus subtilis* (gm +ve) and *Staphylococcus aureus* (gm +ve). Penicillin-g served as the standard drug.

***In silico* study**

In silico study of the titled compound was carried out using SwissADME software. Metochalcone and Marplan (isocarboxazid) are used as the reference standard.

Molecular Docking

Pyrx- Virtual Screening Tools was used for molecular docking of the compound. The RCSB Protein Data Bank was used to retrieve the X-ray



Scheme 2 — Expected mechanism for the synthesis chalcone **3a-e** and isoxazole **4a-e** derivatives

crystallography structure of VEGFR-2 and Caspase-3 (4ASE, 4ASD and 4QTX). Protein preparation was carried out in AutoDockTools-1.5.6 and Visualization of docking was carried out in Discovery studio2021.

Results and Discussion

The synthesis of the chalcone derivative was carried out using Claisen–Schmidt reactions condition *via* a reaction of acetophenone and 2-hydroxy naphthaldehyde using NaOH to form **2a-e** derivative which was further cyclized using hydroxy amine hydrochloride and form final compound **3a-e** (Scheme 2). All the derivatives were confirmed by ^{1}H NMR, IR and Mass analysis. As shown in data ^{1}H NMR and IR data of 1-(3-phenylisoxazol-5-yl) naphthalene-2-ol **(4a)** which showed that 10.26 ppm, 1H, singlet for -OH group and 3329 cm^{-1} (-OH stretch) in ir data similarly the C=N stretch is observed at 1631 cm^{-1}, C-O stretch observed at 1162 cm^{-1}. Isoxazole -CH peak is observed at 6.26 (1H, s) ppm. Similarly, 6.46 ppm doublet is shown for the naphthalene ring and 7.17 ppm also for other -CH groups of the naphthalene ring. Hence from the IR and ^{1}H NMR data compound confirmation of 1-(3-phenylisoxazol-5-yl) naphthalene-2-ol was done and from mass data molecular weight 288.88 of the compound was conformed. Similarly, all the compounds were confirmed.

Antibacterial Activity

The title molecules were evaluated for their antimicrobial activity against *Pseudomonas aeruginosa* (Gram-negative), *Escherichia coli* (Gram-negative), *Bacillus subtilis* (Gram-positive), and *Staphylococcus aureus* (Gram-positive) using the disc diffusion method[19]. The tests were conducted at a concentration of 100 ppm (10 mg/mL) in dimethyl sulfoxide (DMSO) solvent. The disc diffusion technique followed the Kirby-Bauer method. Penicillin G and Azithromycin were used as standard drugs. Each experiment was conducted in duplicate (Table 1, Fig. 1).

In silico ADME evaluation

ADME (Absorption, Distribution, Metabolism, and Excretion) can be evaluated separately using computational study methods. Physiochemical and pharmacokinetic descriptors were calculated through the online tool Swiss ADME[20]. Physicochemical parameters provide insights into the drug-likeness of a

compound, as assessed by measures such as bioavailability, and the criteria established by Ghose, Veber, Egan, and Muegge (Table 2).

If a substance meets at least three of the four Lipinski criteria listed below, its oral absorption is often improved: (i) molecular weight 500, (ii) hydrogen bond acceptors 10, (iii) hydrogen bond donors 5, and (iv) logP 5. Additionally, the synthesized compounds were evaluated according to Veber's rule, which assesses oral bioavailability based on the Topological Polar Surface Area (TPSA) and the number of rotatable hydrogen bonds. It is anticipated that compounds with 10 or fewer rotatable bonds and a TPSA of 140 Å or less will exhibit high oral bioavailability. The results indicated that all synthesized compounds adhered to both Lipinski's rule of five and Veber's rule (Table 3).

The egg boiling representation of the compound provides information on the predicted gastrointestinal absorption and brain penetration of small molecules (Fig. 2).

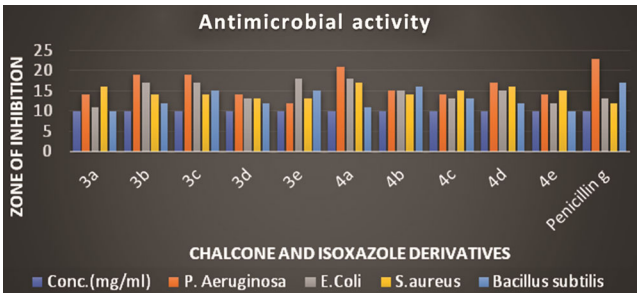


Fig. 1 — Antimicrobial activity of chalone and isoxazole derivatives

Molecular Docking

Molecular docking studies provide insight into the strength of the bond between a drug and its receptor. By analyzing a compound's interactions with a target protein, researchers can uncover the substance's bioactivities. Drug discovery relies heavily on molecular docking as a crucial method for identifying potential drug-target interactions[21,22] (Table 4).

Table 1 — Antimicrobial activity screening result of synthesized compounds

Compd	Antibacterial Activity			
	Microorganisms and zone of inhibition			
	Gram-negative bacteria		Gram-positive bacteria	
	P. Aeruginosa	*E.Coli*	*S.Aureus*	*Bacillus subtilis*
3a	14.20 ± 0.818	11.13 ± 0.152	16.06 ± 0.208	10.03 ± 0.251
3b	18.86 ± 0.321	17.20 ± 0.2	13.96 ± 0.251	12.03 ± 0.351
3c	19.03 ± 0.152	16.96 ± 0.152	14.16 ± 0.378	14.93 ± 0.208
3d	14.03 ± 0.251	13.03 ± 0.152	13.00 ± 0.2	12.06 ± 0.305
3e	12.033 ± 0.450	17.93 ± 0.305	13.23 ± 0.321	15.06 ± 0.208
4a	21.10 ± 0.264	18.10 ± 0.264	17.03 ± 0.251	10.93 ± 0.208
4b	15.033 ± 0.251	14.80 ± 0.435	14.03 ± 0.152	16.03 ± 0.152
4c	13.96 ± 0.251	13.10 ± 0.264	15.06 ± 0.404	13.16 ± 0.208
4d	17.00 ± 0.4	14.96 ± 0.152	16.06 ± 0.208	12.10 ± 0.458
4e	14.10 ± 0.1	11.93 ± 0.208	14.96 ± 0.251	10.20 ± 0.2
Penicillin g	23.15 ± 0.355	12.90 ± 0.360	12.00 ± 0.1	17.00 ± 0.1

Table 2 — Pharmacokinetics, bioavailability and medicinal chemistry for the derived compounds and standard

Compd	Pharmacokinetics			Bioavailability score	Pains	Leadlikness
	GI absorption	BBB permeant	Pgp Substrate			
3a	High	Yes	No	0.55	–	1
3b	High	Yes	No	0.55	–	1
3c	High	No	No	0.55	–	1
3d	High	Yes	No	0.55	–	2
3e	High	Yes	No	0.55	–	1
4a	High	Yes	Yes	0.55	–	1
4b	High	Yes	No	0.55	–	1
4c	High	No	No	0.55	–	1
4d	High	Yes	Yes	0.55	–	2
4e	High	Yes	Yes	0.55	–	1
STD 1	High	Yes	No	0.55	–	1
STD 2	High	Yes	No	0.55	–	1

Table 3 — Veber's rule and Lipinski's rule of five for derived derivatives as well as standard

Compd	Lipinski's Rule of 5					Veber's Rule	
	Log P	Mol.wt.	H-bond acceptors	H-bond donors	Lipinski	Rotatable bonds	TPSA
3a	3.91	274.31	2	1	0	3	37.3
3b	3.7	290.31	3	2	0	3	57.53
3c	3.32	290.31	3	2	0	3	57.53
3d	4.52	319.31	4	1	1	4	83.12
3e	3.53	353.21	2	1	0	3	37.3
4a	3.99	287.31	3	1	0	2	46.26
4b	3.67	303.31	4	2	0	2	66.49
4c	3.36	303.31	4	2	0	2	66.49
4d	4.62	332.31	5	1	0	3	92.08
4e	3.56	366.21	3	1	0	2	46.26
STD 1	3.34	298.33	4	0	0	6	44.76
STD 2	1.53	231.25	4	2	0	5	67.16

STD 1: Metochalcone. STD 2: Marplan(isocarboxazid).

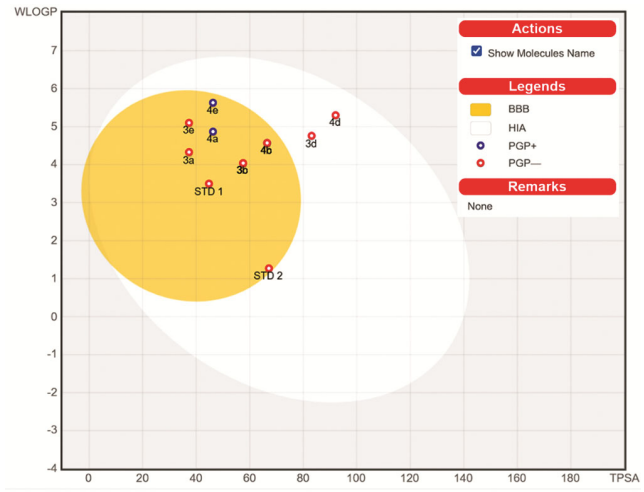


Fig. 2 — BOILED-Egg representation of chalcone derivatives, isoxazole derivatives, and standard Metochalcone and Marplan (isocarboxazid)

Justification for the enhanced potency of novel synthetic 2-hydroxy naphthalene-chalcone and isoxazole derivatives, 3a-e and 4a-e

Molecular docking studies were conducted to assess the increased potency of the novel synthetic 2-hydroxy naphthalene-chalcone and isoxazole derivatives. Docking investigations were performed on VEGFR-2 and Caspase-3 (PDB IDs: 4ASE, 4ASD, and 4QTX). The interaction of compound 3b with VEGFR-2 and Caspase-3 is illustrated in Fig. 3, with docking scores of -9.9 (4ASD), -7.9 (4ASE), and -8.2 (4QTX). The naphthalene ring interacts through van der Waals forces, π-cation interactions, π-sigma interactions, π-sulfur interactions, and π-alkyl interactions. These interactions involve carbon-hydrogen bonding with the amino acids Val916, Lys868, Cys1045, Val848, Arg1051, Phe1047, Asp1056, Thr140, Tyr195, and His266.

Table 4 — Docking scores of the synthesized compounds against protein with PDB IDs

Compd	4asd	4ase	4qtx
3a	–9.5	–7.9	–7.6
3b	–9.9	–7.9	–8.2
3c	–9.5	–7.9	–7.6
3d	–8.6	–8.1	–7.9
3e	–9.8	–7.7	–7.8
4a	–9.6	–8.3	–8.3
4b	–9.6	–8.3	–8.4
4c	–9.4	–8.4	–8.0
4d	–9.8	–8.4	–8.5
4e	–9.7	–8.4	–8.4
Curcumin	–9.4	–9.0	–6.9
Sorafenib	–8.8	–8.7	–8.2

Compound no 4b interaction with VEGFR-2 and Caspase-3 is shown in Fig. 4 with docking scores -9.6 (4ASD), -8.3 (4ASE) and -8.4 (4QTX). where the naphthalene ring interacts with pi-π T-shaped, π-sigma, π-cation, π-anion π-alkyl through carbon-hydrogen bonding. Molecular results revealed that amino acids are active sites with Phe1047, Arg1051, Asp1056 and Lys137. N-H and OH having interaction with conventional hydrogen bonds and amino acids are Thr926, Arg929, Asp1058, Tyr197.

Compound no 4d interaction with VEGFR-2 and Caspase-3 is shown in Fig. 5 with docking scores -9.2 (4ASD), -8.4 (4ASE) and -8.5 (4QTX). where the naphthalene ring interacts with π-μ T-shaped, π-sigma, π-cation, π-anion and π-alkyl through carbon-hydrogen bonding. Molecular results revealed that amino acids are active sites with Phe1047, Phe256, Arg1051, Leu889. N-H having interaction with conventional hydrogen bonds and amino acids

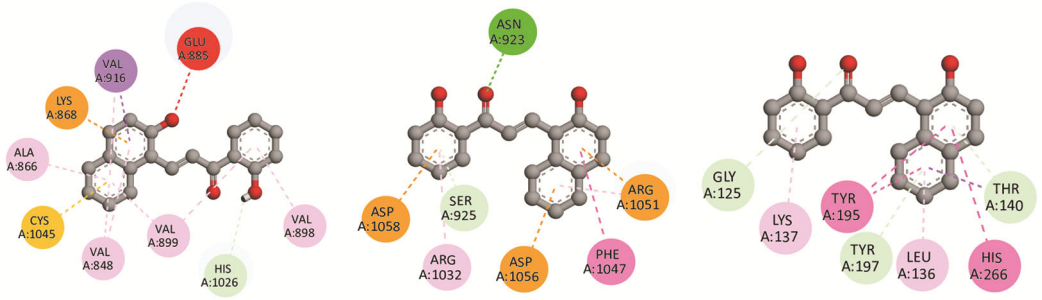


Fig. 3 — **3b** interaction of **3b** with VEGFR-2 enzymes (4ASD, 4ASE) and Caspase-3 enzyme (4QTX)

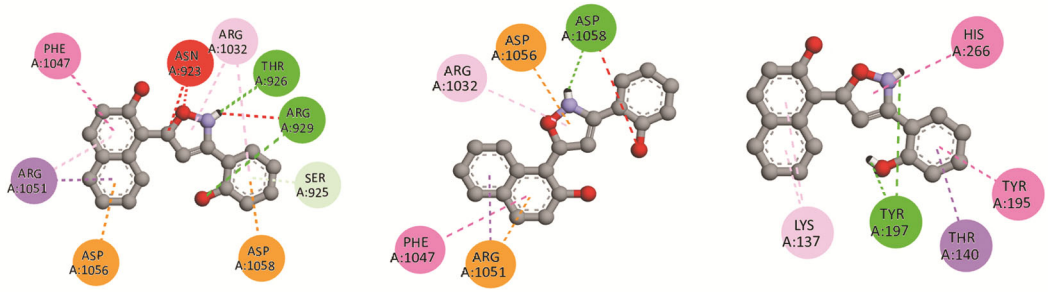


Fig. 4 — **2d** interaction of **4b** with VEGFR-2 enzymes (4ASD, 4ASE) and Caspase-3 enzyme (4QTX)

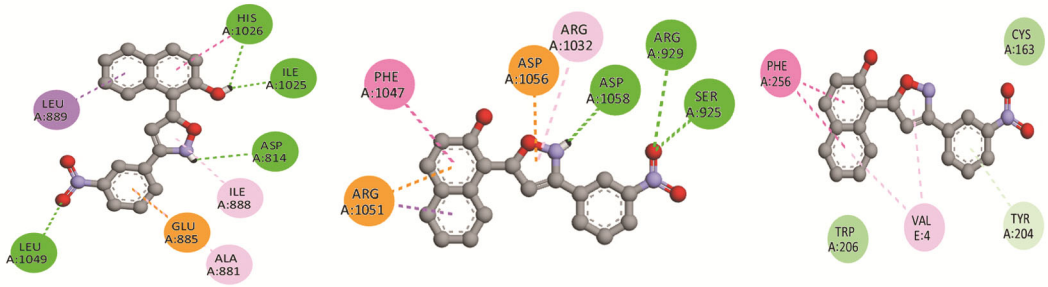


Fig. 5 — **2d** interaction of **4b** with VEGFR-2 enzymes (4ASD, 4ASE) and Caspase-3 enzyme 2D interaction of **4d** with VEGFR-2 enzymes (4ASD, 4ASE) and Caspase-3 enzyme (4QTX)

areAsp814, Asp 1058. Nitro group having interaction with conventional hydrogen bond and Ven Der Waals with amino acid Leu1049, Arg929 Ser925, Gly1102.

Conclusions

The novel 2-hydroxy naphthalene derivatives containing chalcone and isoxazole groups were synthesized and characterized using various spectroscopic methods. Their antimicrobial activity was evaluated, revealing that all compounds exhibited excellent activity against *Escherichia coli* and *Staphylococcus aureus* bacteria. In addition to these findings, computational studies were conducted to assess the potential of the synthesized compounds (3a-e and 4a-e) as drugs. These studies used Lipinski's rules and ADME (absorption, distribution, metabolism, and excretion) analysis, showing a bioavailability of 55% for the compounds. Docking studies revealed that compounds 3b, 3e, 4b, 4d, and 4e had favorable docking scores against all selected proteins, namely VEGFR-2 (4ASD, 4ASE) and Caspase-3 (4QTX), in comparison to the standard drugs curcumin and sorafenib. These results suggest that the synthesized drug molecules may serve as effective inhibitors targeting multiple aspects of cancer cells.

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