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Synthesis, Characterisation, Molecular Docking and Anti-breast Cancer Activity of Scopoletin Derivatives

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Scopoletin is a promising compound for the treatment of cancer. A series of novel scopoletin-based benzylsulfone derivatives (**4a-j**) were synthesised and characterised by FT-IR, ^{1}H NMR, mass spectrometry and elemental analysis. Their anticancer potential was investigated through molecular docking against VEGFR2 (PDB ID: 2XIR) and *in vitro* cytotoxicity studies on MCF-7 and MDA-MB-468 breast cancer cell lines. Docking studies revealed that compound **4h** exhibited the strongest binding affinity (-9.2 kcal mol^{-1}), followed by **4g** (-8.9 kcal mol^{-1}) and **4j** (-8.5 kcal mol^{-1}), exceeding that of the reference inhibitor PF-00337210 (-7.7 kcal mol^{-1}). Cytotoxicity evaluation demonstrated that compound **4h** was the most active derivative, with IC_{50} values of 6.32 and 8.55 µM against MCF-7 and MDA-MB-468 cells, respectively. Compounds **4g** and **4j** also showed promising activity. The observed correlation between VEGFR2 binding affinity and cytotoxic effects suggests that these scopoletin derivatives may act through VEGFR2 inhibition. Among the synthesised compounds, **4h** emerged as a promising lead for further development as a potential anticancer agent.

Keywords: Scopoletin, VEGFR-2 inhibition, Anticancer, *In silico*, MTT assay.

INTRODUCTION

The unchecked proliferation and dissemination of aberrant cells throughout the body is the hallmark of cancer, a complicated and multidimensional disease [1,2]. It is caused by genetic and epigenetic changes that disrupt normal cellular processes like growth, division and programmed cell death [3,4]. These alterations can be brought on by a variety of factors such as exposure to carcinogens, lifestyle choices, environmental impacts and genetic susceptibility [5-7]. The term cancer refers to around 100 distinct forms of the disease, each with unique traits and treatment challenges [8].

Among the prevalent types include skin, lung, breast, colorectal and prostate cancers. Despite enormous advancements in early detection and treatment, cancer still claims millions of lives annually and is a leading cause of death worldwide [9,10]. The burden of cancer extends beyond physical illness, profoundly influencing patients' mental health, family dynamics and healthcare resources worldwide [11]. Increased research efforts to understand the molecular mechanisms behind cancer have led to the development of targeted medications, immunotherapies and personalised medicine techniques [12-14]. These advancements have transformed cancer care and improved many patient outcomes. This essay discusses the molecular causes of cancer, its epidemiology, recent advancements in therapeutic strategies and the ongoing challenges in combating this potent disease [15-17]. By adopting a multidisciplinary perspective, this work seeks to advance efforts toward addressing the global challenges posed by cancer.

Stinging nettle (*Urtica dioica*), chicory, *Artemisia scoparia*, dandelion coffee, passion flower and species of the genus *Scopolia* including *Scopolia carniolica* and *Scopolia japonica*, are among the plants that naturally contain scopoletin, also known as 6-methoxy-7-hydroxycoumarin. The diverse biological activities of this molecule have garnered attention. Antibacterial [18], antitubercular [19], antihypertensive [20], anti-inflammatory [21], anticancer [22,23] antidiabetic [24,25] and insecticidal [26] properties have been demonstrated for scopoletin. These characteristics make it an interesting target for pharmaceutical and medical applications. Scopoletin is a coumarin analogue which is naturally occurring benzopyrones and have diverse biological activities [27,28]. The tropane alkaloid hyoscyamine is hydroxylated in plants to yield scopolamine, which is then further converted to scopoletin. The

pathway highlights the significance of the compound in plant metabolism and underscores its potential therapeutic applications [29].

To identify new VEGFR2-targeted anticancer candidates, molecular docking studies were performed using AutoDock Vina to evaluate the binding affinity of scopoletin derivatives toward VEGFR2. Although scopoletin and its derivatives have previously demonstrated anticancer activity, sulphonyl-linked benzyl-substituted analogues remain largely unexplored. The incorporation of a sulphonyl group was intended to enhance molecular polarity, metabolic stability and protein–ligand interactions, while benzyl substitution was expected to influence target affinity and biological activity. The designed derivatives were evaluated for their interactions within the ATP-binding pocket of VEGFR2, a validated target in tumor angiogenesis. This study aimed to establish structure–activity relationships and identify lead compounds with favourable VEGFR2-binding characteristics and antiproliferative potential against breast cancer cells.

EXPERIMENTAL

All chemicals and reagents were purchased from Sigma-Aldrich and used without further purification. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. The thin-layer chromatography was performed on coated silica gel 60 F_{254} plates to monitor the progress of the reaction. A 630 FTIR spectrometer model Agilent MicroLab was used to measure the infrared (IR) spectra using KBr in the range of 4000-400 cm^{-1}. ^1H NMR was recorded on a Bruker AV-300 spectrometer using DMSO-d_6 as solvent.

General procedure for synthesis of substituted 2-(benzylthio)acetic acid (1a-j): Substituted benzyl chloride (5 mmol) was added to a methanolic solution of mercaptoacetic acid (5 mmol, 15 mL) under stirring. A solution of NaOH (10 mmol) in methanol (5 mL) was then added dropwise and the reaction mixture was stirred at room temperature for 30 min. Upon completion, the mixture was diluted with distilled water and the resulting product was isolated and recrystallised from ethanol to afford the corresponding substituted 2-(benzylthio)-acetic acids (**1a-j**).

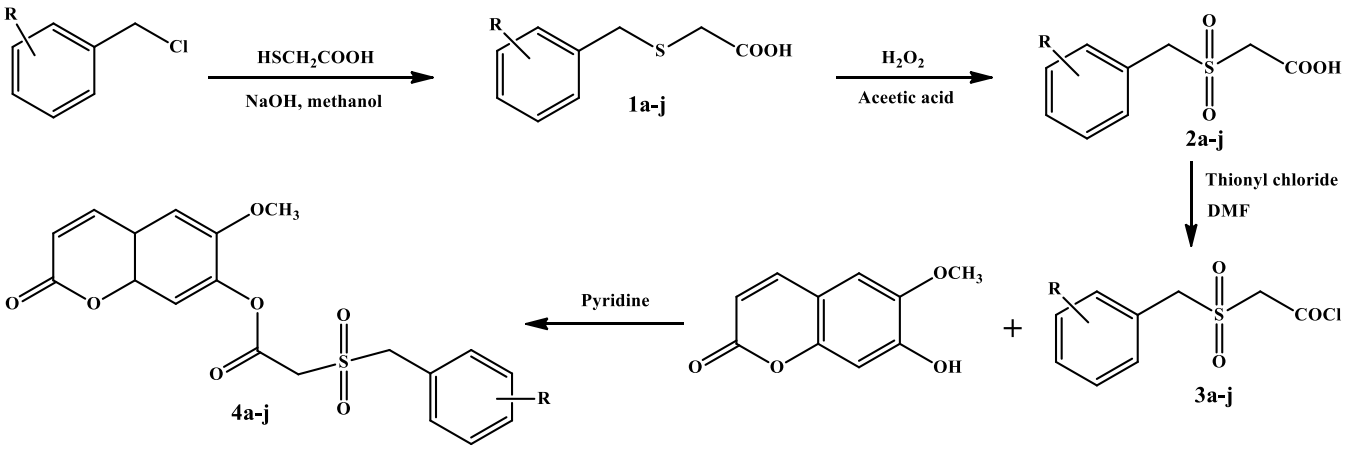
Synthesis of substituted 2-(benzylsulphonyl)acetic acid (2a-j): Compounds **1a-j** (3 mmol) was added to a solution of 30% H_2O_2 aqueous solution (2 mL) in acetic acid (5 mL) and the resulting solution stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O and recrystallised with ethyl alcohol which resulting in the formation of substituted 2-(benzylsulphonyl)acetic acid (**2a-j**).

Synthesis of substituted 2-(benzylsulphonyl)acetyl chloride (3a-j): Compounds **2a-j** (2 mmol) was added to a solution of thionyl chloride (4 mL) in DMF (4 mL) and the resulting solution stirred at room temperature for 3 h. The reaction mixture was recrystallised from ethanol to afford the corresponding substituted 2-(benzylsulfonyl)acetyl chlorides (**3a-j**) as pure products.

Synthesis of substituted 6-methoxy-2-oxo-2*H*-chromen-7-yl-3-(benzylsulphonyl)propanoate (4a-j): Compounds **3a-j** (2 mmol) was added to scopoletin (2 g) in pyridine (5 mL) and the resulting solution stirred at room temperature for 5 h. The reaction mixture was recrystallised with ethyl alcohol results in the formation of 6-methoxy-2-oxo-2*H*-chromen-7-yl-3-(benzylsulphonyl)propanoate (**4a-j**) (**Scheme-I**).

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((2-chlorobenzyl)-sulphonyl)acetate (4a): Yellowish solid; yield: 78%; m.p.: 172-174 ºC; Elemental anal. of $C_{19}H_{15}ClO_7S$: calcd. (found) %: C, 53.97 (53.99); H, 3.58 (3.62); Cl, 8.38 (8.34); O, 26.49 (26.50); S, 7.58 (7.56); IR (KBr, ν_{max}, cm^{-1}): 3030 (Ar–CH), 2950 (aliph. C–H), 1670 (C=O), 1510 (C=C), 1310 (S=O), 1168 (OCH_3), 1110 (C–O), 708 (C–Cl); ^1H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.12-7.46 (m, 4H, Ar–H), 6.32 (d, 1H, H-4), 6.05 (d, 1H, H-3), 5.62 (d, 1H, H-8), 5.41 (d, 1H, H-8′), 5.12 (d, 1H, H-5), 4.71 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.65 (d, 1H, H-4′); MS *m/z*: 422 $(M)^+$;

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((4-chlorobenzyl)-sulphonyl)acetate (4b): Yellowish solid; yield: 80%; m.p.: 170-172 ºC; Elemental anal. of $C_{19}H_{15}ClO_7S$: calcd. (found) %: C, 53.97 (53.95); H, 3.58 (3.62); Cl, 8.38 (3.40); O, 26.49 (26.51); S, 7.58 (7.51); IR (KBr, ν_{max}, cm^{-1}): 3050 (Ar–CH), 2860 (aliph. C-H), 1677 (C=O), 1512 (C=C), 1318 (S=O), 1172 (OCH_3),1105 (C–O), 720 (C–Cl); ^1H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.08-7.51 (m, 4H, Ar–H), 6.28 (d, 1H, H-



Scheme-I: Synthesis of scopolatin derivatives

4), 6.12 (d, 1H, H-3), 5.68 (d, 1H, H-8), 5.54 (d, 1H, H-8′), 5.16 (d, 1H, H-5), 4.77 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.72 (d, 1H, H-4′). MS *m/z*: 422 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((2-bromobenzyl)-sulphonyl)acetate (4c): Yellowish brown solid; yield: 78%; m.p.: 168-170 ºC; Elemental anal. of $C_{19}H_{15}BrO_7S$: calcd. (found) %: C, 48.84 (48.86); H, 3.24 (3.27); Br, 17.10 (17.07); O, 23.97 (23.95); S, 6.86 (6.89); IR (KBr, ν_{max}, cm^{-1}): 3046 (Ar–CH), 2864 (aliph. C-H), 1682 (C=O), 1510 (C=C), 1324 (S=O), 1164 (OCH_3),1112 (C–O), 642 (C–Br). ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.16-7.66 (m, 4H, Ar–H), 6.31 (d, 1H, H-4), 6.08 (d, 1H, H-3), 5.57 (d, 1H, H-8), 5.43 (d, 1H, H-8′), 5.22 (d, 1H, H-5), 4.85 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.67 (d, 1H, H-4′). MS *m/z*: 465 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((2,4-dimethoxy-benzyl)sulphonyl)acetate (4d): Brown solid; yield: 82%; m.p.: 180-182 ºC; Elemental anal. of $C_{21}H_{20}O_9S$: calcd. (found) %: C, 56.25 (56.29); H, 4.50 (4.53); O, 32.11 (32.15); S, 7.15 (7.18); IR (KBr, ν_{max}, cm^{-1}): 3052 (Ar–CH), 2930 (aliph. C-H), 1678 (C=O), 1510 (C=C), 1320 (S=O), 1172 (OCH_3), 1118 (C–O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.05-7.51 (m, 3H, Ar–H), 6.37 (d, 1H, H-4), 6.16 (d, 1H, H-3), 5.63 (d, 1H, H-8), 5.46 (d, 1H, H-8′), 5.28 (d, 1H, H-5), 4.76 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 3.82 (s, 9H, OCH_3), 3.73 (d, 1H, H-4′). MS *m/z*: 448 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((2-methylbenzyl)-sulphonyl)acetate (4e): Brown solid; yield: 68%; m.p.: 148-150 ºC; Elemental anal. of $C_{20}H_{18}O_7S$: calcd. (found) %: C, 59.69 (59.71); H, 4.51 (4.49); O, 27.83 (27.85); S, 7.97 (7.93); IR (KBr, ν_{max}, cm^{-1}): 3042 (Ar–CH), 2815 (aliph. C-H), 1665 (C=O), 1568 (C=C), 1346 (S=O), 1160 (OCH_3),1105 (C–O).^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.19-7.52 (m, 4H, Ar–H), 6.41 (d, 1H, H-4), 6.11 (d, 1H, H-3), 5.68 (d, 1H, H-8), 5.52 (d, 1H, H-8′), 5.20 (d, 1H, H-5), 4.77 (s, 2H, CH_2), 4.26 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.58 (d, 1H, H-4′), 2.25 (s, 3H, CH_3); MS *m/z*: 402 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((3-methylbenzyl)-sulphonyl)acetate (4f): Brown solid; yield: 72%; m.p.: 152-154 ºC; Elemental anal. of $C_{20}H_{18}O_7S$: calcd. (found) %: C, 59.69 (59.616); H, 4.51 (4.52); O, 27.83 (27.85); S, 7.97 (7.99); IR (KBr, ν_{max}, cm^{-1}): 3065 (Ar–CH), 2917 (aliph. C-H),1677 (C=O), 1562 (C=C), 1320 (S=O), 1153 (OCH_3), 1116 (C–O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.15-7.47 (m, 4H, Ar–H), 6.36 (d, 1H, H-4), 6.18 (d, 1H, H-3), 5.57 (d, 1H, H-8), 5.46 (d, 1H, H-8′), 5.27 (d, 1H, H-5), 4.84 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.65 (d, 1H, H-4′), 2.32 (s, 3H, CH_3); MS *m/z*: 402 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl 2-((4-methylbenzyl)-sulphonyl)acetate (4g): Brown solid; yield: 78%; m.p.: 153-155 ºC; Elemental anal. of $C_{20}H_{18}O_7S$: calcd. (found) %: C, 59.69 (56.67); H, 4.51 (4.52); O, 27.83 (27.85); S, 7.97 (7.98); IR (KBr, ν_{max}, cm^{-1}): 3036 (Ar–CH), 2884 (aliph. C-H), 1684 (C=O), 1514 (C=C), 1356 (S=O), 1148 (OCH_3), 1127 (C–O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.02-7.41 (m, 4H, Ar–H), 6.41 (d, 1H, H-4), 6.21 (d, 1H, H-3), 5.62 (d, 1H, H-8), 5.44 (d, 1H, H-8′), 5.32 (d, 1H, H-5), 4.81 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.57 (d, 1H, H-4′), 2.20 (s, 3H, CH_3). MS *m/z*: 402 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((2-nitrobenzyl)-sulphonyl)acetate (4h): Yellowish brown solid; yield: 84%; m.p.: 166-168 ºC; Elemental anal. of $C_{19}H_{15}NO_9S$: calcd. (found) %: C, 52.66 (52.68); H, 3.49 (3.52); N, 3.23 (3.26); O, 33.22 (33.26); S, 7.40 (7.44); IR (KBr, ν_{max}, cm^{-1}): 3045 (Ar–CH), 2870 (aliphatic C-H), 1672 (C=O), 1522 (C=C), 1505 (NO_2), 1322 (S=O), 1142 (OCH_3), 1124 (C–O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.15-7.58 (m, 4H, Ar–H), 6.38 (d, 1H, H-4), 6.17 (d, 1H, H-3), 5.74 (d, 1H, H-8), 5.53 (d, 1H, H-8′), 5.22 (d, 1H, H-5), 4.84 (s, 2H, CH_2), 4.47 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.67 (d, 1H, H-4′); MS *m/z*: 433 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((3-nitrobenzyl)-sulphonyl)acetate (4i): Yellowish brown solid; yield: 80%; m.p.: 170-172 ºC; Elemental anal. of $C_{19}H_{15}NO_9S$: calcd. (found) %: C, 52.66 (52.68); H, 3.49 (3.51); N, 3.23 (3.27); O, 33.22 (33.26); S, 7.40 (7.44); IR (KBr, ν_{max}, cm^{-1}): 3062 (Ar–CH), 2854 (aliph. C-H), 1681 (C=O), 1535 (C=C), 1485 (NO_2), 1312 (S=O), 1142 (OCH_3), 1128 (C–O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.08-7.51 (m, 4H, Ar–H), 6.42 (d, 1H, H-4), 6.22 (d, 1H, H-3), 5.76 (d, 1H, H-8), 5.64 (d, 1H, H-8′), 5.29 (d, 1H, H-5), 4.88 (s, 2H, CH_2), 4.56 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.75 (d, 1H, H-4′); MS *m/z*: 433 $(M)^+$.

6-Methoxy-2-oxo-2*H*-chromen-7-yl-2-((4-nitrobenzyl)-sulphonyl)acetate (4j): Yellowish brown solid; yield: 74%; m.p.: 172-174 ºC; Elemental anal. of $C_{19}H_{15}NO_9S$: calcd. (found) %: C, 52.66 (52.69); H, 3.49 (3.54); N, 3.23 (3.25); O, 33.22 (33.27); S, 7.40 (7.47); IR (KBr, ν_{max}, cm^{-1}): 3055 (Ar–CH), 2876 (aliph. C-H), 1675 (C=O), 1532 (C=C), 1480 (NO_2), 1306 (S=O), 1132 (OCH_3), 1124 (C–O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.17-7.62 (m, 4H, Ar–H), 6.37 (d, 1H, H-4), 6.31 (d, 1H, H-3), 5.64 (d, 1H, H-8), 5.57 (d, 1H, H-8′), 5.42 (d, 1H, H-5), 4.82 (s, 2H, CH_2), 4.47 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.66 (d, 1H, H-4′). MS *m/z*: 433 $(M)^+$.

Molecular docking studies

Ligand and macromolecular preparation: Considering the reported anticancer action of scopoletin, a molecular ligand library was developed with the purpose of verifying its effectiveness against VEGFR2. The VEGFR2 associated with ligand PF-00337210 (pdb id: 2XIR) was downloaded from the protein data bank. The ligand was isolated from the binding site of the VEGFR2 structure was obtained from the Protein Data Bank and prepared for docking by removing water molecules and adding polar hydrogens. The reference ligand, PF-00337210, was constructed and optimised. All rotatable bonds were fixed to maintain its conformation and the prepared structures were saved in PDBQT format for docking studies.

Molecular docking and validation: For molecular docking studies, grid parameters were defined to encompass the entire active site of VEGFR2. The grid box was generated to include all potential ligand conformations and key binding-site residues, with the ligand positioned at the center of the docking region. Following docking, the optimal ligand orientations and binding poses were analysed to identify the most favourable protein–ligand interactions and inhibitor binding

patterns. To validate the docking protocol, the co-crystallised ligand PF-00337210 was re-docked into the VEGFR2 binding pocket, confirming the reliability of the docking parameters and methodology employed.

Design of ligands and molecular docking simulations: From an initial library of 60 flavonoids selected for their reported anticancer potential, ten scopoletin derivatives were shortlisted for further investigation based on their favourable binding energies and docking poses. The objective was to explore their potential mechanism of action through inhibition of human VEGFR2, a key target involved in tumor angiogenesis. Molecular docking simulations were performed using AutoDock Vina integrated with MGL Tools to evaluate the binding affinity of the selected ligands toward VEGFR2. Prior to docking, the protocol was validated by verifying input files, grid map parameters, and atom type assignments. All docking variables were carefully monitored and validated at each stage to ensure the reliability and reproducibility of the results.

Analysis of molecular docking simulation: Ligand compounds were selected based on molecular docking simulation results with human VEGFR2 and their binding energies were utilised for ranking. All molecular docking results were analysed based on the hydrophilic and hydrophobic interactions established between the ligand molecules and the amino acid residues located within the active binding pocket of VEGFR2. Particular attention was given to key interactions including hydrogen bonding, electrostatic contacts and hydrophobic interactions, which contribute to the stability and binding affinity of the protein–ligand complexes.

Cytotoxicity activity: For cytotoxicity evaluation, ten selected compounds were dissolved in sterile deionised water to prepare 10 mM stock solutions, which were filtered through a 0.22 μm syringe filter and diluted with DMEM containing 2% FBS to obtain concentrations ranging from 0.781 to 100 μM. Human breast cancer cell lines MCF-7 and MDA-MB-468 were seeded in 96-well plates at a density of 1×10^4 cells/well and incubated at 37 ºC in a 5% CO_2 atmosphere for 24 ± 2 h to achieve approximately 70% confluency. Following treatment with the test compounds, cell viability was determined using the MTT assay, wherein freshly prepared MTT solution (1 mg L^{-1}) was added and the resulting formazan formation was quantified by measuring absorbance at 570 nm [30]. Cell viability was calculated relative to untreated controls and dose–response curves were generated by plotting percent cell survival against the logarithm of compound concentration. The IC_{50} values, defined as the concentration causing 50% inhibition of cell viability, were determined using a four-parameter logistic (4PL) non-linear regression model.

RESULTS AND DISCUSSION

The synthesis of the target scopoletin derivatives (**4a-j**) was accomplished through a four-step reaction sequence starting from substituted benzyl chlorides. Initially, substituted 2-(benzylthio)acetic acid (**1a-j**) were obtained *via* nucleophilic substitution of mercaptoacetic acid, followed by oxidation with hydrogen peroxide to afford the corresponding substituted 2-(benzylsulphonyl)acetic acid (**2a-j**). Subsequent treatment with thionyl chloride converted these intermediates into substituted 2-(benzylsulphonyl)acetyl chloride (**3a-j**). Finally, esterification of scopoletin with compounds **3a-j** in pyridine yielded the desired scopoletin-based sulphone derivatives (**4a-j**) in good yields (68-84%). The structures of the synthesised compounds were confirmed by elemental analysis, FT-IR, ^{1}H NMR and mass spectrometry, which verified the successful incorporation of the substituted benzylsulphonyl moiety onto the scopoletin framework.

Docking studies of scopoletin derivatives: The validated VEGFR2 receptor was subjected to virtual screening against a library of ten synthesised scopoletin derivatives using molecular docking simulations to identify potential VEGFR2 inhibitors. Binding affinities and protein–ligand interactions were evaluated based on the lowest-energy docking poses. Among the tested compounds, **4h** exhibited the highest binding affinity (-9.2 kcal mol^{-1}), forming key hydrogen bonds with ASP1046 and LYS868. Compound **4g** also showed strong binding (-8.9 kcal mol^{-1}) and interacted with ASN923, ARG-929 and ARG1051 through three hydrogen bonds, along with favourable aromatic and hydrophobic interactions. Compound **4j** displayed a binding energy of -8.5 kcal mol^{-1} and formed a hydrogen bond with LEU1049. The docking results indicate that compounds **4h**, **4g** and **4j** possess promising VEGFR2 inhibitory potential, with their binding modes illustrated in Fig. 1 and the complete docking data summarised in Table-1.

TABLE-1
DOCKING STUDIES OUTCOMES OF
CHOSEN SCOPOLETIN DERIVATIVES

Compound	R	Binding energy (kcal/mol)
4a	2-Chloro	-7.8
4b	4-Chloro	-7.9
4c	2-Bromo	-7.5
4d	2,4-Dimethoxy	-8.2
4e	2-Methyl	-8.0
4f	3-Methyl	-8.0
4g	4-Methyl	-8.9
4h	2-Nitro	-9.2
4i	3-Nitro	-7.7
4j	4-Nitro	-8.5
Inhibitor	PF-00337210	-7.7

Biological evaluation: The anticancer activity of synthesised compounds **4a-j** were evaluated against MCF-7 and MDA-MB-468 breast cancer cell lines using the MTT assay. The dose-dependent effects of each compound on cell survival were analysed and IC_{50} values were determined from the fitted dose–response curves. Several derivatives showed inhibitory activity. Among them compounds **4g**, **4h** and **4j** showed 9.15 μM, 6.32 μM and 10.82 μM as MCF 7 inhibitory activity as well as for MDA-MB-468, 11.02 μM, 8.55 μM and 8.14. The synthesised scopoletin compounds showed moderate to good cytotoxic activity against the breast cancer cell lines MDA-MB-468 and MCF-7. With IC_{50} values of 6.32 μM and 8.55 μM against MCF-7 and MDA-MB-468 cells, respectively, derivative **4h** showed the highest activity among the investigated compounds (Table-2). The results show that structural alteration of the scopoletin scaffold can improve anticancer potential, even though these activities are lower than those of

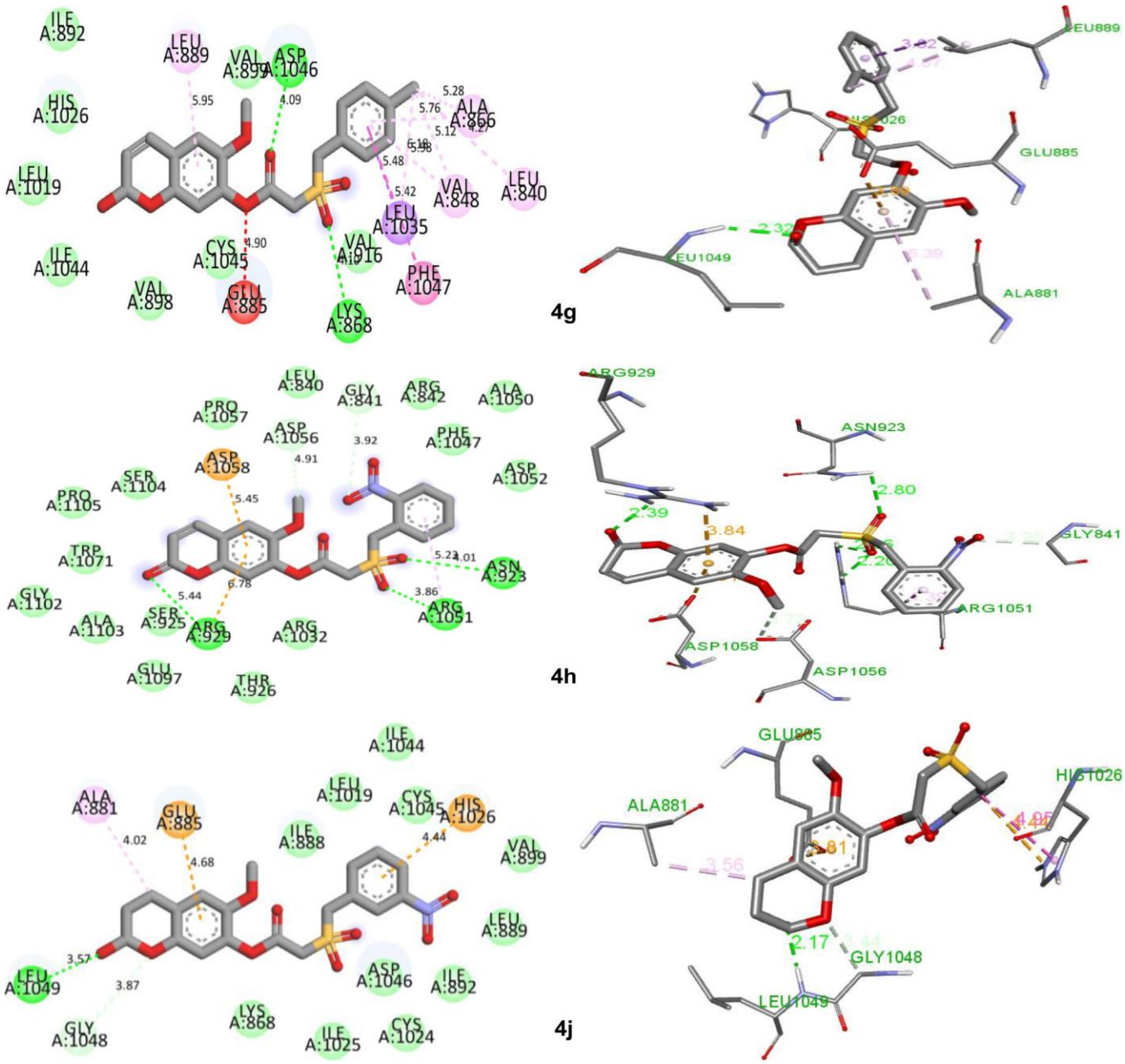


Fig. 1. 2D Representation of the binding modes of **4g**, **4h** and **4j**

TABLE-2
IC_{50} VALUES OF TESTED COMPOUND
AGAINST BOTH THE CELL LINES

Compd.	IC_{50} (μM)	
	MCF-7	MDA-MB-468
4a	22.15	28.36
4b	36.12	25.37
4c	25.08	26.62
4d	24.34	18.66
4e	36.12	28.66
4f	42.04	35.42
4g	9.15	11.02
4h	6.32	8.55
4i	32.25	30.76
4j	10.82	8.14
Doxorubicin	2.20	3.06

the reference drug doxorubicin. These derivatives may be useful lead compounds for additional optimisation based on the reported activity and good VEGFR2 binding interactions found in molecular docking studies. Therefore, although further structural optimization and detailed mechanistic investigations are required to enhance their potency and therapeutic potential, the present findings provide promising preliminary evidence supporting the development of scopoletin-based derivatives as potential anticancer agents.

Conclusion

A series of ten novel scopoletin-based benzylsulphonyl derivatives (**4a-j**) were successfully synthesised and structurally characterised by FT-IR, ^{1}H NMR, mass spectrometry and elemental analysis. Molecular docking studies against VEGFR2

revealed favourable binding interactions for several derivatives, with compound **4h** exhibiting the strongest binding affinity (-9.2 kcal mol^{-1}), followed by **4g** (-8.9 kcal mol^{-1}) and **4j** (-8.5 kcal mol^{-1}). The docking results suggested that hydrogen-bonding and hydrophobic interactions within the ATP-binding pocket of VEGFR2 play a significant role in stabilizing the ligand–receptor complexes. Biological evaluation against MCF-7 and MDA-MB-468 breast cancer cell lines demonstrated moderate to good antiproliferative activity, with compound **4h** emerging as the most active derivative, exhibiting IC_{50} values of 6.32 and 8.55 μM, respectively. The correlation between docking scores and cytotoxicity results suggests that VEGFR2 inhibition may contribute to the observed anticancer activity. In particular, nitro-substituted derivatives showed superior performance, highlighting the importance of electronic effects in modulating biological activity. Compound **4h** as a promising lead scaffold for the development of VEGFR2-targeted anticancer agents. Although the activities remain lower than those of doxorubicin, the findings provide valuable structure–activity relationship insights and establish a foundation for further optimization.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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