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SYNTHESIS, ANTI-CANCER ACTIVITY AND MOLECULAR DOCKING STUDIES OF THIAZOLIDINE-4-CARBOXYLIC ACIDS

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ABSTRACT

Angiogenesis is encouraged when tumor tissues require nutrients and oxygen. VEGF is an important growth factor that regulates the process of angiogenesis. Its overexpression is observed in many cancers like breast, cervical, hepatocellular, non-small cell lung cancer, etc. Targeting the VEGFR-2 is a useful strategy for developing selective and specific anticancer agents. Thiazolidine-4-carboxylic acid (Tz4C) is a five-membered saturated and privileged pharmacophore that has been explored as a selective anticancer agent since the 1980s. It can be derived from natural amino acid, L-cysteine and the developed molecules can be lesser toxic in the human body. The current work describes synthesis, biological evaluation and molecular docking studies of these compounds for their ability to inhibit the growth of cancer cells. From this study, 5 analogues had comparable potency to the standard drug Sorafenib.

KEYWORDS: VEGFR-2, Thiazolidine-4-carboxylic acid, thiaproline, Cancer.

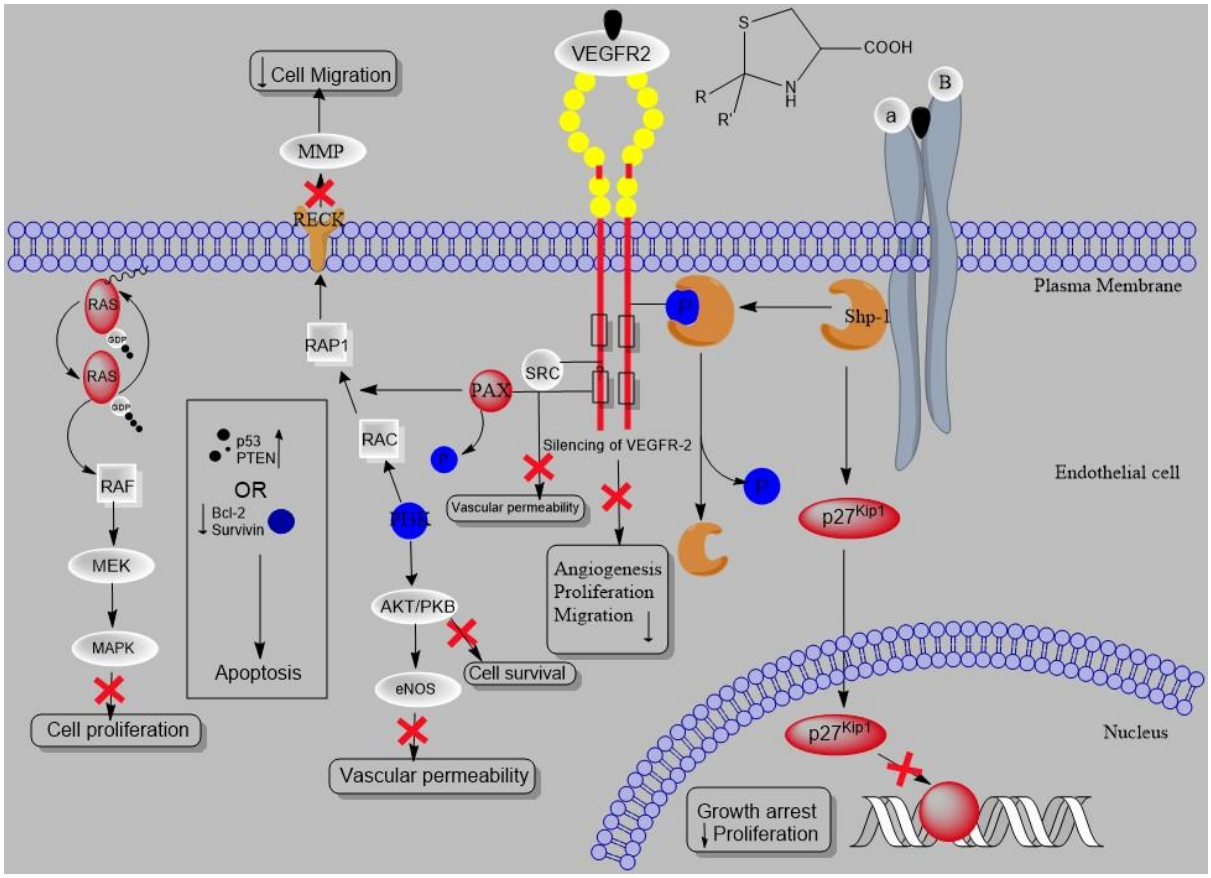


Figure 1: **Proposed *in-vitro* activity map of Tz4C analogues. The anticancer activity of Tz4C analogues is associated with growth inhibition, cell cycle arrest, cell death (apoptosis), and metastasis inhibition. Therapy can inhibit cancer cell viability by inactivating the cell survival signalling pathways.**

eNOS, Endothelial Nitric Oxide Synthase; MAPK, Mitogen-Activated Protein Kinase; MMP, Matrix metalloproteinases; Pax, paxillin; P, phosphor; PI3K, Phosphatidylinositol 3′ Kinase; p27Kip1, cyclin-dependent kinase inhibitor p27Kip1; PTEN, phosphatase and tensin homolog; VEGFR, Vascular Endothelial Growth Factor Receptor;

1. INTRODUCTION

In a healthy body, around 30 trillion cells live in an intricate, mutually dependent condominium and initiate division promptly. In stark contrast, cancer cells violate this scheme; they retaliate against the usual pedals of proliferation and dictate their reproduction.

They can migrate from the initiation site and start invading adjacent tissues and forming masses at distant sites in the body. Such aggressive tumours become lethal when they disrupt the tissues and organs needed for the survival of the organism as a whole. The GLOBOCON

2020 estimated 19.3 million new cancer cases and 10.0 million cancer deaths worldwide. Death rates for female breast were considerably higher (15.0 per 100,000).[1]

Our effort was to address the need of improved antitumour therapy which will be less toxic and more selective in nature, as there is always a requirement to put the patient at ease, especially with the increasing burden. Gonsalvez in 1979 termed 'reverse transformation' in his study with thiazolidine-4-carboxylic acids (T4C). He tested on 32 cancer patients and observed a complete remission in the cell membrane functioning for head and neck cancer when treated with Tz4C.[2] A phase-II trial carried out in Spain stated that 2-amino-2-thiazoline (revercan) showed no toxicity at 1.5-6 mg/kg dose when used for recurrent or advanced transitional bladder carcinoma.[3] One of the 2010 studies elaborated how 2-Arylthiazolidine-4-carboxylic acid amides (ATCAA) targeted AMPK/mTOR and PI3K/Akt/mTOR pathways in prostate, lung, cervical and uterine sarcoma cancer cells. It dephosphorylated Akt which confirms the targeting of PI3K/Akt pathway regardless of cell line and stimulated phospho-AMPK by depleting ATP hence targeting AMPK/mTOR pathway.[4] And a recent research by Keith in 2019 described *in-vivo* administration of thiaproline decreased the median tumour weight by 80% and inhibited tumour growth in 10 days while being non-toxic. It controlled the collagen production by mesothelioma cells as studied for tumour growth in murine model of malignant mesothelioma tumour.[5]

Apart from this, the PPAR-γ inhibitors, thiazolidinediones (TZDs) that contain the basic ring of thiazoline showed anti-tumour activity. This is because many human cancer cell lines have been reported to exhibit high levels of PPARc expression. A retrospective analysis from 10 Veteran Affairs medical centres in the USA observed a 33% reduction in lung cancer risk among TZD users compared with nonusers after adjusting for confounder interactions. Thus assessing clinical usefulness of TZDs.[6] This added to our curiosity of considering thiaproline's mechanism of action as a potential anti-cancer agent.

The Vascular Endothelial Growth Factor Receptor (VEGFR) is the most studied target as its overexpression is seen in neovascular tumour endothelial cells compared to normal cells.[7] VEGFR has a bilobed structure and encompasses the catalytic domain with a larger C-lobe and smaller N-lobe.[8] These lobes are linked by a linker which contains hinge and motif regions. Apart from these, it has 2 clefts called front and back cleft. The front cleft acts as a binding site for ATP.[9] It is activated when the growth factor Vascular Endothelial Growth Factor (VEGF) binds and a phosphorylation reaction is relayed which results in endothelial

cell proliferation and migration.[10] Developing a VEGFR-2 blocker will abstain the receptor dimerization and the subsequent auto-phosphorylation which will in turn block the proliferation, migration, and angiogenesis process.[11]

Thiazolidine-4-carboxylic acid holds a five-membered saturated pharmacophore having an amine at position 3, a sulphur at position 1 and carboxylic acid at position 4. Thiazolidine is one of the privileged scaffolds being extensively explored to show anti-inflammatory, antitumor, antimicrobial, antidiabetic, and antibacterial activity. The research on this ring in medicinal chemistry has increased dramatically since the 1960s yet the clinical application remains unexplored.[12]

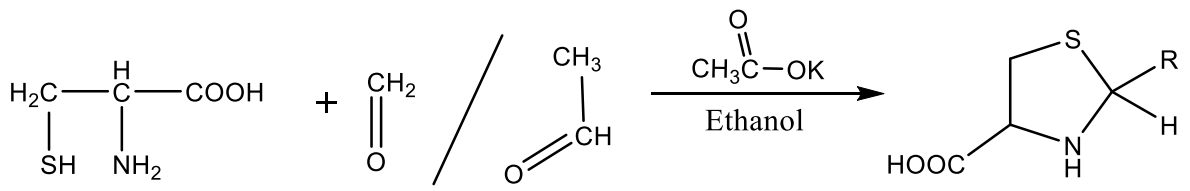
In the present research work, we explore the anti-cancer activity of Tz4C by first mapping computer-aided drug design (CADD) approach of molecular docking study against the protein (PDB ID: 4ASD). The successful binding helped us in designing and synthesizing 15 novel analogues of Tz4C which were further analysed by spectral and chromatographic analysis (FTIR, Mass and ^{1}H NMR spectroscopy). In vitro antiproliferative activity using MTT assay was carried out on human breast cancer cells (MCF-7).

2. MATERIALS AND METHODS

All chemicals utilized were obtained from Sigma Aldrich and Merck. The reaction's progress was tracked via thin layer chromatography, utilizing Merck TLC silica gel 60 F254 aluminum sheets. Melting points were assessed using the open capillary tube technique and are uncorrected on the Digital melting point device. FT-IR spectra were obtained using JASCO FT-IR 4100 with KBr powder as a reference. Mass spectra were obtained using the Agilent Technologies System. ^{1}H NMR was performed at 500MHz employing $CDCl_3$ as the solvent.

2.1. Synthesis

2.1.1. Scheme 1: Synthesis of 2-substitued thiazolidine-4-carboxylic acids



L-cysteine formaldehyde acetaldehyde

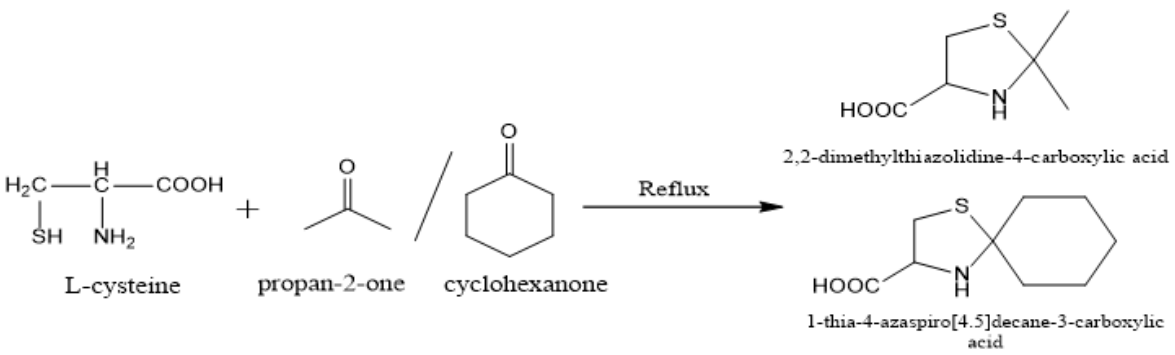
R= H, CH_3, Phenyl

The synthesis of thiazolidine-4-carboxylic acids adhered to a straightforward chemical synthesis process as illustrated in **2.1.1. Scheme 1** and **2.1.2. Scheme 2**. The analogues were synthesised through the condensation of cysteine with both aliphatic and aromatic aldehydes in a one pot reaction carried out at low temperature (20-22℃) followed by addition of a base. The yield percentage varied from 73-82%.[17]

Reduction of ketones under reflux conditions led to the formation of two distinct compounds, 2,2-dimethylthiazolidine-4-carboxylic acid and 1-thia-4-azaspiro[4.5]decane-3-carboxylic acid, as outlined in **2.1.2. Scheme 2:**. The yield percentage was 77% for VG3 and 82% for VG12.

The identity and purity of all synthesized compounds were verified using various analytical methods, such as TLC, IR, ^{1}H NMR spectroscopy, Mass Spectrometry and, in certain cases, Elemental Analysis.

2.1.2. Scheme 2: Synthesis of 2-substitued thiazolidine-4-carboxylic acids



2.2 Computational methods

2.2.1 Molecular docking

Molecular docking studies were performed to assess the interactions between ligands and amino acids in the binding pocket, identifying the arrangements that aid in stabilizing docked complexes. The AutoDock Vina software from the Scripps Research Institute toolkit was employed for these investigations. The crystal structures of VGFR obtained through X-ray analysis (PDB ID: 4 ASD) were sourced from the RCSB. Protein Data Bank. All ligand structures were created with ChemBioDraw Ultra 14.0, and their preparation and energy optimization were conducted with ChemBio3D Ultra 14.0. through the use of MMFF94 force field and their related charges. Protein preparation was conducted and executed with

AutoDock Tools-1.5.6, and the docking analyses were carried out adhering to standard procedures where an essential factor, namely grid box, was created surrounding the active regions of VEGFR, The ligands that were co-crystallized within the protein structures were redocked. The effectiveness of compounds interacting with macromolecules was measured and represented in kcal/mol, as indicated in the generated log files throughout the simulation experiments. The results of the docking were visualized. conducted using PyMOL 2.1.1® and Discovery Studio Visualizer 2020.[13]

2.3. ADME Predictions

2.3.1. ADME Predictions

Examining the uptake, distribution, metabolism, elimination, and toxicity profile and drug likeness are crucial for assessing the feasibility of chemical substances as a possible drug candidate. For this reason current study, digital resources such as SwissADME and pkCSM-pharmacokinetics were utilized to predict the ADMET characteristics and evaluate adherence to Lipinski's Rule of Five.[14,15,16]

2.4 Acute Oral Dose in mice

Acute oral toxicity denotes the harmful effects that arise when a substance is ingested orally in single or multiple doses within a 24-hour period, with monitoring typically extending up to 14 days. This research serves as a crucial initial phase in toxicological assessment to detect potential hazards linked to short-term exposure and sets acceptable dose thresholds for upcoming pharmacological investigations. Acute toxicity is typically assessed using rodents, like mice or rats. The median lethal dose (LD_{50}) refers to the quantity necessary to induce death in 50% of the experimental group and is expressed in mg/kg of body weight. The research is typically conducted following OECD standards, which encompass the Fixed Dose Procedure, the Acute Toxic Class Method (OECD 423), and the Up-and-Down Procedure (OECD 425). Throughout the research, animals are observed for death rates, alterations in behavior, signs of toxicity, and variations in body weight.

According to the Globally Harmonized System (GHS) and EU CLP classification, compounds with an oral LD_{50} value greater than 2000 mg/kg are considered to have low acute toxicity and do not require acute toxicity categorization.[19]

2.5 Biological Assay

The anti-proliferative activities of all the synthesized compounds have been evaluated against human breast cancer cell line using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT). and sulforhodamine B (SRB) assay.

The EZcount MTT cell assay kit was employed to determine the cell viability and cell proliferation of the derivatives. The absorbance was measured at 570nm using EPOCH microplate reader (BioTek-Agilent, USA). Half maximal inhibitory concentration (IC_{50}) values were obtained using four parameter logistic regression model.[14] The ability of thiazolidine derivatives to inhibit the growth of human breast cancer cell line is summarized in Table 3. Not surprising, dacarbazine (DTIC) was inactive (IC_{50} > 100 μM) in our *in vitro* assay due to lack of bioactivation.[17]

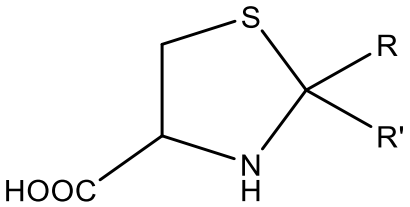
QSAR study is comprehensive analysis underscores the significance of tailored molecular modifications and their impact on the antiproliferative properties of these compounds, providing valuable insights for future drug development efforts.[18,20]

3. RESULT AND DISCUSSION

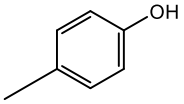
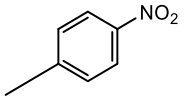
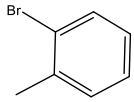
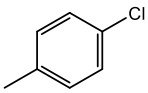
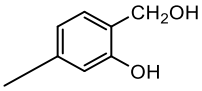
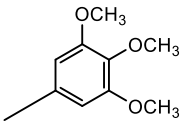
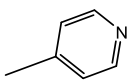
3.1. Molecular docking

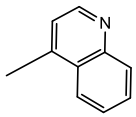
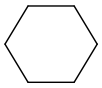
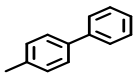
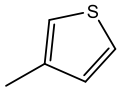
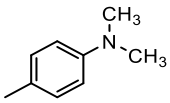
Subsequently, molecular docking was performed and docking scores were calculated. The most favourable binding poses of the ligands within the VEGFR-2 active site were identified based on the lowest binding energy and are presented in **Table 1**.

Table 1: Binding approach of derivatives with the protein.



Sr no.	Name of compound	Ligands		Binding energy (Kcal/mol)	Interacting amino acids
		R	R’		
VG1	thiazolidine-4-carboxylic acid	H	H	Not observed	Not observed
VG2	2-methylthiazolidine-4-carboxylic acid	CH_3	H	-3.8	Phe1047, Asp1046, Glu885 His1026,

					Cys1045, Ile888, Cys817
VG3	2,2-dimethylthiazolidine-4-carboxylic acid	CH_3	CH_3	-4.3	Asp1046, Glu885, Phe1047 Ile888, Lys868, His1026
VG4	2-(4-hydroxyphenyl)thiazolidine-4-carboxylic acid		H	-5.7	Phe1047 Thr926
VG5	2-(4-nitrophenyl)thiazolidine-4-carboxylic acid		H	-5.9	Asp1046, Phe1047, Glu885 Ile888, Leu840, Val898, His1026
VG6	2-(2-bromophenyl)thiazolidine-4-carboxylic acid		H	-5.5	Asp1046, Phe1047, Glu885 Ile888, His1026
VG7	2-(4-chlorophenyl)thiazolidine-4-carboxylic acid		H	-6.1	Phe1047, Asp1046, Glu885 His1026, Ile888, Cys817, Val898
VG8	2-(3-hydroxy-4-(hydroxymethyl)phenyl)thiazolidine-4-carboxylic acid		H	-6.0	Asp1046, Phe1047, Glu885 Ile888, Lys868, His1026, Cys1045, Val848
VG9	2-(3,4,5-trimethoxyphenyl)thiazolidine-4-carboxylic acid		H	-6.4	Asp1046, Glu885, Leu889, His1026, Arg1027, Leu1049
VG10	2-(pyridin-4-yl)thiazolidine-4-carboxylic acid		H	-5.3	Asp1046, Phe1047, Glu885 His1026, Ile888, Thr926

VG11	2-(quinolin-4-yl)thiazolidine-4-carboxylic acid		H	-5.7	Asp1046, Phe1047, Glu885 His1026, Lys868, Cys1045, Ile888, Thr926
VG12	1-thia-4-azaspiro[4.5]decane-3-carboxylic acid		-	-4.9	Phe1047, Asp1046, Glu885 Leu840, His1026, Ile888, Cys817
VT13	2-([1,1'-biphenyl]-4-yl)thiazolidine-4-carboxylic acid		H	-8.4	Leu889, Asp1046, Glu885, Lys868, Leu1049, Gly1048
VT15	2-(thiophen-3-yl)thiazolidine-4-carboxylic acid		H	-5.4	Asp1046, His1026, Ile892, Leu1019
VT15	2-(4-(dimethylamino)phenyl)thiazolidine-4-carboxylic acid		H	-6.3	Asp1046, Ile888, Cys1024, Leu1019, Ile1025, Leu889, Ile892, Glu885, Gly1048, Leu1049
Std	Sorafenib			-7.0	Asp1046, Phe1047, Glu885 Ile888, Leu840, Lys868, Val848, His1026, Cys1045, Cys919,Thr916, Leu1035, Lys920, Phe918, Ile892

From the obtained molecular docking results, it is observed that all studied ligands have a similar position and orientation inside the recognized binding site of VEGFR-2. All 15

derivatives exhibit interactions with at least one, if not all, of the three critical amino acids (Asp1046, Glu885, and Phe1047) within the VEGFR-2 macromolecule, with the exception being the unsubstituted thiazolidine-4-carboxylic acid. Based on these findings, we made the decision to assess these compounds for their potential anti-cancer properties, as outlined in the succeeding results.

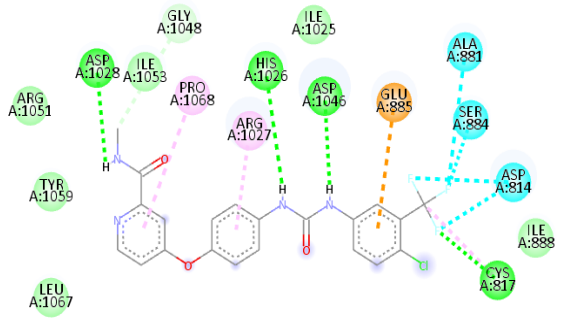


Figure 2a: Ligand and amino acid residue interaction of sorafenib.

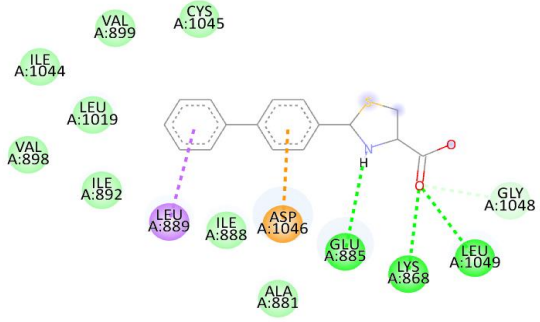


Figure 2b: Ligand and amino acid residue interaction of VT13.

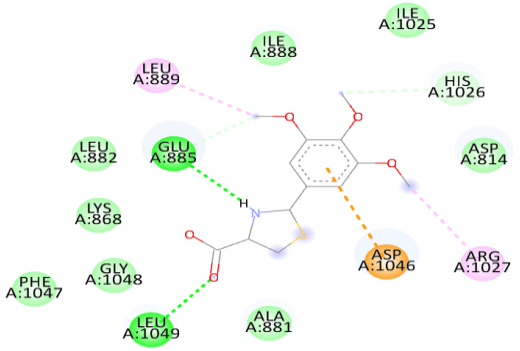


Figure 2c: Ligand and amino acid residue interaction of VT9.

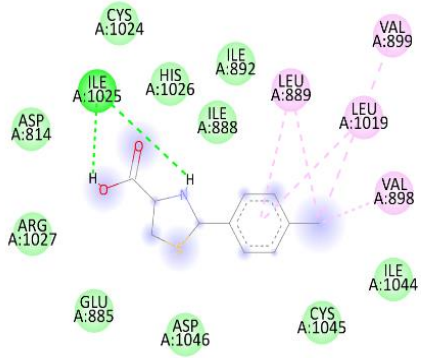
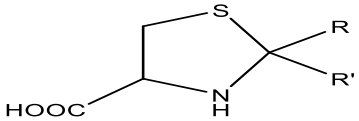


Figure 2d: Ligand and amino acid residue interaction of VT7.

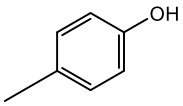
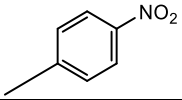
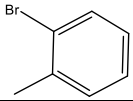
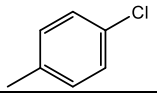
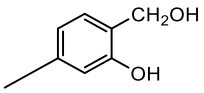
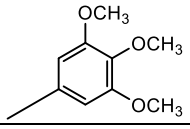
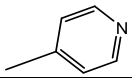
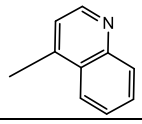
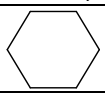
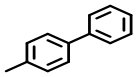
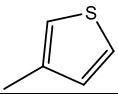
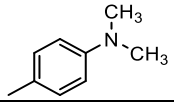
3.2 ADME Predictions

The SwissADME predictor was utilized to perform prognostic assessments concerning the logarithm of the partition coefficient (logP) and the solubility characteristics of the compound. The results are depicted in **Table 2**.

Table 2: ADME properties of the derivatives.



Sr no.	Ligands		cLogP	MR	Total Polar Surface Area (A°)
	R	R'			
VG1	H	H	0.7	35.31	74.63

VG2	CH_3	H	0.9	40.11	74.63
VG3	CH_3	CH_3	1.28	44.96	74.63
VG4		H	1.04	61.82	94.86
VG5		H	1.05	68.62	120.45
VG6		H	1.73	67.49	74.63
VG7		H	1.66	64.8	74.63
VG8		H	1.08	67.95	115.09
VG9		H	2.08	79.27	102.32
VG10		H	0.84	57.59	87.52
VG11		H	1.69	75.1	87.52
VG12		-	1.65	57.27	74.63
VT13		H	2.01	85.23	74.63
VT14		H	1.31	57.67	102.87
VT15		H	1.62	74	77.87

cLogP; calculated partition coefficient, MR; molecular refractivity, Electronic effect parameters are not considered.

3.3 Acute Oral Dose in mice

Acute toxicity study of all compounds was carried out on ICR mice *in vivo* to evaluate the safety in a dose escalation fashion at 500, 1000, 1500 and 2000 mg/kg. As shown in figure compared with the control group, there were no changes observed in the study drug group. The results showed no adverse event after the administration of compounds. No significant weight loss and toxic reactions were observed. The mortality rate of mice was 0% one week later. These results indicated that compounds were safe candidates for further drug-like study.

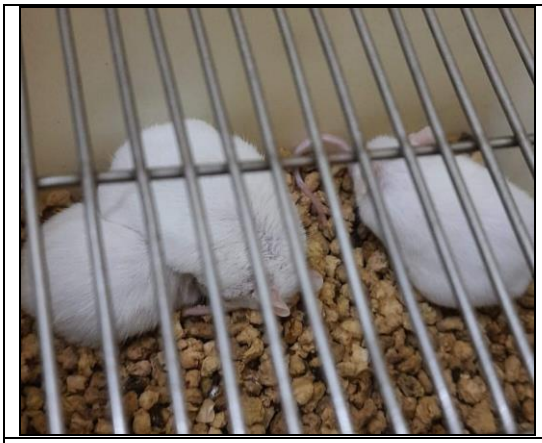


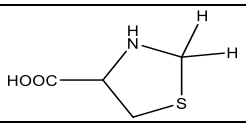
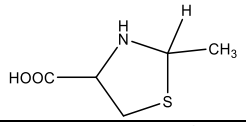
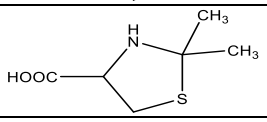
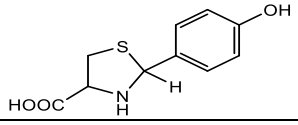
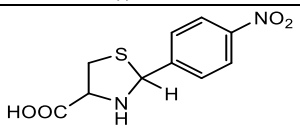
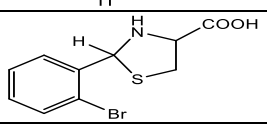
Figure 3a: Study group of mice.

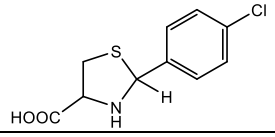
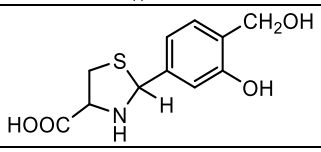
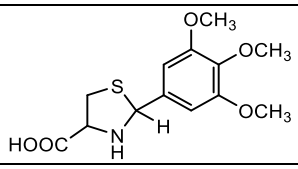
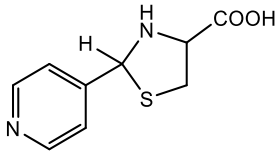
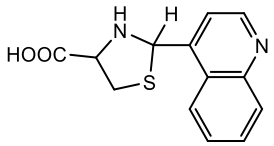
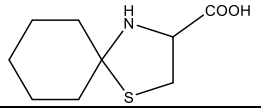
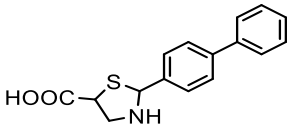
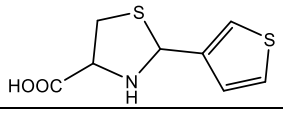
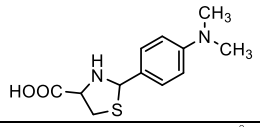
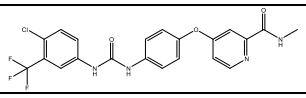
Figure 3b: Control group of mice.

3.4 Biological Assay

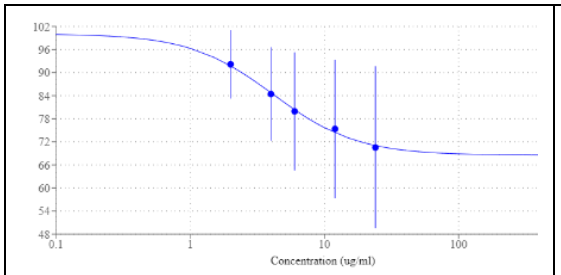
As shown in **Table 3**, thiazolidinone-4-carboxylic acid (VG1) was unable to inhibit the growth of the cancer cells. However, the corresponding branching chains (VG2-VT15) showed higher activities. The *in vitro* assay indicated that compound VG6, VG7, VG8 and VG9 were more potent and selective and VG11 somewhat showed similar inhibitory activity against melanoma cells as the standard, as indicated by its IC_{50} values (in the range of 3-4 µM for test compounds *vs.* 5.4 µM for sorafenib). Surprisingly, the outcomes from the SRB assay were disheartening when compared to the MTT assay. The results are tabulated in **Table 4** and **Table 5.**

Table 3: Activity of thiazolidine-4-carboxylic acids against MCF-7 cell lines.

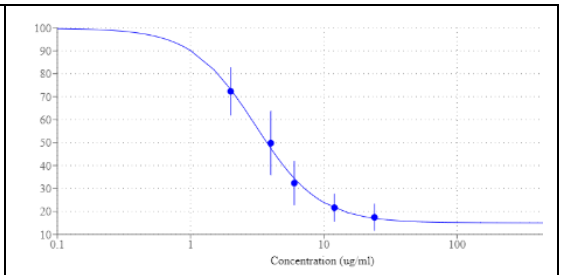
Compound No.	Molecular structure	IC_{50} (µM)	pIC50 µM
VG1		22.324	4.66
VG2		17.617	4.76
VG3		14.933	4.83
VG4		7.623	5.12
VG5		7.348	5.14
VG6		4.162	5.38

VG7		3.901	5.41
VG8		3.782	5.43
VG9		3.075	5.11
VG10		6.665	5.18
VG11		5.86	5.23
VG12		10.18	4.99
VT 13		5.863	5.24
VT 14		6.60	5.18
VT 15		6.16	5.21
Sorafenib		**5.4**	**5.27**

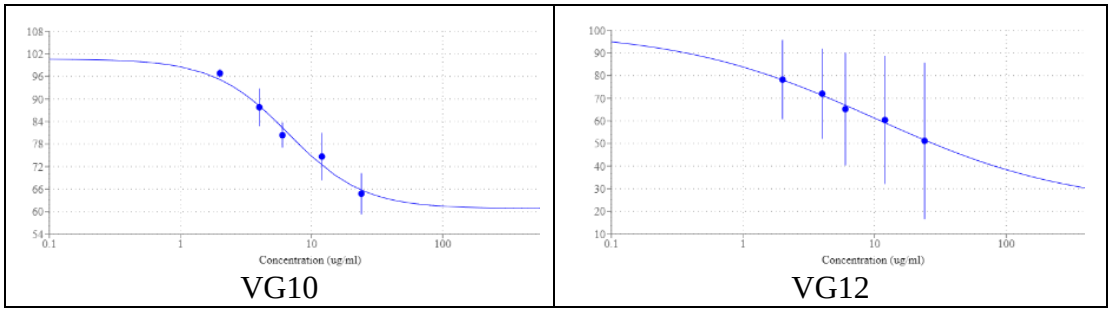
$pIC_{50} = -\log (IC_{50})$



VG6



VG9



VG10 VG12

Figure 4: IC_{50} values for VG6, VG9, VG10 and VG12.

Table 4: Cell Viability (%) against MCF-7 cell line.

Conc (µg/ml)		VG6		VG9	
	0h	6h	12h	6h	12h
0	100	100.00	100.00	100	100
2	100	79.77	96.7	82.79	61.9
4	100	70.47	82.8	63.72	35.8
6	100	62.79	77.0	41.86	22.8
12	100	57.67	68.4	27.67	15.6
24	100	52.33	59.3	23.26	11.6

Conc (µg/ml)		VG10		VG12	
	0h	6h	12h	6h	12h
0	100	100.00	100.00	100.00	100.00
2	100	95.81	97.9	77.44	57.2
4	100	92.79	82.8	61.16	54.9
6	100	83.72	77.0	51.16	44.4
12	100	80.93	68.4	45.35	35.8
24	100	70.23	59.3	26.74	26.7

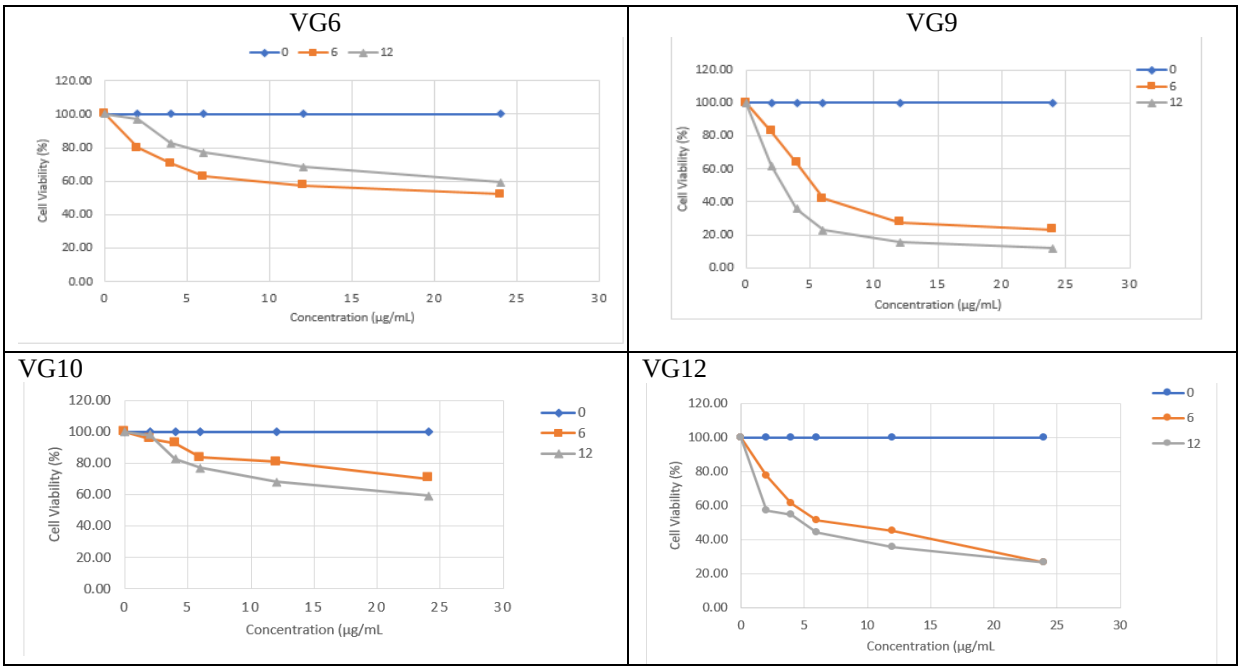


Figure 5: Cell viability (%) against Concentration (ug/ml).

Table 5: Cell growth (%) against MCF-7 cell line (SRB assay).

	% Control Growth (Average Values)			
Molar Drug Concentrations	**10**	**20**	**30**	**40**
VG1	93.3	93.8	94.6	95.8
VG2	91.3	93.1	94.3	93.1
VG3	91.3	92.8	92.8	93.6
VG4	90.4	88.9	88.7	88.9
VG5	88.6	87.7	89.8	83.9
ADR	49.9	40.8	33.9	24.6

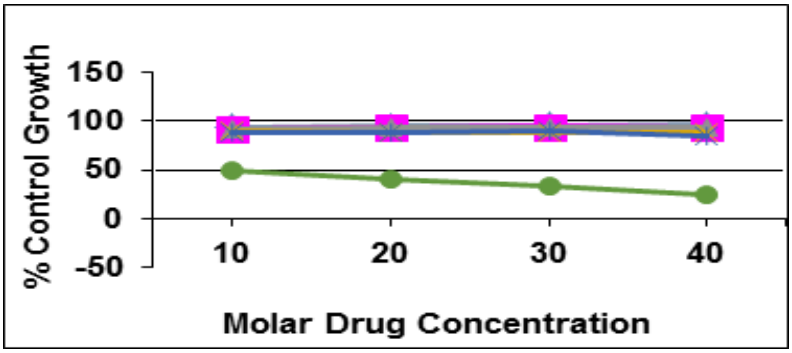


Figure 6: Growth Curve: Human Breast Cancer Cell Line MCF-7.

3.5 Structure activity relationship.

Through a comprehensive examination of the anti-proliferative effects of various substitutions, we uncovered a nuanced relationship between molecular structure and biological activity. Specifically, our findings shed light on the pivotal role of electron-withdrawing groups when introduced to the phenyl ring in compounds VG5, VG6, VG7, VG8, VG9, and VG11. These electron-withdrawing substitutions were associated with heightened efficacy in suppressing cell proliferation, underlining their importance in designing potent compounds for this purpose.

Conversely, our investigation revealed that compounds featuring minimal substitutions, such as VG1, VG2, and VG3, exhibited a relatively lower capacity to inhibit cell proliferation. Additionally, those compounds incorporating electron-donating groups onto the phenyl ring, as exemplified by VG4, VG10, VG12, VT13 and VT15 displayed diminished potency in comparison.

4. CONCLUSION

Cancer is a condition where certain cells in the body multiply excessively and disseminate to different areas of the body. Typically, human cells develop and replicate (via a process

known as cell division) to create new cells as the body requires them. As cells age or sustain damage, they perish, and new cells replace them. Occasionally, this systematic procedure fails, leading to the growth and multiplication of abnormal or damaged cells when they should not. These cells can develop into tumors, which are masses of tissue. Tumors may be malignant or benign.

A series of thiazolidine-4-carboxylic acid analogues were prepared. These molecules were docked into VEGFR-2 inhibitor complexed with Sorafenib and they showed cytotoxicity when screened against MCF-7 cell line. The compound VG9 has an IC_{50} value of 3.08 hence shows almost similar potency to that of the standard drug Sorafenib (5.4) indicating the scope for further research in thiazolidine analogues as potent anti-cancer molecules. These molecules are also subjected to SRB assay and the results showed absence of cytotoxicity.

5. ACKNOWLEDGMENTS

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docking and dynamics simulation studies of 1, 6-naphthyridines and pyridopyrimidines. Journal of Biomolecular Structure and Dynamics, 41(8): 3591-3606.

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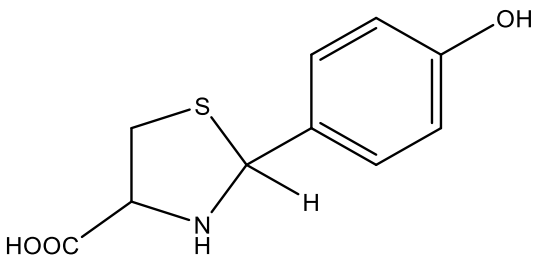
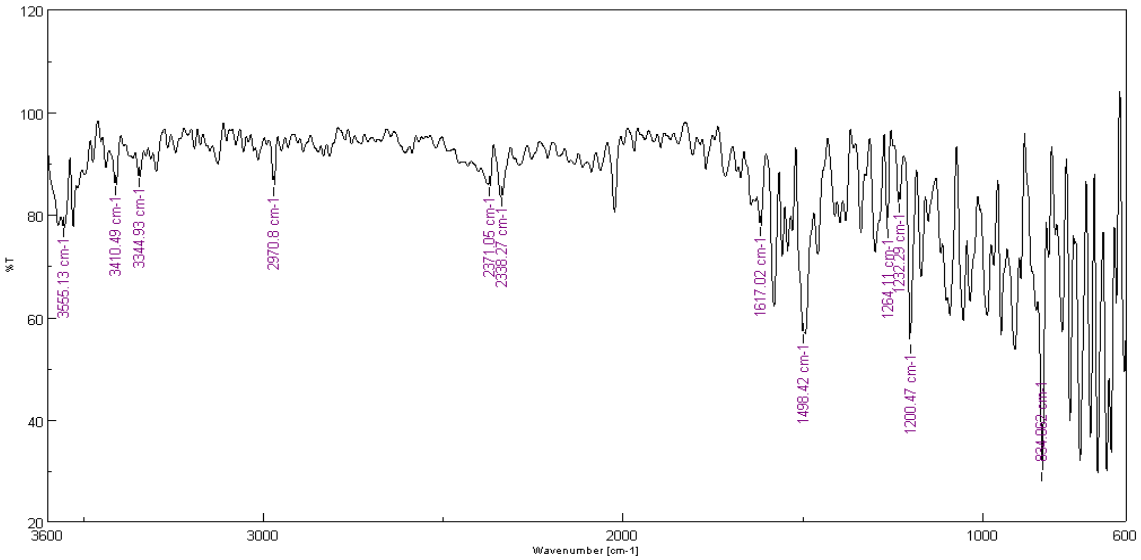
Supplementary material

The following characterization of compound may be used as reference. All other compounds were tested in similar manner.

1 Infrared Spectroscopic Analysis

i) 2-(4-Hydroxyphenyl)thiazolidine-4-carboxylic acid



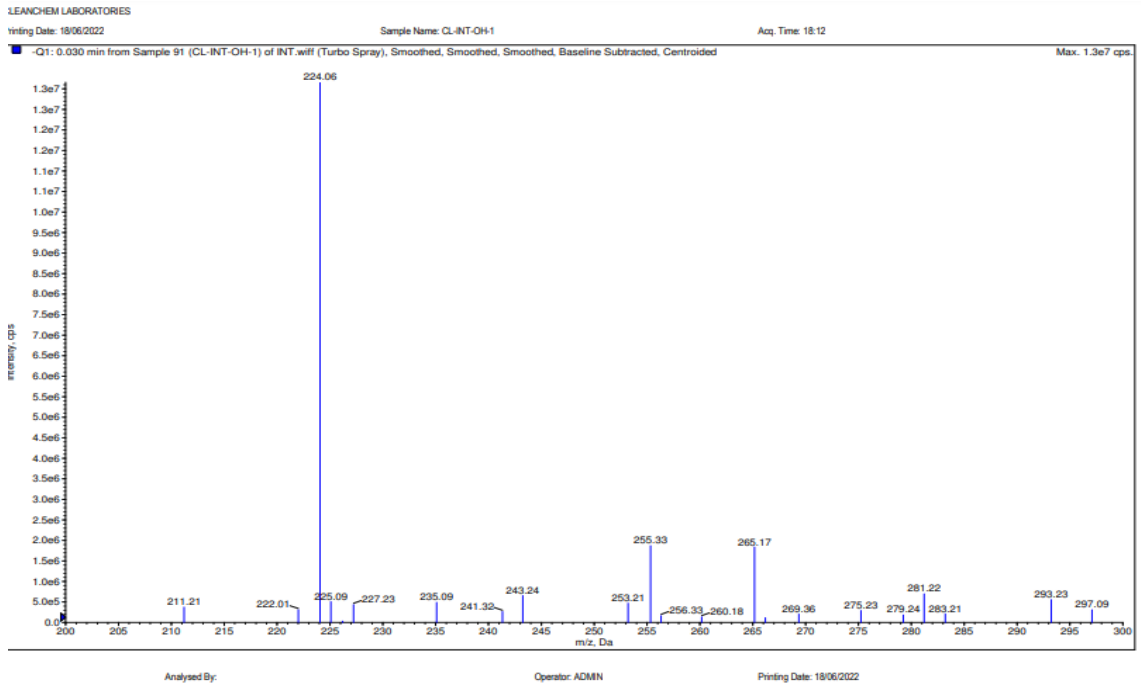


Functional groups	Wave number(cm^{-1})
O-H stretch	3555.13
N-H stretch	3344.93
Aliphatic C-H stretch	2967.08

Aromatic C-H stretch	1617.02
C=O of COOH	1498.42

2 Mass Spectroscopy

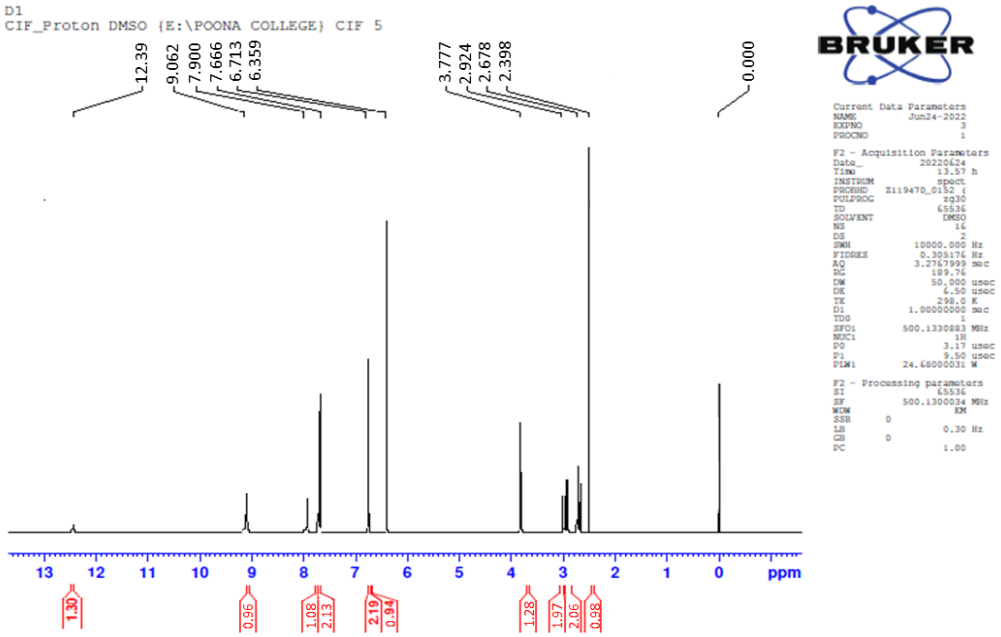
i) 2-(4-Hydroxyphenyl)thiazolidine-4-carboxylic acid



Mass= 225.04 g/mol M-1 m/z= 224.06

3 Nuclear Magnetic Resonance Spectroscopy

i) 2-(4-Hydroxyphenyl)thiazolidine-4-carboxylic acid



^{1}H NMR (500 MHz, DMSO-d6)

δ carboxylic acid 12.39 (s, 1H), alcohol 9.062 (s, 1H), 2^{o} amine 7.900 (s, 1H), aromatic 7.666 (d, 2H), aromatic 6.713 (d, 2H), methine 6.359 (s, 1H), methine 3.777 (t, 1H), methylene 2.924 (m, 2H), methylene 2.678 (m, 2H),