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Ionic Liquid Mediated Synthesis and Anticancer Activity of 5-((1, 3-DIPHENYL-1H-PYRAZOL-4-YL) METHYLENE) THIAZOLIDINE-2, 4-DIONES

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Abstract: ***A series of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives were synthesised by the Claisen-Schmidt condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with thiazolidine-2,4-dione using Ionic liquid under both conventional heating method and microwave irradiation method. All the synthesised derivatives were screened for their anticancer activity against three different human cell lines as cervix (SiHa), brest (MDA-MB-231) and pancreatic carcinoma (PANC-1) using the Sulforhodamine B assay method.***
Keywords: Ionic liquid, microwave irradiation, thiazolidine-2,4-dione, pyrazole, and anticancer activity

I. INTRODUCTION

In the realm of pharmaceutical chemistry, 2,4-thiazolidinedione and its derivatives have a wide range of uses[1]. Due to their participation in numerous physiological processes, there has been an increase in interest in the synthesis of thiazolidinedione (TZD)-based heterocyclics in recent years. In clinical settings, TZDs like rosiglitazone and pioglitazone are used to treat diabetes mellitus and related conditions[2]. Additionally, this group of chemicals are used for a wide range of biological actions, including antimicrobial[3], anti-malarial[4], antiviral[5], anti-inflammatory[6], and antagonist for thyroid hormone receptor[7], are known to be present in anti-diabetic medications made up of the TZD scaffold. The core nucleus of several anti-diabetic medications, including pioglitazone[8], rosiglitazone[9], KRP-297[10], lobiglitazone[11], and DRF-2189[12], has been discovered in TZD's structure. The development of the 2,4-thiazolidinedione (TZD) class of molecules, which reduces insulin resistance and, as a result, normalizes high blood glucose, lipid, and insulin levels in rodent models of Type 2 diabetes and obesity[13], has changed the treatment of Type 2 diabetes mellitus. Peroxisome profililator activator gamma receptors (PPAR gamma) are a class of receptors known as TZDs[14]. Pyrazole is an important biologically active scaffold that possesses nearly all types of biological activities[15]. Pyrazoles are a promising scaffold for many anticancer agents[16]. Several clinical anticancer therapeutics, such as crizotinib, ruxolitinib, niraparib, encorafenib, and darolutamide, currently consist of a pyrazole moiety [17]. Therefore, in the past decades, many pyrazolyl analogues were synthesized and tested as anticancer agents. On the other hand, Ionic liquids (ILs) are developed as a sustainable alternative to most of the volatile organic solvents. As the research on ILs progress, they emerged also as suitable catalysts and reagents. ILs possess unique set of properties with respect to their cationic and anionic components, which allows ILs to be used in varied fields. They overcome many of the traditional limitations related to conventional organic synthesis. Encouraged by the above different applications, we have synthesised a series of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione derivatives by the Claisen-Schmidt condensation of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with thiazolidine-2,4-dione using Ionic liquid under both conventional heating method and microwave irradiation method, reported reaction time, and obtained yield data and then evaluated the resulting molecules for their anticancer potential.

II. RESULT AND DISCUSSION

A series of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones were synthesized in three chemical transformation such as synthesis of 1-(1-Arylethylidene)-2-phenylhydrazines, 1-Phenyl-3-(pyridin-3-yl)-1H-pyrazole-4-carbaldehyde and 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione. 1-(1-Arylethylidene)-2-phenylhydrazines **(3a-3j)** were synthesized by the condensation of aryl methyl ketones **(1a-1j)** with phenyl hydrazine **(2)** in the presence of acetic acid in the methanol medium at heating condition to get solid 1-(1-Arylethylidene)-2-phenylhydrazines **(3a-3j).** 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes **(4a-**

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4j) were synthesized by reacting 1-(1-Arylethylidene)-2-phenylhydrazines **(3a-3j)** with Vilsmeir-Haack reagent at room temperature for 8hr in good yields. Finally the compounds 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones **(6a-6j)** by the condensation of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehyde with thiazolidinedione in the presence of N-(4-sulfonic acid) butyl triethylammonium hydrogen sulphate ([**TEBSA][HSO$_4$**]) under both conventional heating and microwave irradiation method to get corresponding 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones **(6a-6j)**. The structures of the products were established based on spectral analysis. In general, in the ^{1}HNMR (DMSO-d$_6$, 400MHz) the compound showed a characteristic peak at δ7.18 ppm as singlet was assigned for endo=CH proton and another characteristic proton was observed at 8.38 ppm as singlet was corresponding to pyrazole ring proton. The remaining aromatic protons were observed in between 7.37-8.00ppm. In the ^{13}C-NMR spectrum (DMSO-d$_6$, 100 MHz) the compound showed two peaks at δ 183.7 and 202.1 ppm were corresponding to C=O and C=S carbons respectively. The carbon spectrum showed peaks at δ 159.4, 152.5, 139.1, 136.3, 129.7, 129.6, 126.6, 126.1, 124.6, 118.6, 118.2, 114.2 and 111.7. In the mass spectrum the compound showed a peak at m/z 348 (100%) as $[M+H]^+$ peak.

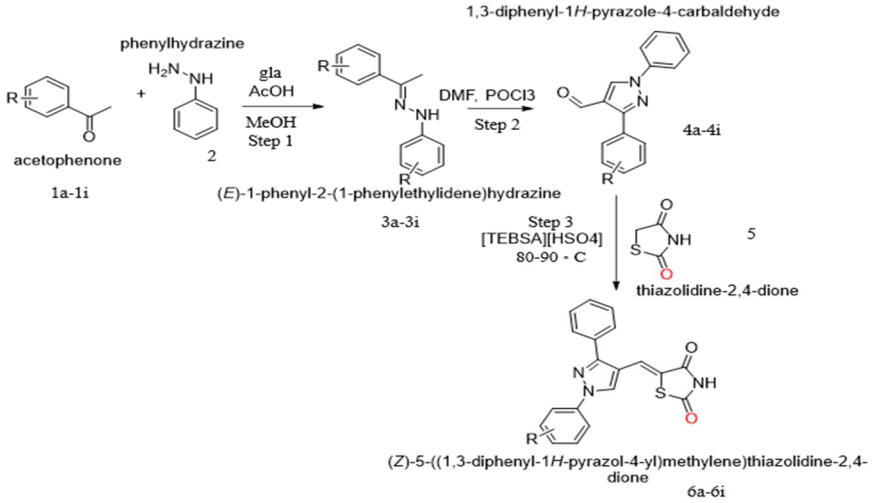


Table-1: Physical data of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (6a-6j)

S. No	Compound	M.F. (M.Wt.)	m.p.	Rea[n] time (min)		Yield (%)	
				Conven	MWI	Conven	MWI
1	Phenyl	$C_{19}H_{13}N_3O_2S$ (347)	185-187	18	8	80	86
2	4-Methyl phenyl	$C_{20}H_{15}N_3O_2S$ (351)	190-192	18	8	78	82
3	4-Methoxy phenyl	$C_{20}H_{15}N_3O_3S$ (377)	185-187	20	8	74	82
4	4-Fluorophenyl	$C_{19}H_{12}FN_3O_2S$ (365)	200-202	20	8	79	84
5	4-chlorophenyl	$C_{19}H_{12}ClN_3O_2S$ (381)	158-160	15	8	73	80
6	4-Bromophenyl	$C_{19}H_{12}BrN_3O_2S$ (425)	193-195	20	8	76	82
7	4-Hydroxyphenyl	$C_{19}H_{13}N_3O_3S$ (363)	187-189	20	8	78	82
8	4-Nitrophenyl	$C_{19}H_{12}N_4O_4S$ (392)	183-185	20	8	80	85
9	2,4-Dichlorophenyl	$C_{19}H_{11}Cl_2N_3O_2S$ (415)	143-145	20	8	79	80
10	3,4-Dimethoxy phenyl	$C_{21}H_{17}N_3O_4S$ (407)	158-161	18	8	75	80

[a] isolated yield we encouraged to us to synthesis of pyrazolone-pyrazole derivatives

III. ANTICANCER ACTIVITY

5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones (6a-6j) were evaluated for their anticancer activity against three different human tumor cell lines as cervix (SiHa), breast (MDA-MB-231) and pancreatic carcinoma (PANC-1) (SiHa, MDA-MB-231 and PANC-1 using the Sulforhodamine B assay method. Doxorubicin is used as standard. The GI_{50} values are listed in Table 2. From the screening results, Interestingly, the compounds 6c, 6g and 6h showed potent activity against as Cervix (SiHa) cell lines with compared to doxorubicin, the compounds 6c, 6d and 6j showed good anticancer activity on breast (MDA-MB-231) cell lines and the compounds 6d, 6h and 6i exhibited maximum anticancer activity on pancreatic carcinoma (PANC-1).

Table-2: Anticancer activity of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones (6a-6j) (GI_{50} values).

Compound	SiHa	MDA-MB-231	PANC-1
6a	1.81	--	--
6b	0.89	--	--
6c	2.50	2.10	2.56
6d	--	1.57	4.10
6e	--	0.98	1.77
6f	--	0.73	--
6g	2.06	1.44	2.25
6h	1.98	--	4.01
6i	0.97	0.85	3.56
6j	1.45	1.11	--
Doxorubicin	2.31	1.15	3.10

- *Experimental:* Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254}(Merck). IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H& ^{13}C NMR spectrums were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer.

General procedure for the preparation of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones (6a-6j):

1) *Microwave Irradiation Method:* A mixture of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes **(4a-4j)** (1.0mmol) and thiazolidine-2,4-dione **(5)** (1.0 mmol) in [TEBSA][HSO_4] (0.1mmol) was taken in a microwave vial and irradiated at 120W for 8 min. Reaction progress monitored by TLC. After completion of the reaction. Cooled to RT and added ice cold water to get solid to give corresponding 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones **(6a-6j)**
2) *Conventional Stirring Method:* A mixture of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes **(4a-4j)** (1.0 mmol), thiazolidine-2,4-dione **(5)** (1.0 mmol) and [TEBSA][HSO_4] (0.1 mmol) in ethanol (10.0 ml) was taken in a RB flask and stirred at 80-90°C for up to 20 min. Reaction progress monitored by TLC. After completion of the reaction. Cooled to RT poured into ice cold water to get to get solid to give corresponding 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones **(6a-6j)**.

IV. SPECTRAL DATA

(Z)-5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6a)

IR (KBr): υ 3450 1698 and 1627cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 7.20 (s, 1H, HC=C), 7.37-7.42 (t, 1H, Ar-H), 7.44-7.63 (m, 5H, Ar-H), 7.93-8.01 (m, 4H, Ar-H), 8.42 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 112.4, 118.4, 118.7, 119.2, 122.1, 127.7, 128.5, 128.6, 129.1, 129.7, 131.2, 134.8, 138.5, 152.6, 174.3, 184.6; *MS* 348 $(M+H)^{+}$.

(Z)-5-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6b)

IR (KBr): υ 3390, 1696 and 1574 cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 2.39 (s, 3H, CH_3), 7.19 (s, 1H, HC=C), 7.35-7.36 (m, 3H, Ar-H), 7.52-7.56 (m, 4H, Ar-H), 7.91-7.93 (d, 2H, Ar-H), 8.39 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 20.8, 111.7, 118.3, 118.7, 119.1, 126.2, 126.7, 128.3, 129.3, 129.6, 136.4, 137.8, 139.1, 152.3, 174.6, 182.4; *MS* 362 $(M+H)^{+}$.

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(Z)-5-((3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6c)
IR (KBr): υ 3391, 1673 and 1618cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 3.84 (s, 3H, OCH_3), 7.10-7.12 (d, 2H, Ar-H), 7.18 (s, 1H, HC=C), 7.34-7.37 (t, 1H, Ar-H), 7.52-7.57 (m, 4H, Ar-H), 7.90-7.92 (d, 2H, Ar-H), 8.38 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 55.2, 111.7, 114.2, 118.2, 118.6, 124.6, 126.1, 126.6, 129.6, 129.7, 136.3, 139.1, 152.5, 159.4, 174.6, 182.4; *MS* 378 $(M+H)^+$.

(Z)-5-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6d)
IR (KBr): υ 3450 1698 and 1627cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 7.16 (s, 1H, HC=C), 7.35-7.42 (m, 3H, Ar-H), 7.52-7.56 (m, 2H, Ar-H), 7.66-7.69 (m, 2H, Ar-H), 7.92-7.94 (d, 2H, Ar-H), 8.42 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 111.7, 115.6, 115.8, 118.2, 118.8, 126.4, 126.8, 128.7, 129.6, 129.7, 130.4, 130.5, 136.5, 139.0, 151.4, 161.0, 174.7, 182.3; *MS* 366 $(M+H)^+$.

(Z)-5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6e)
IR (KBr): υ 3391, 1671 and 1609cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 7.18 (s, 1H, HC=C), 7.36-7.40 (t, 1H, Ar-H), 7.53-7.68 (m, 6H, Ar-H), 7.92-7.94 (d, 2H, Ar-H), 8.44 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 111.2, 118.4, 118.8, 119.2, 126.5, 126.9, 128.8, 129.6, 130.0, 131.1, 133.2, 137.0, 139.0, 151.0, 174.6, 182.3; *MS* 382 $(M+H)^+$.

(Z)-5-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6f)
IR (KBr): υ 3388, 1675 and 1612 cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 7.17 (s, 1H, HC=C), 7.36-7.40 (t, 1H, Ar-H), 7.53-7.61 (m, 4H, Ar-H), 7.75-7.77 (d, 2H, Ar-H), 7.92-7.94 (d, 2H, Ar-H), 8.43 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 111.2, 118.4, 118.8, 119.2, 126.6, 126.9, 129.6, 130.3, 131.7, 133.2, 135.7, 137.1, 139.0, 151.0, 174.5, 182.3; *MS* 427 $(M+H)^+$.

(Z)-5-((3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6g)
IR (KBr): υ 3380, 1642 and 1615 cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 6.98-7.00 (d, 2H, Ar-H), 7.18 (s, 1H, HC=C), 7.36-7.41 (m, 3H, Ar-H), 7.53-7.59 (m, 4H, Ar-H), 7.94-7.96 (d, 2H, Ar-H), 8.44 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 107.8, 111.4, 117.9, 118.5, 124.0, 126.2, 126.4, 129.5, 129.8, 139.0, 152.3, 156.3, 174.6, 183.4; *MS* 364 $(M+H)^+$.

(Z)-5-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6h)
IR (KBr): υ 3414, 1642 and 1591 cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 7.18 (s, 1H, HC=C), 7.36-7.41 (t, 1H, Ar-H), 7.53-7.57 (m, 2H, Ar-H), 7.59-7.61 (d, 2H, Ar-H), 7.81-7.83 (d, 2H, Ar-H), 7.99-8.01 (d, 2H, Ar-H), 8.45 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 111.6, 118.7, 118.9, 122.2, 127.5, 127.7, 129.6, 130.4, 131.5, 132.0, 133.7, 136.0, 139.3, 151.6, 174.7, 183.5; *MS* 393 $(M+H)^+$.

(Z)-5-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6i)
IR (KBr): υ 3351, 1678 and 1611 cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 7.08 (s, 1H, HC=C), 7.17-7.20 (m, 2H, Ar-H), 7.35-7.38 (m, 1H, Ar-H), 7.53-7.62 (m, 3H, Ar-H), 7.92-7.94 (d, 2H, Ar-H), 8.44 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 111.5, 115.5, 118.3, 118.8, 120.5, 124.3, 124.7, 126.7, 126.8, 129.5, 130.2, 134.1, 134.5, 138.8, 151.5, 174.6, 183.0; *MS* 417 $(M+H)^+$.

(Z)-5-((3-(2,4-dimethoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidin-2,4-dione (6j)
IR (KBr): υ 3382, 1672 and 1618 cm^{-1}; ^{1}H NMR spectrum, δ, ppm: 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.97 (s, 1H, Ar-H), 7.05-7.07 (d, 1H, Ar-H), 7.17 (s, 1H, HC=C), 7.35-7.38 (m, 1H, Ar-H), 7.53-7.63 (m, 3H, Ar-H), 7.94-7.96 (d, 2H, Ar-H), 8.38 (s, 1H, pyrazole ring proton); ^{13}C NMR spectrum, δC, ppm: 55.1, 56.0, 98.5, 110.5, 111.6, 114.0, 118.1, 118.8, 124.3, 126.7, 126.8, 129.5, 129.7, 138.8, 152.7, 154.0, 159.3, 174.5, 183.4; *MS* 408 $(M+H)^+$.

V. CONCLUSION

We have successfully developed a new green synthetic ionic liquid based synthesis of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione from 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes and thiazolidine-2,4-dione under both conventional and microwave irradiation method. The microwave irradiation method to be an easy, gave higher yield with lower reaction times, greater selectivity and more eco-friendly.

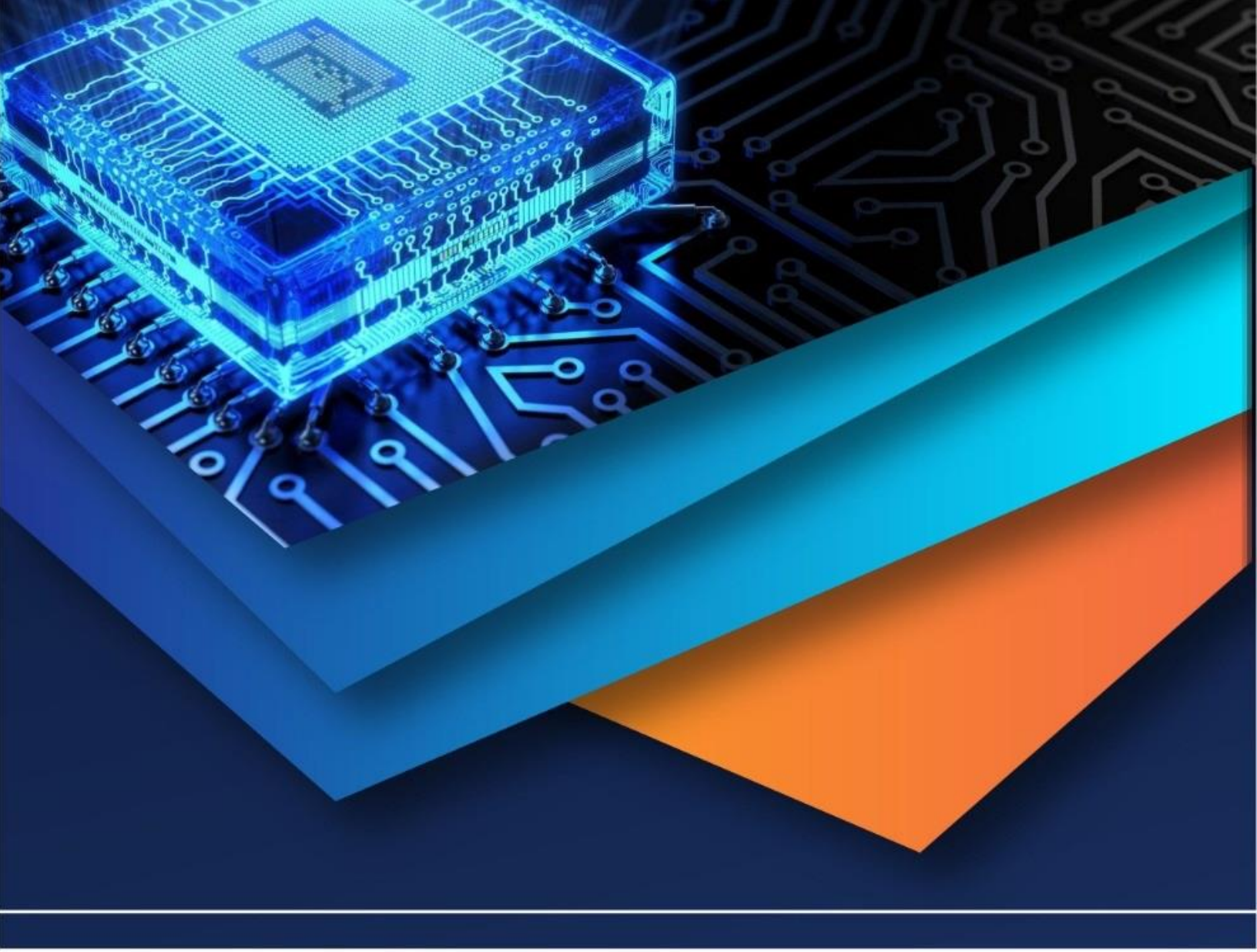
The synthesised compounds were evaluated for their anticancer activity against three different human tumor cell lines SiHa, MDA-MB-231 and PANC-1, among the compounds 6c, 6g and 6h showed potent activity against as Cervix (SiHa) cell lines with compared to doxorubicin, the compounds 6c, 6d and 6j showed good anticancer activity on breast (MDA-MB-231) cell lines and the compounds 6d, 6h and 6i exhibited maximum anticancer activity on pancreatic carcinoma (PANC-1).

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