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Synthesis, Characterisation and in Vitro Disease Oriented Anticancer and Antimicrobial Screening of some Novel Thiazolidinones

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Abstract: ***Thiazolidinones are significant group of compounds in regards to diverse biological activities. In view of the same, efforts have been made to synthesize some novel substituted thiazolidinones (series A) and to study their antimicrobial as well as anticancer activities. The reactions are further extended to synthesize fused thiazolidinones. Thus compounds of series B – pyranothiazoles (two fused rings) and the compounds of series C- thiazoloquinolines (3- fused rings) are also prepared by simple condensation reactions. Changing –R groups, total nine compounds have been prepared, analysed by ir and nmr and finally screened against three bacterial stains and three fungal stains. Also one compound A3 is tested against nine cancer cells. The anticancer activities were conducted by the Department of Health and Human Services, NationalInstitute of Health, National Cancer Institute, Bethesda, Maryland. The results found are quite encouraging.***
Key words: anticancer, antimicrobial, pyanothiazoles, Thiazolidinones, thiazoloquinolines.

I. INTRODUCTION

Thiazolidinones are classified as doubly unsaturated five membered heterocyclic compounds containing one nitrogen, one sulphur and three carbon including a carbonyl group,Thiazolidinones exhibit wide spectrum of pharmacological activities[1]. They are found to possess fungicidal[2,3,4,5], bactericidal[6,7,8] ,herbicidal[9], insecticidal[10], antiviral[11], antihelmintic[12], and cytocidal[13] activities. Thiozolidinones and their derivative display a large variety of activities such as antibiotic, diuretic, organoleptic, antileukaemic, tuberculostic and antiparasitical[14,15]. Cancer is one of the most challenging problems in health related issues. Both animals and plants are found to suffer with malignant tumours of diverse kind. Since this is not a disease caused by pathogens, all anticancer drugs affect malignant tumour cells as well as healthy cells. Thus they badly affect the health of the individual who is suffering with this illness. Therefore it is always a matter of research to synthesize newer drugs which would target the cancer cells in particular causing least damage to the healthy cells. At the same time many malignant cells have become resistant towards conventional chemotherapeutic drugs. Therefore, there is an urgent need for more selective and potential anticancer drugs[16]. Derivatives of thiazolidinones are well reported to show anticancer activities[17,18] as well as antifungal [19] and antibacterial[20] activities.

The awareness of broad spectrum of biological activities of thiazolidinones has led to the idea of synthesizing some new derivatives of thiazolidinones. The effort is extended to fuse it with ethyl acetoacetate (EAA) to give pyranothiazolbenzamides. Thiazolidinones are further fused with anthranilic acid to give rise to three membered fused ring systems - thiazoloquinolin . The route of synthesis is exhibited in the scheme below. All steps involve simple condensation reaction involving enolate formation. The purity of the compound prepared has been ascertained by chromatographic methods. Melting points of the recrystallized product are taken in open capillaries and are uncorrected. The ir and nmr of the newly synthesized compounds are recorded on JEOL GS – 400 model and ir on KBr pallets and Nijol solution on Perkin Elmer-R-32 spectrometer at 90 MHz respectively. Anticancer activities are tested against nine cancer cells.

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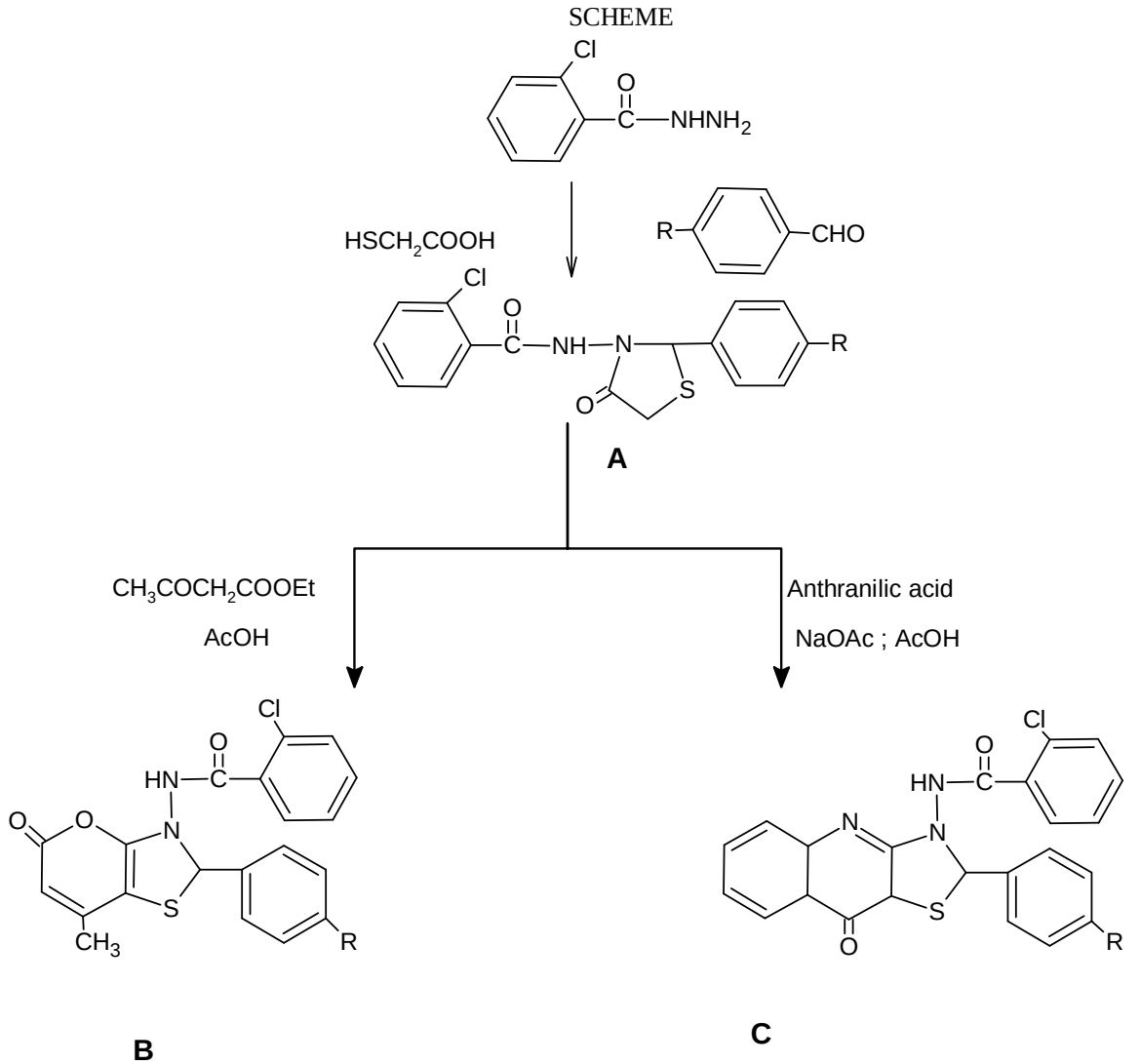

R= -H, 4-Cl, 4-OMe

II. EXPERIMENTAL

A. Instrumentation And Methodology

All together nine compounds have been prepared under series A, B and C. All the compounds are chacterised by ir, nmr and elemental analyses. All the chemicals and solvents were purchased from sigma - Aldrich and E. Merk (India). All the compounds were purified by Chromatographic technique and recrystallization. The reaction were monitored by thin layer chromatography (TLC) on percoated Silica Gel 60 F254 (mesh) and spots were visualised with Iodine Chamber. Melting points of all synthesized compounds were determined by using open capillary method and may be uncorrected. All the synthesized compounds were characterized by elemental analysis on Carlo Elba 1108 Heraeus. NMR spectra were recorded on JEOL GS-400 model FT-NMR (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer and processed with Delta software. The chemical shift were measured in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) taking as refrence. Infrared red spectra were recorded on KBr pallets and Nujol solution on Perkin Elmer –R-32 spctrometer at 90 MHz.

Synthesis of compound s of series A: 2-chloro-N-(4-oxo-2-aryl-1,3-thiazolidin-3-yl)benzamides

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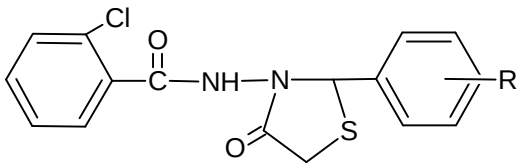
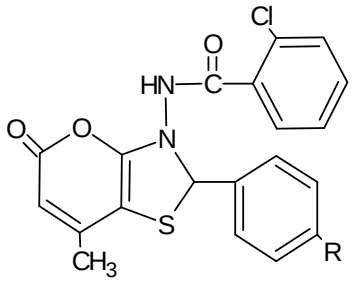


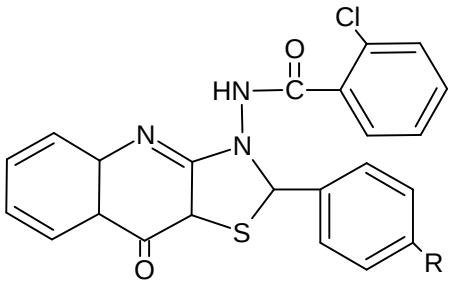
A mixture of 2-chlorobenzohydrazide (2.15 g, 0.01M), arylbenzaldehyde (0.01M) and thioglycollic acid (1.20g,0.01M) in 20ml methanol was heated under reflux for twenty hours, excess methanol was distilled off and the residue was poured into water. It was made alkaline with $NaHCO_3$, stirred and kept overnight. The resulting product was filtered off, washed, dried and recrystallized from aqueous ethanol (50%).

Synthesis of compounds of series B: 2-chloro-N-(7-methyl-5-oxo-2-aryl-2H-pyrano[2,3-d][1,3]thiazol-3(5H)-yl)benzamides



A mixture of 2-chloro-*N*-(4-oxo-2-aryl-1,3-thiazolidin-3-yl)benzamide (0.005M), glacial acetic acid (3.0 ml) and ethyl acetoacetate (0.72g, 0.0055M) was gently refluxed for six hours and cooled. The resulting mass was poured into cold aqueous ammonia and stirred. The solid obtained was filtered washed and recrystallized from aqueous ethanol (50%).

Synthesis of compounds of series C: 2-chloro-N-(9-oxo-2-aryl-4a,8a,9,9a-tetrahydro[1,3]thiazolo[4,5-b]quinolin-3(2H)-yl)benzamides



A mixture of 2-chloro-*N*-(7-methyl-5-oxo-2-aryl-2*H*-pyrano[2,3-*d*][1,3]thiazol-3(5*H*)-yl)benzamide (0.005M), anthranilic acid (1.37g, 0.01M), glacial acetic acid and fused sodium acetate (2.0g) was refluxed for six hours. After cooling the contents were poured into cold ammonia and stirred, filtered, wased and recrystallized from aqueous alcohol (50%).

Table 1: Characterisation data of all the compounds:

SL.No.	COMPOUND NO.	R	M.P.(^{0}C)	% Yield	ELEMENTAL ANALASIS			SPECTRAL DATA	
					S	O	N	ir γ_{max} (cm^{-1})	nmr δ (TMS)
1	A1	H	150-151	62	7.86	12.04	6.89		
2	A2	4-OCH_3	162-163	77	7.26	11.22	6.34	1660 C=O (β-lactum),C-S-C (820), C-Cl (730)	8.1(1H,S,NH), 3.7-3.8 (3H,S,-OCH_3), 1.6-1.8 (3H,d,-CH_3)

3	A3	4-Cl	170-171	48	7.24	12.43	7.24		
4	B1	H	160-161	92	8.03	12.03	7.02		
5	B2	4-OCH_3	175-176	51	7.40	11.07	6.46	C=O(β-lactum)1670, C=O(CONH), C-S-C (820), C-Cl (730)	9.3 (1H,S, NH), 3.7-3.8 (3H,S,-OCH_3), 1.8-1.5 (3H,d,-CH_3)
6	B3	4-Cl	165-168	82	8.26	14.92	6.53		
7	C1	H	189-190	70	8.13	7.34	9.63		
8	C2	4-OCH_3	200-201	75	7.53	6.80	8.93		
9	C3	4-Cl	208-209	63	2.32	10.30	9.01	C=O (1680), C=O (CONH) 1600, C-S-C (820), C-Cl (730)	8.5 (1H, S, NH),5.4-5.6 (1H,S,C(2)H), 2.3-2.2 (1H,S, CH)

III. RESULT AND DISCUSSION

The compounds of series A were successfully prepared by condensation reaction of 2-chlorobenzohydrazide and arylbenzaldehydes resulting into thiazolidinones in quantitative yields. The structure is established by both ir and nmr data which clearly show two important peaks, one at γ_{max} 1660cm^{-1} for cyclic C=O (β-lactum), the other at γ_{max} 820cm^{-1} for cyclic C-S-C group. This proves that the ring thiazolidinones have been prepared. Nmr data also support the formation of thiazolidinones.

The presence of active methylene is indicated by δ 2.6-2.8 singlet peak for two hydrogens. These compounds are further condensed with ethylacetoacetate (EAA) to give rise to compounds of series B in which EAA was condensed with thiazolidinone at its enolic site giving rise to a two membered fused ring system - pyranothiazoles. Again the ir spectrum supports its structure by giving important peaks at C=O (β-lactum) 1670, C=O (CONH), C-S-C (820), C-Cl (730) and nmr data 9.3 (1H, S, NH), 3.7-3.8 (3H, S, -OCH_3), 1.8-1.5 (3H, d, -CH_3).

The compounds of series A in turned condensed with anthranilic acid with the help of fused sodium acetate giving rise to a three membered fused ring resembling anthracene. Its structure have been established by ir and nmr data C=O (1680), C=O (CONH) 1600, C-S-C (820), C-Cl (730), 8.5 (1H, S, NH), 5.4-5.6 (1H, S, C (2)H), 2.3-2.2 (1H,S, CH). All the physical data of characterisation of the newly synthesized compounds are given in Table 1.

A. In Vitro Anti-Cancer Activity Test On Human Cell Lines

The *in-vitro* anticancer screening was done at the Department of Health and Human Services, National Institutes of Health, Bethesda, Maryland 20892. All the compounds have been screened against nine type of most common cancer panels. For each panel different cell lines have been chosen. The growth percent and growth inhibition are recoded taking 50% growth inhibition as standered.

Total growth inhibition and lethal concentration (LG_{50}) causing standered 50% growth inhibition are also estimated. Compound A3 is found active against leukaemia, non-small cell lung cancer, colon cancer, melanoma, renal cancer and breast cancer. The activity ranges between low to moderate. Compound A3 is most active against leukaemia and it is found quite comparable to convententional drugs being used. GI_{50} value is as high as 1.00 with percentage growth only nine for leukaemia (SR cell lines).

Table 2: Anticancer activities of compound A 3 showing Growth percent (%) and Growth inhibition(GI_{50}) for compound and Lehal Concentration (LC_{50}) A1

Panel/cell lines	Growth percent (%)	Growth inhibition (GI_{50})	Lethal concentration (LC_{50})
Leukemia			
CCRF-CEM	126	1.00E-04	1.00E-04
HL-60(TB)	110	2.82E-05	1.00E-04
MOLT-4	96	3.27-05	1.00E-04
RPMI-8226	98	2.98E-05	1.00E-04
SR	97	8.30E-05	1.00E-04
	110	2.19E-05	1.00E-04
Non-small cell lung cancer			
A549/ATCC	101	6.26-05	1.00E-04
EKVX	96	1-00E-04	1.00E-04
HOP-62	102	1.00E-04	1.00E-04
HOP-92	92	5.73E-05	1.00E-04
NCI-H226	91	1.00E-04	1.00E-04
NCI-H23	103	1.00E-04	1.00E-04
NCI-H460	98	1.00E-04	1.00E-04
NCI-H460	107	1.00E-04	1.00E-04
NCI-H522	89	6.46E-05	1.00E-04
COLON Cancer			
COLO 205	99	1-00E-04	1.00E-04
HCC-2998	107	1.00E-04	1.00E-04
HCT-116	79	3.49E-05	1.00E-04
HT29	108	1.00E-04	1.00E-04
KM12	104	1.00E-04	1.00E-04
SW-620	99	1.00E-04	1.00E-04
	101	1.00E-04	1.00E-04
CNS-cancer			
SF-268	96	1.00E-04	1.00E-04
SF-295	98	6.87E-05	1.00E-04
SF-539	110	1.00E-04	1.00E-04
SNB-75	89	1.00E-04	1.00E-04
U259	104	1.00E-04	1.00E-04
	102	1.00E-04	1.00E-04
Melanoma			
LOX IMVI	96	1.00E-04	1.00E-04
MI 4	105	1.00E-04	1.00E-04
SK-MEL-2	107	1.00E-04	1.00E-04
SK-MEL-28	101	1.00E-04	1.00E-04
SK-MEL-5	99	1.00E-04	1.00E-04
UACC-257	112	1.00E-04	1.00E-04
UACC-62	104	1.00E-04	1.00E-04
Ovarian cancer			
IGROVI			
OVCAR-3	97	1.00E-04	1.00E-04
OVCAR-4	106	1.00E-04	1.00E-04

OVCAR-5	97	1.00E-04	1.00E-04
OVCAR-8	93	1.00E-04	1.00E-04
SK-OV-3	95	1.00E-04	1.00E-04
	103	1.00E-04	1.00E-04
Renal cancer			
786-0	89	7.44E-05	1.00E-04
A498	114	1.00E-04	1.00E-04
ACHN	98	1.00E-04	1.00E-04
CAKI-1	101	1.00E-04	1.00E-04
RXF 393	105	6.13E-05	1.00E-04
SN12C	88	7.47E-05	1.00E-04
TK-10	110	1.00E-04	1.00E-04
UO-31	95	1.00E-04	1.00E-04
Prostate cancer			
PC-3	105	1.00E-04	1.00E-04
DU-145	102	1.00E-04	1.00E-04
Breast cancer			
MCF7	96	9.23E-05	1.00E-04
NCI/ADR-RES	100	1.00E-04	1.00E-04
MDA-MB-231/ATCC	106	1.00E-04	1.00E-04
HS 578T	96	1.00E-04	1.00E-04
MDA-MB-434	98	7.53E-05	1.00E-04
MDA-N	97	5.78E-04	1.00E-04
BT-549	102	1.00E-04	1.00E-04
T-47D	104	6.35E-05	1.00E-04

B. Antimicrobial Activity

All the nine compounds of this series have been screened against three bacteria S. aureus (ATCC 25323), E.faecalis (ATCC 29212), E.coli (ATCC 35218) and three fungus stains C. albicans (ATCC-90028. C. albicans C. Tropicanlis (ATCC-750**)(**Clinical). The bactericidal and fungicidal data are recorded in table3. All synthesized compound of series (A, B and C) were screened for their antimicrobial activities. Minimum inhibitory concentration (MIC) against broad spectrum of bacterial stains. The potency of the compounds as antibacterial was appraised for their studies against gram+ve and gram-ve stains. The activity results obtained as MIC are summarised in Table 3. Most of the synthesized compounds showed excellent potency with less MIC as compounds to control drug ciprofloxacin. DMSO was also taken as control which showed no effect in the experiment, but most compounds are found to show low to moderate type of activities.

Table 3: Antimicrobial activities (MIC µg/mL) of ompounds 1-9

S.No.	Compounds	R	Bacteia G+	Bacteria G+	Bacteria G+	Fungus	Fungus	Fungus
			S. aureus (ATCC 25323)	E. faecalis (ATCC-29212)	E. coli (ATCC-35218)	C. albicans (ATCC-90028)	C. albicans (Clinical)	C. tropicanlis (ATCC-750)
1	A1	H	12.25	50	100	100	100	12.12
2	A2	4-OCH_3	12.50	25	25	12.50	6.25	12.50

3	A3	4-Cl	1.56	6.25	12.50	3.12	12.50	25
4	B1	H	3.12	12.50	25	6.25	12.50	12.50
5	B2	4-OCH_3	2.25	12.50	25	6.50	12.25	12.25
6	B3	4-Cl	6.25	6.26	12.50	12.50	12.50	25
7	C1	H	1.25	6.25	12.50	3.12	6.25	25
8	C2	4-OCH_3	2.25	12.50	3.12	12.50	6.25	12.50
9	C3	4-Cl	6.25	25	2.50	2	25	25
10	Ciproflo xacin	-	6.25	6.25	3.12	-	-	-
11	Flucona zole	-	-	-	-	6.25	3.12	6.25

IV. CONCLUSION

Total nine compounds have been synthesized successfully purified by recrystallization and tested with melting points. Representative compounds have been characterized by ir, and nmr spectroscopy. The spectral data found are quite satisfactorily fitting to the anticipated structures of the compounds. The strategy has been to synthesize fused thiazolidinones which are structural analogues of nucleotides and thus strategically thought of being anticancer agents. Alongside antimicrobial screening have been also performed as guided by the literature. The hypothesis is well established looking at the screening data both antimicrobial and anti-cancer. Some of the compounds show very promising activities quite comparable to commercial drugs. Compound A3 show upto 50% growth inhibition. Thus it is very evident that these compounds can be developed as drugs. This research effort results into positive outcome and is very successful in its contents.

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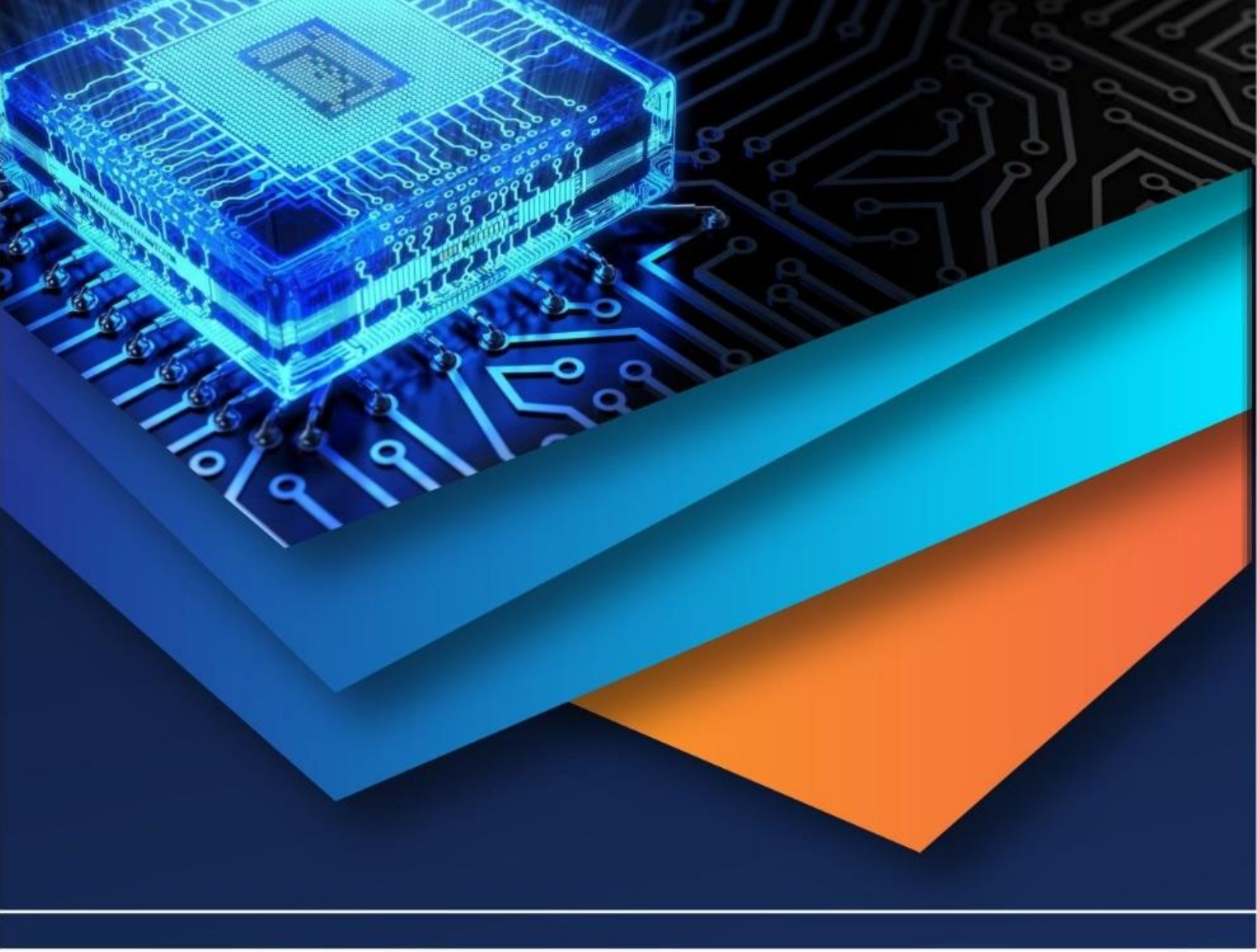

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