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Synthesis and ADMET Study of Some 1, 8-Naphthyidine and Quinoline 3-Carboxylic Acid Derivatives

Vinod Kumar Gurjar[1], Shingala Akash B[2], Patel Prashant G[3], Shaikh Mois A[4], Solanki Divyaben L[5], Patel Parth K[6]
[1]*Assistent Professor, School of pharmacy, Parul University Vadodara, Gujarat, India*
[2, 3, 4, 5, 6]*Sudent, Department of Industrial Chemistry Parul Institute of Applied Science, Parul University, Vadodara, Gujarat, India*

Abstract: ***The extremely drug resistant may be a worldwide public ill health in recent years. Molecules with newer targets and an alternate mechanism of action is an urgent requirement of improvement of latest drugs. The utilization of heterocyclic compounds has been increased dramatically over the last 70 years due to their wide selection of technical applications and their favorable environmental and toxicological properties The 1,8-naphthyridine and quinoline 3-carboxylic acid derivatives that we'll manufacture during this method will change the potency and specificity of fluoroquinolones. Taking under consideration the findings, the goal is to style and manufacture 1, 8-naphthyridine and quinoline 3-carboxylic acid derivatives. The synthesized compounds are going to be characterized using multiple analytical techniques, virtual screening, and in-silico ADME/T prediction.***

Keywords: 1, 8-Naphthyridine, Quinoline, ADMET, Heterocyclic Compound

I. INTRODUCTION

The majority of prescription medicines include heterocycles. In 2007, a study of the structures of the top marketing logo call pills revealed that heterocycles are present in eight of the top ten and seventy-one of the top a hundred pills. Given that heterocycles have dominated medicinal chemistry since the beginning, this isn't unexpected. Heterocyclic compounds are included in a large number of U.S. patents filed by pharmaceutical companies, indicating their relevance. For example, a review of the patent literature from 1976 to September 2008 found that the term “pyridine” appears in 1729 patents awarded to Pfizer as a consulting firm. In the United States, the word pyridine appears in 3504 Merck patents. Many pharmaceutically active compounds contain samples of indoles, quinolines, azepines, and pyrimidine, although this isn't always the case with pyridine and other heterocycles in medicine. Although the five agencies' selection is uneven and leaves out a large variety of heterocycles, it is meant to offer examples of heterocycle usage in medicine. This categorization is also oversimplified. Many therapeutic compounds employ a variety of ring structures. A benzimidazole structure can be found in pyridine complexes used as proton pump inhibitors, for example. The indole ring is included in dimebon, which is introduced in the pyridines section. This is also only a portion of the story, and it's not meant to indicate that the pyridine structure is more significant for Alzheimer's therapy than the indole structure. One monograph32 categorizes the medicines based on their chemical forms, with heterocycles reoccurring throughout the book. Heterocycles with five members include five-membered heterocycles, six-membered heterocycles, five-membered heterocycles fixed to one benzene ring, six-membered heterocycles fused to one benzene ring, bicyclic-fused heterocycles, and polycyclic-fused heterocycles [1].

II. OBJECTIVES OF THE STUDY

The major goal of this research is to provide new, efficient, convenient, selective, and environmentally friendly synthetic techniques in organic chemistry that will aid in drug discovery, medicinal chemistry, and agrochemicals. Nitrogen-containing heterocycles are the most important class of all-heterocyclic chemicals identified so far in the pharmaceutical and agrochemical sectors. Nitrogen heterocycles can be found in the fundamental structure of a number of pharmaceuticals sold across the world. Because of the relevance of nitrogen heterocycles in medicinal chemistry, the pharmaceutical industry, and different drug development fields, as well as their value in material science, their synthesis and characterization are given sufficient attention. The combination of a few nitrogen-containing heterocycles, 1,8-naphthyridin and quinoline 3-carboxylic acid, piqued our curiosity. Although several improved techniques for the synthesis of these types of compounds have been described, the majority of the procedures are still carried out in organic solvents with prolonged reaction times, high temperatures, and costly catalysts. Furthermore, most known techniques have the drawback that the catalyst is destroyed during the work-up and cannot be retrieved or reused. Few heterogeneous catalysts have been reported in nature, either extremely basic or acidic. Catalysis has received a lot of interest in recent years as a result of both the novelty of the idea and, more significantly, the fact that the efficiency and selectivity of many catalytic reactions are comparable to those of start reactions. Similar or less closely related processes may be promoted by catalysis of the corresponding class.

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Because it provides a new way to tackle the issue of energy and sustainability, catalysis is becoming a crucial field of research. These issues are resonating with the global view of social difficulties and the global economy. The notion of green chemistry, which is becoming a leitmotiv in each major initiative dealing with this key sector of research, was born out of social pressure. Green chemistry's concept, which makes catalytic research even more creative, has become a critical component of sustainability. According to a thorough review of the literature, 1,8-naphthyridine and quinoline 3-carboxylic acid has been shown to be a potent pharmacological activities . It also exhibits antiplatelet, PDE inhibitory, anti-inflammatory, 5HT3 antagonistic, and adenosine antagonistic properties.

III.MATERIAL AND METHODS

A. Experimental

All experiments were carried out under air atmosphere unless stated otherwise. Reagents were generally the best quality commercial-grade products and were used without further purification. Melting points were measured with an X4 apparatus and were uncorrected. FTIR spectra were recorded on (Bruker) spectrometer. Thin layer chromatography (TLC) analysis was performed on silica gel GF254 purchased from Himedia. Preparation of derivatives

B. Chemistry

The target compounds were synthesized according to the reported method (Scheme) [2,3]. Aniline or 2-Aminopyridine (0.01 mol) and diethyl methoxy methylene malonate (0.01 mol) was heated at 120-130° for 2 h, the resulting ethanol was evaporated to obtain crude malonate (1), which was purified by recrystallization from light petroleum ether. Crude ester (1) 0.017 mol and diphenyl ether in access were heated at 240-250° for 2 hrs and the resultant solution was cooled to room temperature and washed with petroleum ether. The resulted white malonate (2) powder was collected and recrystallized from dimethylformamide. The A mixture of 1,8-naphthyridine and quinoline 3- ester (2) 0.01 mol and appropriate cyclic amines 0.1 mol heated in a sealed tube at 120° for 24 h. After cooling the reaction mixtures was reacted with ethyl ether to yield the pure titled compounds.

C. Physicochemical Characteristics of 1, 8-naphthyridines (3A-3E)

N-(3-chlorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (3A) yield- 76.6 %; melting point (mp)- >300°; IR (vmax' cm-1):3112.7, 3086.0 (C-H aromatic) 1686.4 (C=O amide), 1651.1 (C=O ring), 734 (C-Clchemical formula: C15H9ClFN3O2, molecular weight (MW) 317.70, anal: C, 56.71; H, 2.86; Cl, 11.16; F, 5.98; N, 13.23; O, 10.07.

N-(3,4-dichlorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (3B) yield- 76 %; mp- 193-195°; IR (vmax' cm-1): 3112.7, 3086.0 (C-H aromatic) 1686.4 (C=O amide), 1651.1 (C=O ring), 737 (C-Cl); chemical formula: C15H8Cl2FN3O2, MW 352.15, anal: C, 51.16; H, 2.29; Cl, 20.14; F, 5.40; N, 11.93; O, 9.09.

6-fluoro-3-(piperidine-1-carbonyl)-1,8-naphthyridin-4(1H)-one (3C) yield- 55 %; mp- 181-183°; IR (vmax' cm-1): 3069.1, 2998.7 (C-H),1714.0 (C=O keto), 1692.1 (C=O ring), chemical formula: C14H14FN3O2, MW: 275.28, anal: C, 61.08; H, 5.13; F, 6.90; N, 15.26; O, 11.62.

6-fluoro-3-(morpholine-4-carbonyl)-1,8-naphthyridin-4(1H)-one (3D) yield- 76.6 %; mp- 147-149°; IR (vmax' cm-1): 3069.1, 2998.7 (C-H), 1714.0 (C=O keto), 1692.1 (C=O ring), chemical formula: C13H12FN3O3, MW: 277.25 anal: C, 56.32; H, 4.36; F, 6.85; N, 15.16; O, 17.31.

6-fluoro-4-oxo-N-phenyl-1,4-dihydroquinoline-3-carboxamide (3E) yield- 76.6 %; melting point (mp)- >300°; IR (vmax' cm-1):3112.7, 3086.0 (C-H aromatic) 1686.4 (C=O amide), 1651.1 (C=O ring), chemical formula: C16H11FN2O2, molecular weight (MW) 282.27, anal: C, 68.08; H, 3.93; F, 6.73; N, 9.92; O, 11.34.

Absorption, distribution, metabolism, excretion, and toxicity (ADME/T) study

The toxicological properties of these compounds was predicted using the Swiss ADME and PreADMET Toxicity server. The compounds (3A-E) were predicted for Caco-2 cell permeability, MDCK cell and blood-brain barrier (BBB), human intestinal absorption, skin permeability and plasma protein binding [4, 5]. Compounds containing the chlorine atom exhibited improved oral absorption, skin penetration, and membrane permeability [6].

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IV. RESULTS AND DISCUSSION

A. Synthetic Chemistry

A series of cyclic amine substituted 1,8-naphthyridine and quinoline-3-carboxylic acid analogues was efficiently synthesized based on the methods we had developed in our previous schemes [2]. The key compounds, ethyl 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate and ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate were prepared as outlined via a two-step methodology in excellent yield. The condensation reaction of 2-aminopyridine with ethoxy methylene malonate by Gould–Jacobs reaction yielded diethyl 2-((pyridine-2-ylamino) methylene) malonate 1 that was cyclized during refluxing with phenoxy ether to give ethyl 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate 2 [7]. The coupling step was achieved in 24 h by heating the corresponding esters with the appropriate in a dry DMF solution in a sealed tube. The target compounds 3A-E were purified by recrystallization from appropriate solvents.

The synthesized compounds were purified via column chromatography using a methanol: chloroform (10: 40) mixture as the eluent. Characterization of the synthesized molecules was performed using FTIR spectroscopy confirmed the formation of the structure. All new compounds were characterized by using IR. Their spectral analyses were consistent with the assigned structures and listed in the experimental section. The FTIR spectra showed the presence of characteristic peak at 1650-1692 and 3300 cm−1 (for CO and -NH stretching), 3100-3000 cm−1 (phenyl group), and 1380 cm−1 (for ether linkage).

B. Drug Likeness and ADME Analysis

The toxicity was predicted using the Swiss ADME and PreADMET Toxicity server (http://preadmet.bmdrc.org/) and the result shown in Table 1,2 and 3. The compounds were found non-mutagenic. The compounds were predicted to give negative Ames test and these parameters indicated that the synthesized compounds were safe. Also, the hERG inhibition prediction indicated medium cardiotoxic potential. According to the results of lipophilicity-activity relationship analysis, log P is not the main factor that influences cholinesterase inhibitory activity of this set of compounds. The SwissADME wave server evaluated the pharmacokinetics parameter, drug likeness, and medicinal chemistry friendliness for small molecules. The molecular properties such as molecular weight <500 g/mol, <5 numbers of hydrogen bond donors, <10 numbers of hydrogen bond acceptors, and <10 rotatable bonds were chosen as criteria [8]. The toxicological property from chemical structures of the compounds was predicted using SwissADME server and the compounds were found non-mutagenic and safer. BBB score was found significant for tested compounds and comparable to that of control. SwissADME measures the log P value (partition coefficient) which is a well-established assessment for the hydrophilicity of compounds. Higher log P value results in lower hydrophilicity and, thus, lower absorption, and penetration. The log S value serves as solubility; the lower the log S value, the greater the solubility which would improve the absorption of the drug candidate [9]. The higher TPSA score is interrelated with lower membrane penetration and compounds with increased TPSA were better substrates for p-glycoprotein. Thus, comparing the derivatives, poor TPSA score was favourable for the druggable property. It was also analysed that a compound with better CNS permeation should have lower TPSA score [10,11].

Table 1. Physicochemical descriptors and ADME parameters

Physicochemical descriptors	Compounds				
	3A	3B	3C	3D	3E
BBB	0.189524	0.397218	0.260511	0.0448478	0.155216
Buffer solubility_mg_L	2.09477**	1.262**	15.1258	107.981	11.0443**
Caco2 cell	21.0006	19.9642	18.5279	6.67702	16.573
Human Intestinal Absorption	93.86097	94.70921	95.43804	94.65395	92.95923
MDCK	21.4123	1.91664	15.1206	0.860476	29.6904
Pgp_inhibition	Non	Non	Non	Non	Non
Plasma_Protein_Binding	82.55485	86.33921	56.13712	36.36064	75.05523
Pure_water_solubility_mg_L	1.93823	0.276726	176.522	650.966	6.12942
Skin_Permeability	-4.20356	-4.14231	-4.44514	-4.63902	-4.2886
SKlogD_value	2.74319	3.41465	1.36081	0.216320	2.16993
SKlogP_value	2.74319	3.41465	1.36081	0.216320	2.16993
SKlogS_buffer	-5.180890**	-5.445670**	-4.26006	-3.40953	-4.435790**
SKlogS_pure	-5.21462	-6.10468	-3.19298	-2.62932	-4.69151

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However, the lack of significant correlation does not diminish the importance of determined ClogP values, as log P is an essential physicochemical parameter related to drug intestinal absorption and BBB permeation. The lipophilicity of these compounds is within the range defined by the rule-of-five, thus predicting good intestinal permeability. The lipophilicity indicated that ClogP values ranged from 0.21 to 2.7. enhanced the overall hydrophobic nature and this might have enabled these molecules to penetrate the complex mycobacterial cell wall. As the target molecules' values are less than 5, it indicated a reasonable probability that these compounds would be well absorbed.

Table 2. Drug likeness prediction

Parameter	Compounds				
	3A	3B	3C	3D	3E
CMC_like_Rule	Qualified	Qualified	Qualified	Qualified	Qualified
CMC_like_Rule_Violations	0	0	0	0	0
Lead-like_Rule_Violation_Fields		Molecular_weight		AlopP98_value	
Lead_like_Rule	Suitable if its binding affinity is greater than 0.1 microM	Violated	Suitable if its binding affinity is greater than 0.1 micro M	Violated	Suitable if its binding affinity is greater than 0.1 micro M
Lead_like_Rule_Violations	0	1	0	1	0
MDDR_like_Rule	Mid-structure	Mid-structure	Mid-structure	Mid-structure	Mid-structure
MDDR_like_Rule_Violation_Fields	No_Rotatable_bonds	No_Rotatable_bonds	No_Rotatable_bonds	No_Rotatable_bonds	No_Rotatable_bonds
MDDR_like_Rule_Violations	1	1	1	1	1
Rule_of_Five	Suitable	Suitable	Suitable	Suitable	Suitable
Rule_of_Five_Violation_Fields					
Rule_of_Five_Violations	0	0	0	0	0
WDI_like_Rule	In 90% cutoff	In 90% cutoff	In 90% cutoff	In 90% cutoff	In 90% cutoff
WDI_like_Rule_Violation_Fields					
WDI_like_Rule_Violations	0	0	0	0	0

Table 3. Toxicity study

SN ADMET properties	Compounds				
	3A	3B	3C	3D	3E
Ames_test	mutagen	mutagen	mutagen	mutagen	mutagen
Carcino_Mouse	negative	negative	negative	negative	negative
Carcino_Rat	positive	negative	negative	negative	positive
daphnia_at	0.113061	0.0466786	0.556703	2.0678	0.200353
hERG_inhibition	medium_risk	medium_risk	low_risk	low_risk	medium_risk
medaka_at	0.023665	0.00467542	0.425025	5.31984	0.0658695
minnow_at	0.0215379	0.0060585	0.255285	2.22602	0.035309
TA100_10RLI	positive	negative	positive	positive	negative
TA100_NA	positive	positive	positive	positive	positive
TA1535_10RLI	negative	negative	negative	negative	negative
TA1535_NA	positive	negative	negative	negative	negative

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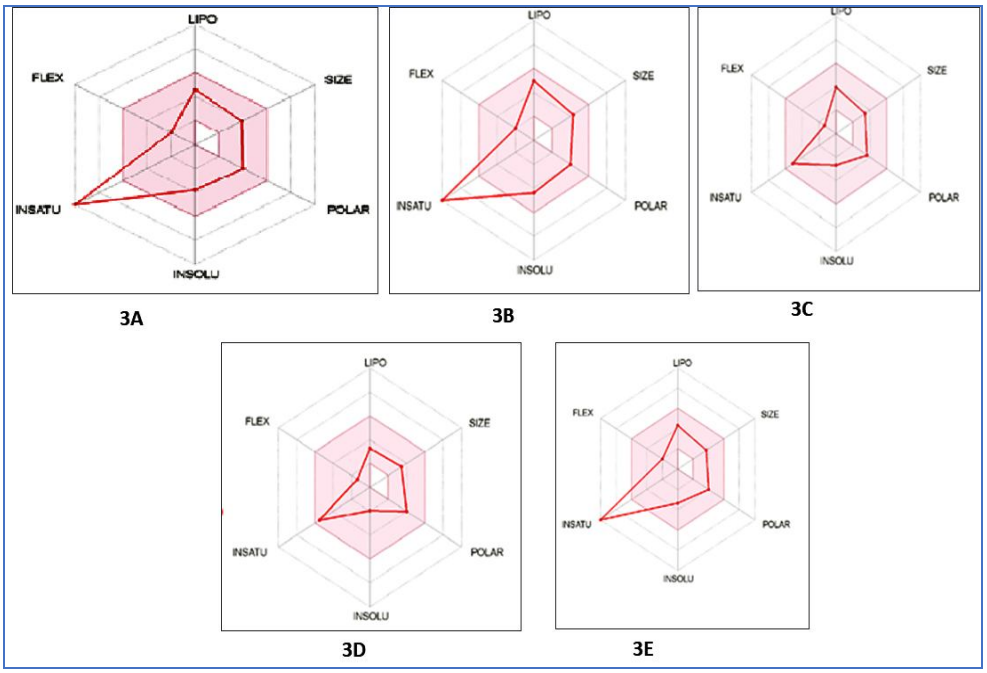

Fig. 1. Bioavailability radar graph of compounds (pink area reflects the allowed values of drug likeness properties of the molecule).

The analysis indicates that the derivatives fell within the permissible range of standard drugs, as is evident from the boiled-egg diagram and radar graph (Fig. 1 and 2)

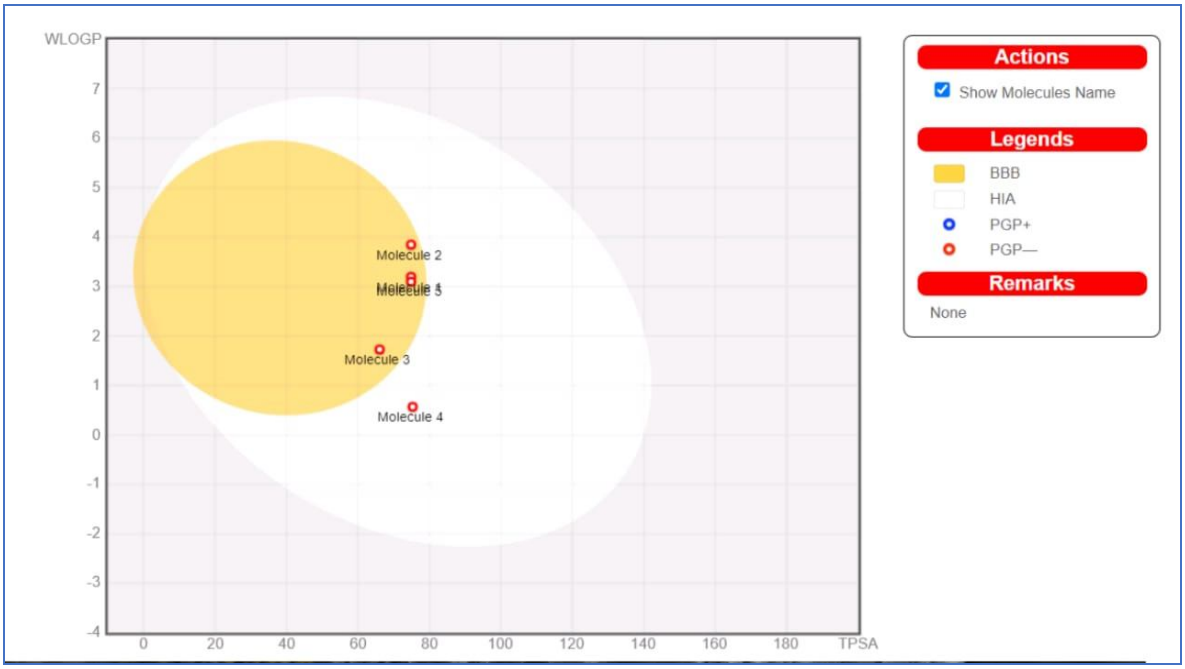

Figure: 2. ADME properties of compounds by graphical representation (boiled-egg) (predict gastrointestinal absorption and brain penetration of small molecules).

V. ACKNOWLEDGMENT

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REFERENCES

[1] Dua, R. Shrivastava, S. Sonwane, SK. Srivastava, SK. 2011. Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review. Advances in Biological Research, (Rennes), 5,120–144.
[2] Gurjar, VK. Pal, D. 2018. Design, synthesis, biological evaluation, and in silico ADMET studies of 1,8-naphthyridine derivatives as an H1-receptor inhibitor. International Journal of Pharmaceutical and Biological Science Archive, 9:265-273.
[3] Ferrarini, PL. Manera, C. Mori, C. Badawneh, M. Saccomanni, G. 1998. Synthesis and evaluation of antimycobacterial activity of 4-phenyl-1,8-naphthyridine derivatives. Il Farmaco, 53:741-746.
[4] Clark, DE. 2003. In silico prediction of blood-brain barrier permeation. Drug Discovery Today, 8:927-933.
[5] Didziapetris, R. Japertas P, Avdeef A, Petrauskas A. 2003. Classification analysis of P-glycoprotein substrate specificity. Journal of Drug Targeting, 11:391-406.
[6] Gentry, CL. Egleton, RD. Gillespie, T. Abbruscato, TJ. Bechowski, HB. Hruby, VJ et al. 1999 The effect of halogenation on blood-brain barrier permeability of a novel peptide drug. Peptides 20:1229-1238.
[7] Vilar Santiago ,Sobarzo-Sanchez Eduardo ,Santana Lourdes ,Uriarte Eugenio, “Molecular Docking and Drug Discovery, 2017. Molecular Docking and Drug Discovery in β-Adrenergic Receptors, Current Medicinal Chemistry 24, 4340–4359.
[8] Daina, A. Michielin, O. Zoete, V. 2017. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Science Report, 7:42717.
[9] Ji, C. Svensson, F. Zoufir, A. Bender, A. 2018. EMolTox: Prediction of molecular toxicity with confidence. Bioinformatics 2018;34:2508-9.
[10] Veber, DF. Johnson, SR. Cheng, HY. Smith, BR. Ward, KW. Kopple, KD et al. 2002. Molecular properties that influence the oral bioavailability of drug candidates. Journal of Medicinal Chemistry, 45: 2615-2623.
[11] Blake, JF. 2000. Chemoinformatics-predicting the physicochemical properties of ‘drug-like’ molecules. Current Opinion in Biotechnology, 11:104-107.

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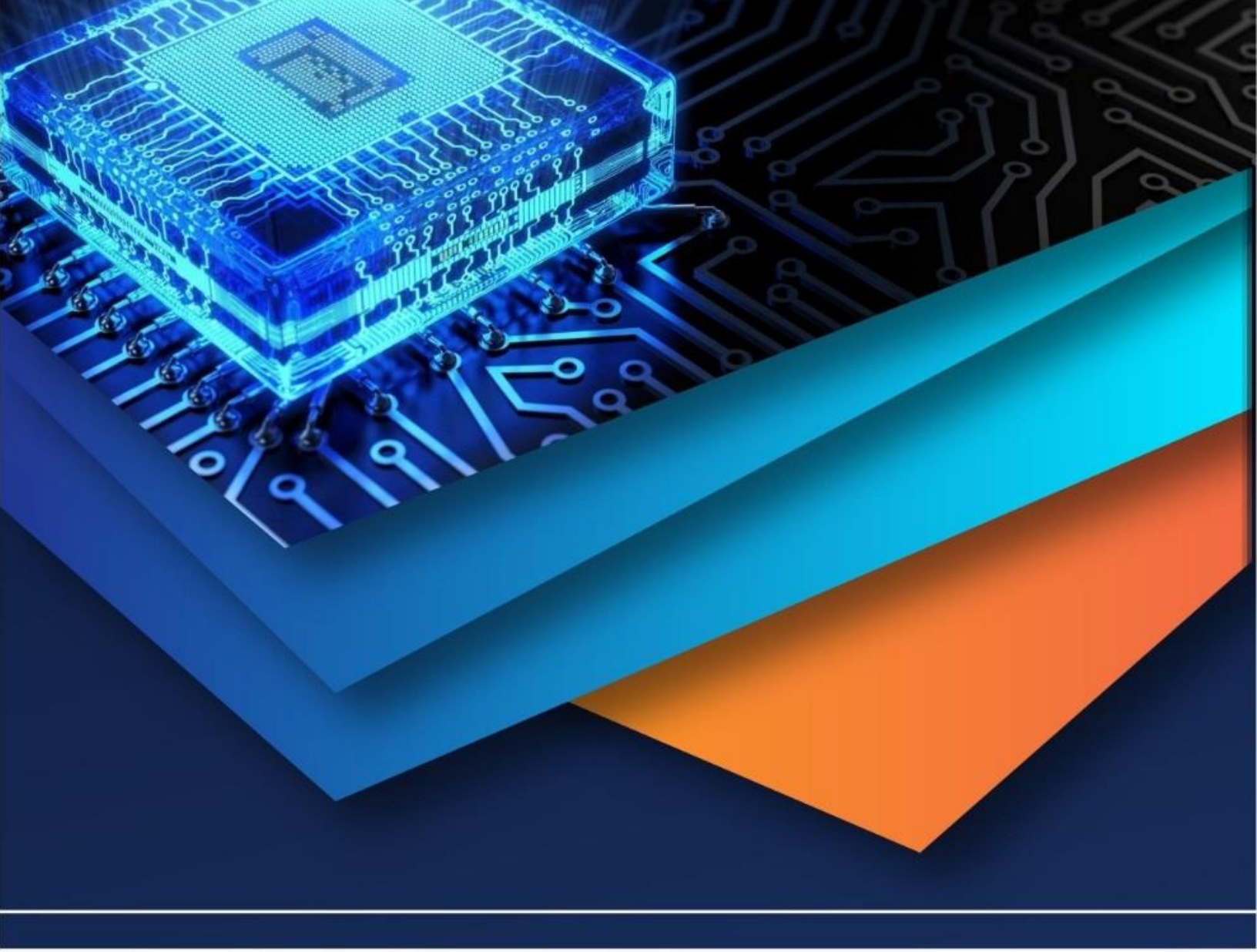

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