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Synthesis of 1, 2 Disubstitued Benzimidazoles using $SiO_2/CaCl_2.2H_2O$ as a Catalyst

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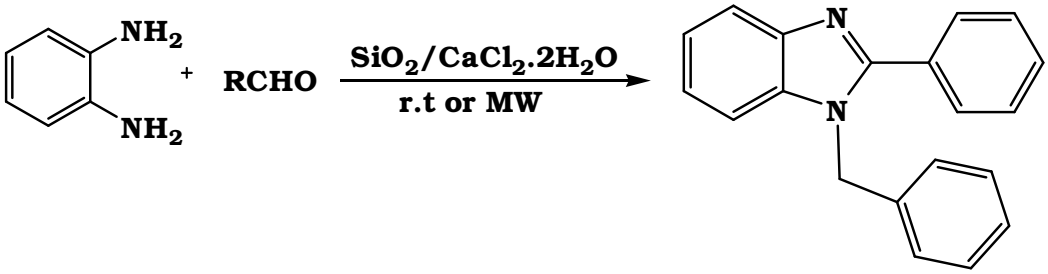
***Abstract:** 1, 2 disubstituted bezimidazole derivatives have been synthesized with excellent yield using $SiO_2/CaCl_2.2H_2O$ as a catalyst with o-phenylenediamine and various aldehydes by convenstional as well as microwave irradiation method. The advantage of this synthetic method i.e. greener protocol, easy handling and commercially available inexpensive catalyst.*



***Keywords:** 1, 2 disubstituted bezimidazole, o-phenylenediamine, greener protocol, easy handling, commercially available, inexpensive catalyst.*

I. INTRODUCTION

1, 2-Disubstituted benzimidazoles are an important class of heterocyclic compounds that exhibit diverse biological activities and have applications in medicinal chemistry and materials science. Several synthetic methods have been developed to access these compounds, and catalytic systems play a crucial role in achieving efficient and selective transformations. In recent years, SiO2/CaCl2·2H2O has emerged as a promising catalyst for the synthesis of 1,2-disubstituted benzimidazoles due to its excellent catalytic activity, low cost, and easy availability.

In organic synthesis, having the lots of the biological activity and numerous natural products heterocyclic compounds are very important (1). Benzimidazole are a important class of heterocyclic compounds which have a charaterstic fusion of six membered benzene ring and five membered imidazole ring. Due to this fusion benzimidazole has an important pharmacophore. It have immense importance in medicinal and drug development area due to its privileged structure. Naturally occurring biologically active substances such as Vitamin B12 and purine bases include magical benzimidazole nucleus in their Structure (2). Benzimidazoles are one of the most biologically active class of compounds, having wide spectrum of activity. It plays an important role with Numerous therapeutic activities such as antiulcer (3), anti-inflammatory, analgesic (4-6), anti-fungal (7), anti-microbial (8-9), antihelminthic (10), anti-cancer (11), antihistaminic compounds (12-13) antiviral derivatives, anticonvulsant (14,15) etc. They are also inhibitors of photosynthesis, aldose reductase and antagonist of neurotransmitter receptors and They also are found to exhibit appreciable herbicidal activity (16).

Most of the described methods uses volatile organic solvent and used solid phase synthesis via o-nitroanilines or the condensation of o-phenylenediamines with carboxylic acid derivatives, esters, aldehydes and aryl halides for the synthesis of benzimidazole and their derivatives.

More recently, cleaner protocols have been described, including solvent-free conditions and the use of water and ionic liquid as green solvents. However, most of these protocols use expensive and toxic reagents and/or long reaction times. Thus the development of clean, general, and selective routes to synthesize benzimidazole, including the use of new catalysts, alternative or non-solvents, and non-classical energy sources continues to be a important field of research. Many synthetic pathways have been developed due to immense importance of benzimidazoles. The most recognize synthesis pathways involve the condensation of an arylenediamine with a carboxylic acid or its derivative under harsh dehydrating reaction conditions.

Other method is the condensation of an aldehyde with arylenediamine (17-18). According to the literature studies it reveales that several procdure for synthesis of benzimidazole and its derivatives using hypervalent iodine as oxidant (19), oxalic acid (20), H_2O_2/HCl (21), $TiCl_4$ (22), PPA (23), $SOCl_2/SiO_2$ (24), L-Proline (25), Sulphamic acid (26) and Zeolite (27). Expensive reagents, oxidation processes, and long reaction times are the considerable drawbacks of these methods. In connection with our ongoing research for the development of simple and efficient methods for synthesis of benzimidazole compounds, now we report Syntheis of 1, 2 disubstitued benzimidazoles using $SiO_2/CaCl_2.2H_2O$ as a catalyst (28, 29)

Advantages of $SiO_2/CaCl_2 \cdot 2H_2O$ Catalyst

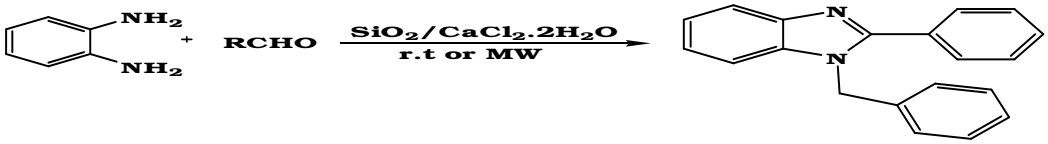
1) High Catalytic Activity: $SiO_2/CaCl_2 \cdot 2H_2O$ catalyst has demonstrated excellent catalytic activity in various synthetic transformations. It promotes the reactions efficiently, resulting in high yields of desired products
2) Wide Applicability: The $SiO_2/CaCl_2 \cdot 2H_2O$ catalyst has been successfully employed in diverse organic transformations, including the synthesis of 1,2-disubstituted benzimidazoles, as well as other heterocyclic compounds and carbon-carbon bond forming reactions. Its versatility makes it a valuable tool for synthetic chemists.
3) Cost-effective and Readily Available: The catalyst is composed of silica (SiO2) and calcium chloride (CaCl2·2H2O), which are inexpensive and commercially available materials. This makes the $SiO_2/CaCl_2 \cdot 2H_2O$ catalyst a cost-effective option for both academic and industrial applications.
4) Easy Separation and Recycling: $SiO_2/CaCl_2 \cdot 2H_2O$ is a heterogeneous catalyst, which means it exists in a different phase from the reaction mixture. This property allows for easy separation by filtration or centrifugation. Moreover, the catalyst can be recovered and reused multiple times without significant loss of activity, leading to reduced waste generation and cost saving.
5) Mild Reaction Conditions: The $SiO_2/CaCl_2 \cdot 2H_2O$ catalyst operates under mild reaction conditions, typically at ambient temperature or low to moderate temperatures, and atmospheric pressure. This mildness contributes to improved safety and energy efficiency during the synthesis process.
6) Environmentally Friendly: $SiO_2/CaCl_2 \cdot 2H_2O$ is a solid catalyst, which eliminates the need for hazardous and volatile solvents often used in liquid catalyst systems. This feature enhances the environmental sustainability of the synthesis, reduces waste generation, and minimizes potential hazards associated with handling and disposal of toxic material.
7) Scalability: The $SiO_2/CaCl_2 \cdot 2H_2O$ catalyst has demonstrated its effectiveness not only in laboratory-scale reactions but also in larger-scale industrial processes. Its scalability makes it suitable for applications ranging from small-scale research to industrial production (29-31).

II. MATERIALS AND METHODS

1) *Formation of Solid supported Catalyst:* To a 100-mL beaker, silica gel- 60 (7.5 g), $CaCl_2.2H_2O$ (2.5 g), and water (3.0 mL) were added. The suspension was stirred for 15 min at room temperature, dried at 80^0C for 3h and for additional 15h at 150 ^{0}C in an oven and then cooled in a desicator.
2) *Procedure for the synthesis of 1, 2 disubstitued benzimidazoles:*

a) *Method A:* To a mixture of aldehyde (2 mmol) and o-phenylenediamine (1 mmol) was added 0.120 g of SiO_2/ $CaCl_2.2H_2O$, and the mixture was stirred at room temperature. The reaction progress was monitored over TLC. After stirring for 5.0 min to 8 hours, ethyl acetate (10 mL) was added, and the organic solution was separated from $SiO_2/CaCl_2.2H_2O$ by filtration. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over silica gel eluting with hexanes:AcOEt 9:1 mixture, yielding the products.

b) *Method B:* $SiO_2/CaCl_2.2H_2O$ (0.120 g) was added to the mixture of 1, 2 phenylenediamine (1 mmol), and aldehydes (2 mmol). The mixture was placed under microwave irradiation for a period of 2-4 minutes. After the completion of the reaction (monitored over silica gel TLC) the reaction mixture was cooled to room trempture and was extracted with ethyl acetate. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (silica gel) eluting with hexanes:AcOEt 9:1 mixture, yielding the products.



R= C_6H_5CHO, 3-NO_2, 4-NO_2, 4-CH_3, 4-F, 4-Cl, 2-Cl, 4-MeO, 3-MeO, 4-OH, 3-OH

Figure: 1. Scheme of the synthesis of 1, 2 disubstitued benzimidazole derivatives using $SiO_2/CaCl_2.2H_2O$ as a catalyst

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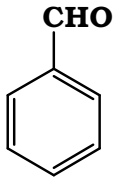
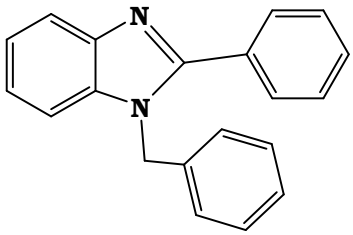
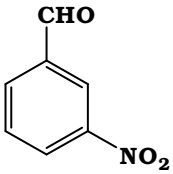
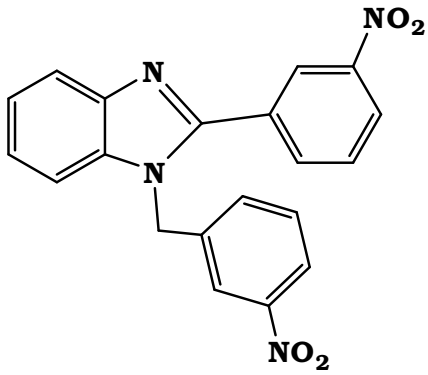
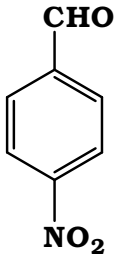
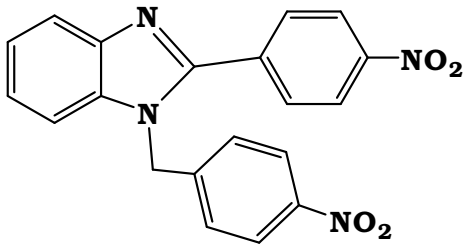
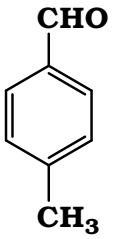
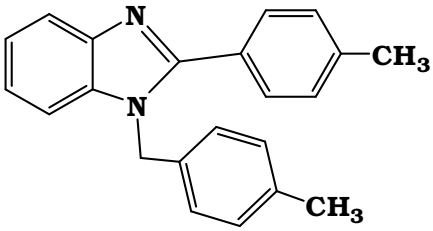
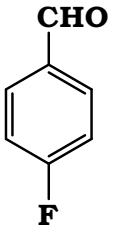
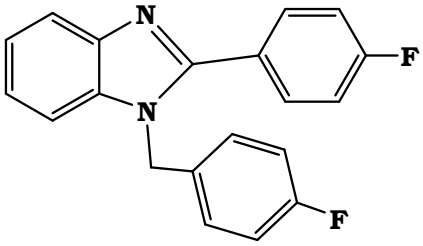
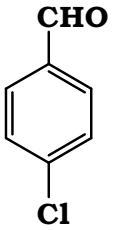
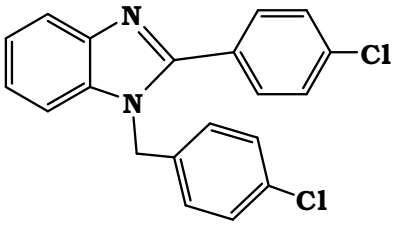
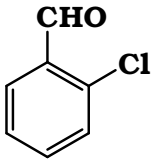
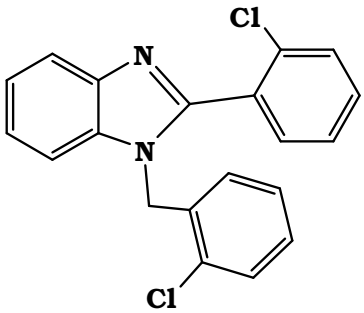
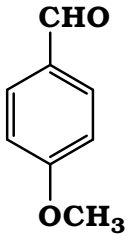
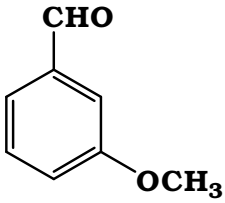
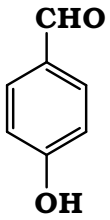
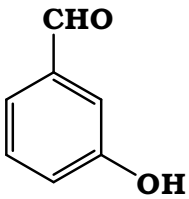
III. RESULT AND DISCUSSION

The 1, 2-disubstitued benzimidazoles were prepared in good yield by microwave assisted method by the reaction of two mole equivqlents of aromatic aldehyde and one mole equivalent 1, 2 phenylenediamine using silica supported calcium chloride dihydrate as catalyst without solvent. The silica supported calcium chloride dihydrate is a new catalyst reported first time for this reaction. The compounds synthesized and their yields are presented in Table 1.

Table 1: Synthesis of 1, 2 disubstitued benzimidazole derivatives catalysed by $SiO_2/CaCl_2.2H_2O$

Entry	Aldehyde	Product		MW yield	Yield
1.		 **1-benzyl-2-phenyl-1*H*-benzo[*d*]imidazole**	d1	78%	76%
2.		 **1-(3-nitrobenzyl)-2-(3-nitrophenyl)-1*H*-benzo[*d*]imidazole**	d2	83%	82%
3.		 **1-(4-nitrobenzyl)-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole**	d3	84%	82%

4.		 **1-(4-methylbenzyl)-2-(4-methylphenyl)-1*H*-benzo[*d*]imidazole**	d4	82%	80%
5.		 **1-(4-fluorobenzyl)-2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazole**	d5	83%	82%
6.		 **1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole**	d6	84%	81%
7.		 **1-(2-chlorobenzyl)-2-(2-chlorophenyl)-1*H*-benzo[*d*]imidazole**	d7	80%	77%

8.		**1-(4-methoxybenzyl)-2-(4-methoxyphenyl) -1*H*-benzo[*d*]imidazole**	d8	83%	80%
9.		**1-(4-methoxybenzyl)-2-(4-methoxyphenyl) -1*H*-benzo[*d*]imidazole**	d9	83%	79%
10.		**1-(4-hydroxybenzyl)-2-(4-hydroxyphenyl) -1*H*-benzo[*d*]imidazole**	d10	81%	80%
11.		**3-(1-(3-hydroxybenzyl)-1*H*-benzo [*d*]imidazol-2-yl)phenol**	d11	81%	80%

1, 2 phenylenediamine reacts with aldehyde to form 1, 2 disubstitued benzimidazoles. A possible mechanism is depicted in the Figure 2 based on Jacob et al., 2009. The reaction takes place with the formation of dibenzilidene diamine from phenylenediamide and arylaldehyde followed by 1, 3-hydride transfer as suggested by previous workers. Herein it is proposed that $SiO_2/CaCl_2.2H_2O$ acts as catalyst in the same way as $ZnCl_2$ the electrophilicity of $CaCl_2.2H_2O$ is comparable with $ZnCl_2$.

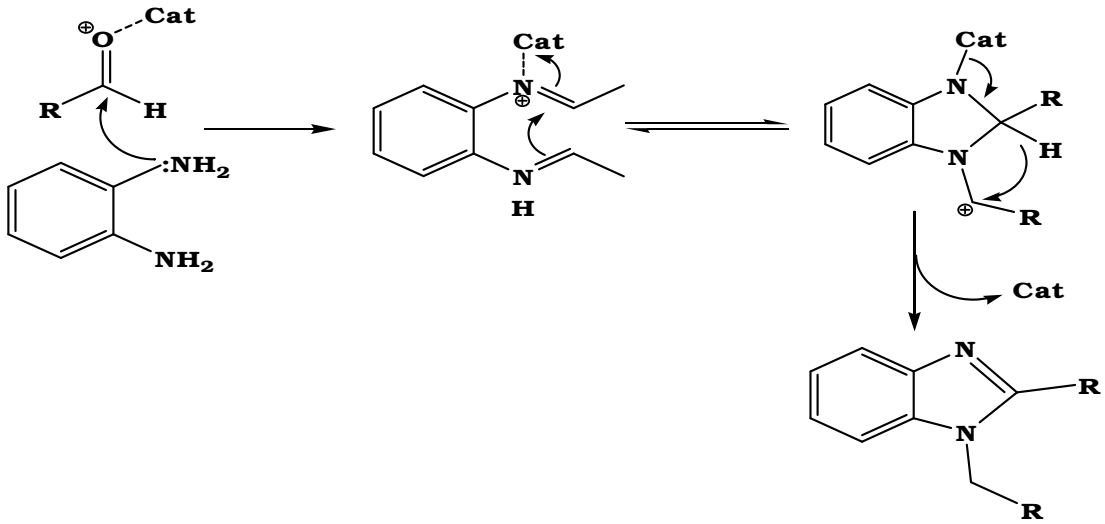


Figure 2: Probable mechanism of formation of 1, 2disubstitued benzimidazoles catalysed by $SiO_2/CaCl_2.2H_2O$ (30)

In conclusion we have reported here a facile method for selective synthesis of 1, 2disubstitued benzimidazoles by the condensation of O-phenylenediamine and aldehyde using solid supported catalyst ($SiO_2/CaCl_2.2H_2O$). Moreover catalyst works well under microwave irradiation as well as under conventional methodology involving simply stirring of reaction mixture. The reaction time for conventional method is in hours (3 hours) which is reduced to minutes (1-3) under microwave irradiation.

IV. ACKNOWLEDGEMENT

The authors are thankful to the Dean, College of Basic Sciences and Humanities and Director Experiment Station, G.B. Pant University of Agriculture and Technology, Pantnagar for providing necessary facilities.

Spectral Characterisation Data of Synthesized Compound

1) d1: IR (KBr) 3030, 1697, 1602, 1446, 1361 cm^{-1}.
^1H NMR (400 MHz, CDCl3): d = 5.5 (s, 2H, CH_2): 7.15 (d, 2H, J=7.9 Hz, Ph): 7.2-7.3 (m, 6H, Ph): 7.35-7.40 (m, 3H, Ph): 7.9 (d, 1H, J=8Hz, Ph): 7.8 (dd, 2H, J=8.4, 2.5 Hz, Ph).

2) d3: IR (KBr) 3035, 1693, 1602, 1448, 1361 cm^{-1}.
^1H NMR (400 MHz, CDCl3): d = 5.59 (s, 2 H), 7.19 (dd, *J* = 8, 1 Hz,1 H), 7.28 (d, *J* = 9 Hz, 2 H), 7.35 (td, *J* = 9, 1 Hz, 1 H), 7.41 (td, *J* = 7, 1 Hz, 1 H), 7.84 (d, *J* = 9 Hz, 2 H), 7.93 (dd, *J* = 8, 1 Hz, 1H), 8.24 (d, *J* = 8 Hz, 2 H), 8.33 (d, *J* = 9 Hz, 2 H).

3) d4: IR (KBr) 3032, 1698, 1602, 1447, 1362 cm^{-1}
^1H NMR (400 MHz, CDCl3): d = 2.32 (s, 3 H), 2.39 (s, 3 H), 5.39(s, 2 H), 6.98 (d, *J* = 8 Hz, 2 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.19 (m, 2H), 7.24 (d, *J* = 8 Hz, 2 H), 7.28 (m, 1 H), 7.58 (d, *J* = 8 Hz, 2 H), 7.85 (m, 1 H).

4) d5: IR (KBr) 3065, 2900, 1604, 1510, 1460, 1329 cm^{-1}.
^1H NMR (400 MHz, CDCl3): d=5.4 (2H, s, CH_2), 7.0-7.2 (m, 4H, Ph), 7.3-7.8 (m, 8H, Ph).

5) d6: IR (KBr) 3063, 2900, 1605, 1511, 1462, 1328 cm^{-1}.
^1H NMR (400 MHz, CDCl3): d = 5.40 (s, 2 H), 7.02 (d, *J* = 9 Hz, 2H), 7.19 (d, *J* = 8 Hz, 1 H), 7.36–7.24 (m, 4 H), 7.43 (m, 2 H), 7.58(m, 2 H), 7.86 (d, *J* = 8 Hz, 1 H).

6) d7: IR (KBr) 3062, 2900, 1603, 1510, 1463, 1329 cm^{-1}.
^{1}H NMR (400 MHz, CDCl3): d = 5.40 (s, 2 H), 7.02 (d, *J* = 9 Hz, 2H), 7.19 (d, *J* = 8 Hz, 1 H), 7.36–7.24 (m, 4 H), 7.43 (m, 2 H), 7.58(m, 2 H), 7.86 (d, *J* = 8 Hz, 1 H).

7) d8: IR (KBr) 3060, 2900, 1609, 1512, 1463, 1328 cm^{-1}.
^{1}H NMR (400 MHz, CDCl3): d = 3.77 (s, 3 H), 3.83 (s, 3 H), 5.37(s, 2 H), 6.84 (d, *J* = 8 Hz, 2 H), 6.94 (d, *J* = 9 Hz, 2 H), 7.02 (d,*J* = 9 Hz, 2 H), 7.20 (m, 2 H), 7.30–7.23 (m, 1 H), 7.62 (d, *J* = 9 Hz,2 H), 7.83 (d, *J* = 8 Hz, 1 H).

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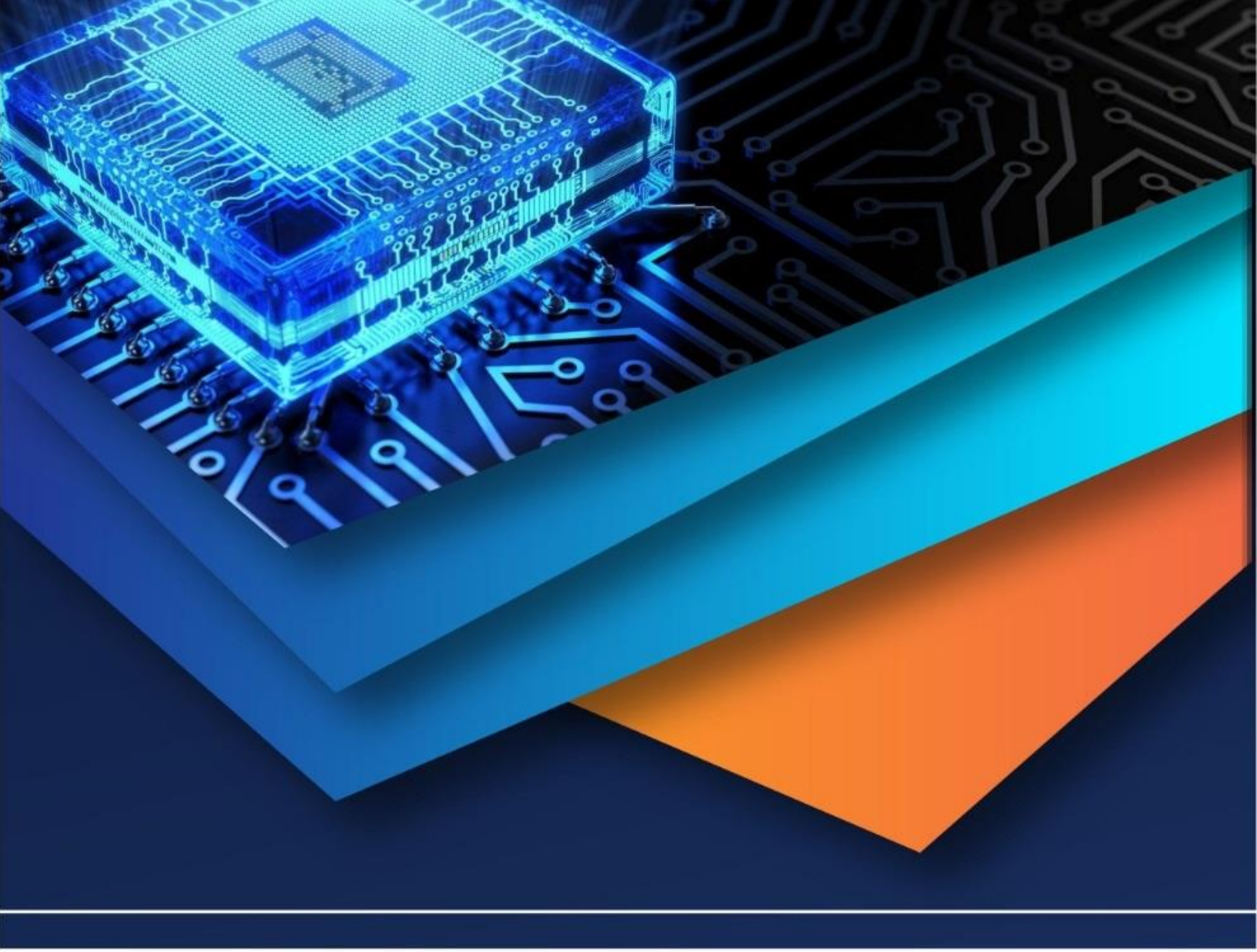

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