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Nano flakes of $NaMgBi_{0.85}Eu_{0.15}WO_6$ as catalyst for simple and efficient green synthesis of Dihydropyridines

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Abstract: 1, 4-Dihydropyridine derivatives have been synthesized utilizing nano flakes of $NaMgBi_{0.85}Eu_{0.15}WO_6$ as photo-catalyst. The method adopted is more convenient and cost effective in the conversion of aldehydes with β-ketoester and ammonium acetate to give a range of Hantzsch pyridines in magnificent yields. This multicomponent reaction occurred easily in water reflux paving the way for an efficient green synthesis of new Dihydro pyridines.

Keywords*: 1,4-dihydropyridine, Hantzsch reaction, Aldehydes, Diketones, Ammonium acetate, Multi component reaction*

I. INTRODUCTION

Synthesis of 1, 4 dihydro pyridines by the Hantzsch reaction [1] stands as one of the earliest examples of multi component reactions (MCRs) where all the starting materials are taken in just one-pot and reacted under set conditions. Production of a wide array of lead compounds in pharmaceutical industry relies largely on the specific synthetic strategies adopted for MCRs [2]. Multi component synthesis methods offer great advantages over routine direct synthetic protocals giving products with differing activities required for the discovery of new drugs leading to product development utilizing combinatorial science [3]-[4]. In 1882, Arthur Rudolf Hantzsch, a German scientist, announced a cyclo-condensation among ethyl acetoacetate, aldehydes and aqueous ammonium hydroxide to yield the valuable heterocyclic product of 1,4-dihydropyridine; from that point onwards, it was popularly called as Hantzsch reaction [5].

The di hydro pyridine derivatives display a vast scope of diverse applications [6]-[8], for example, anticonvulsant, antitumor, antianxiety, vasodilator, bronchodilator, energizer, pain relieving, sleep inducing, calming and neuro-protectants and in addition platelet anti-aggregatory specialists. Dihydro-pyridines are economically utilized as calcium channel blockers [8] for the treatment of cardiovascular infections (Figure 1). The colossal natural action of Hantzsch pyridines attracted numerous analysts and academicians. Subsequently, a few endeavours have been made to synthesize 1,4-dihydropyridine subsidiaries utilizing different catalysts and reaction conditions, for example, metal triflate [9], $NaHSO_4$-SiO_2 [10], molecular iodine [11], ionic liquid [12], Ni nanoparticles [13], Bi_2WO_6 [14], Magnetic Fe_3O_4 [15] have been used to synthesize 1,4-DHPs.

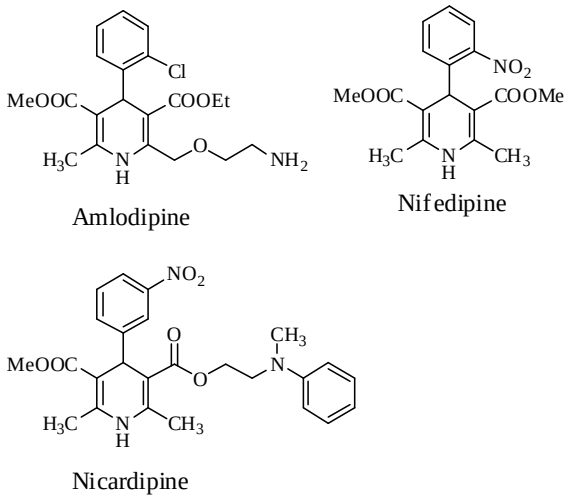

Fig. 1: Biologically active dihydropyridine derivatives

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However, most of the synthetic strategies adopted are experiencing a few disadvantages, for example, long response time, low yields, dreary workup techniques and the utilization of costly catalysts. Therefore, the need for an effective synthetic method is still sought after. As part of our discovery program in growing new strategies, we report thus a straightforward and effective strategy for the synthesis of 1,4-dihydropyridine derivatives utilizing a rare earth doped double perovskite as a catalyst. The Bismuth containing double perovskite ($NaMgBi_{0.85}Eu_{0.15}WO_6$) is a non-hygroscopic yellowish white solid with nanoflake structure, is used for the green synthesis of new 1, 4 Dihydropyridines.

II. MATERIALS AND METHODS

Reagents and chemicals were acquired from chemical suppliers and utilized without further purification. IR spectra were recorded on a thermo Nicolet Nexus 670 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 (Bruker, Germany; 300.132 MHz for ^{1}H, 75.473 for ^{13}C) or Varian FT-200 MHz (Gemini) spectrometer in $CDCl_3$. The chemicals shifts (δ) and coupling constants (J) cited in hertz are accounted for in parts per million in respect to tetra methyl silane (δ = 0.00 ppm) (for ^{1}H) as an interior standard. The resonances of leftover proton and those of carbons in deuterated solvents $CDCl_3$ (δH = 7.26 ppm, δc = 77.0 ppm) and DMSO-d6 (δH = 2.50 ppm, δc = 39.52 ppm) were utilized as inside models. Solvents for chromatography (n-hexane, acetonitrile, cyclohexane, and EtOAc) were refined preceding use. For thin-layer chromatography, Merck pre-covered silica gel 60 F-254 plates were utilized; the spots were identified utilizing UV light (254 nm) or iodine vapour.

A. General procedure

A mixture of benzaldehyde (1 mmol, 106 mg), ethyl acetoacetate (2 mmol, 260 mg), ammonia derivative (4 mmol, 308 mg), and the nano flake structured $NaMgBi_{0.85}Eu_{0.15}WO_6$ (200 mg) will be combined in a round flask in water (10 mL) at Room Temperature (RT) for 2h. The progress of the reaction will be checked by TLC. After completion of the reaction, the catalyst is isolated by utilizing a magnet and reused for further study. The reaction mixture will be diluted with EtOAc (10mL) and washed with brine water (2x10 mL), dried over anhydrous Na_2SO_4, and dissipated *in vacuo*, and the subsequent item will be subjected to column chromatography on silica gel with 5% EtOAc in hexane to isolate pure dihydropyridine.

B. Synthesis of nano $NaMgBi_{0.85}Eu_{0.15}WO_6$:

$NaMgBi_{0.88}Eu_{0.12}WO_6$ nano catalyst was initially prepared by a sol–gel method. The particle size was contemplated by SEM and the distinguishing proof of $NaMgBi_{0.85}Eu_{0.15}WO_6$ morphology depended on the examination of SEM pictures. The SEM pictures of nano-particles plainly demonstrate that $NaMgBi_{0.85}Eu_{0.15}WO_6$ nano-particles have flake like structure.

C. Selected Spectroscopic Data

1) Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate: Yellow crystalline solid: mp 154-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.27 (d, J = 7.5 Hz, 2 H), 7.19 (t, J = 7.3 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1 H), 6.21 (br s, 1 H), 4.99 (s, 1 H), 4.08 (q, J =7.2 Hz, 4 H), 2.28 (s, 6 H), 1.21 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 167.8, 147.9, 144.3, 127.9, 127.8, 126.1, 103.9, 59.7, 39.6, 19.3, 14.2; MS (ESI) m/z 330$(M+H)^+$; HRMS (ESI) Calcd for $C_{19}H_{24}NO_4$ $(M+H)^+$ 330.1705., found 330.1693.

2) Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate : Yellow crystalline solid: mp 150-152 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ (ppm) 1.20(t, 6H, J=7.18), 2.26(s, 6H), 3.71(s, 3H), 3.93-4.09(m, 4H), 4.78(s, 1H), 6.66(d, 2H, J=8.50), 7.07(d, 2H, J=8.50), 8.29(s, 1H); ^{13}C NMR(75 MHz, d_6-DMSO) δ (ppm) 14.10, 18.16, 37.94, 54.75, 58.89, 102.13, 113.09, 128.29, 140.52, 144.94, 157.41, 166.98; MS (ESI) m/z 382$(M+Na)^+$; HRMS (ESI) Calcd for $C_{20}H_{25}NO_5Na$ $(M+Na)^+$ 382.1630., found 382.1635.

3) Diethyl 2,6-dimethyl-4-(naphthalen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate: Yellow crystalline solid: mp 137-139 °C; ^{1}H NMR (300 MHz, CDCl3) δ(ppm) 7.75 (dd, J = 7.3 and 4.6 Hz, 2 H), 7.69 (d, J = 8.5 Hz, 1 H), 7.67 (s, 1 H), 7.48 (dd, J = 8.5 and 1.5 Hz, 1 H), 7.39 (app qu, J = 8.8 Hz, 2 H), 5.64 (br s, 1 H), 5.17 (s, 1 H), 4.08 (m, 4 H), 2.36 (s, 6 H), 1.22 (t, J =7.1 Hz, 6 H); 13C NMR (75 MHz, CDCl3) δ (ppm) 167.6, 145.2, 143.8, 133.3, 132.3, 127.8, 127.4, 127.4, 127.1, 126.3, 125.5, 125.0, 104.1, 59.7, 39.9, 19.6, 14.2; MS (ESI) m/z 402$(M+Na)^+$; HRMS (ESI) Calcd for $C_{23}H_{25}NO_4Na(M+Na)^+$ 402.1681., found 402.1668.

4) Diethyl 4-(2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate: Yellow crystalline solid: mp 148-152 °C; ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 7.28 (t, J = 7.5 Hz, 1 H), 7.05 (d, J = 6.2 Hz, 1 H), 6.95 (t, J = 7.4 Hz, 1 H), 6.86 (t, J = 8.9 Hz, 1 H), 6.64 (s, 1 H), 5.24 (s, 1 H), 4.02 (q, J = 7.2 Hz, 4 H), 2.22 (s, 6 H), 1.16 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz,

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CDCl3) δ (ppm) 167.8, 159.6, 145.0, 135.2, 131.0, 127.6, 123.6, 114.8, 102.6, 59.7, 34.1, 19.0, 14.0; MS (ESI) m/z 370$(M+Na)^+$; HRMS (ESI) Calcd for $C_{19}H_{22}NO_4FNa(M+Na)^+$ 370.1431., found 370.1428.

5) Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate: Orange crystalline solid: mp 153-155 °C; ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 7.18 (s, 1 H), 6.18 (br s, 2 H), 5.91 (d, J = 4.8 Hz, 1 H), 5.18 (s, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 2.29 (s, 6 H), 1.24 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 167.5, 158.7, 145.3, 140.8, 110.0, 104.4, 100.5, 59.8, 33.4, 19.3, 14.3; MS (ESI) m/z 320$(M+H)^+$; HRMS (ESI) Calcd for $C_{17}H_{22}NO_5$ $(M+H)^+$ 320.1498., found 320.1493.

6) Diethyl 4-(3,4-dihydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate: ^{1}H NMR(500 MHz, $CDCl_3$) δ (ppm) 1.21(t, 6H, J=6.98), 2.24(s, 6H), 3.97-4.08(m, 4H), 4.71(s, 1H), 6.43-6.61(m, 3H), 8.22(s, 1H); ^{13}C NMR(75 MHz, d_6-DMSO) δ (ppm) 14.19, 18.20, 40.94, 55.76, 61.24, 102.13, 116.09, 117.29, 120.76, 128.29, 140.52, 144.94, 147.45, 157.41, 167.58;MS (ESI) m/z 362$(M+H)^+$; HRMS (ESI) Calcd for $C_{20}H_{26}NO_6(M+H)^+$ 362.1604., found 362.1600.

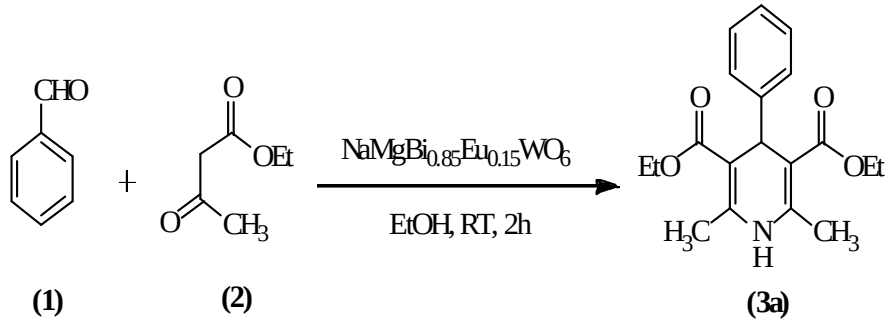
7) Diethyl 4-(3-hydroxy-4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate: ^{1}H NMR(300 MHz, $CDCl_3$) δ (ppm) 1.23(t, 6H, J=7.18), 2.25(s, 6H), 3.77(s, 3H), 3.96-4.10(m, 4H), 4.75(s, 1H), 6.51-6.61(m, 2H), 6.71(s, 1H), 8.21-8.32 (bs, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm) 14.25, 19.35, 39.01, 55.65, 59.60, 103.97, 110.90, 113.85, 120.34, 140.09, 143.81, 145.77, 167.76; MS (ESI) m/z 376$(M+H)^+$; HRMS (ESI) Calcd for $C_{20}H_{26}NO_6(M+H)^+$ 376.1755., found 376.1760.

8) Diethyl 4-(4-(3-fluoro-4-nitrophenoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate: ^{1}H NMR(300 MHz, $CDCl_3$) δ (ppm) 1.23(t, 6H, J=6.80), 2.33(s, 6H), 4.00-4.21(m, 4H), 4.95(s, 1H), 6.60(dd, 1H, $J_{(1,2)}$=2.27, $J_{(1,3)}$=9.82), 6.75-6.83(m, 1H), 6.92(d, 2H, J=8.31), 7.24-7.34(m, 3H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 14.22, 19.3, 39.6, 59.7, 102.77, 106.92, 115.08, 117.45, 126.1, 127.9, 130.33, 135.67, 144.3, 147.92, 154.08, 155.65, 164.09, 167.8; MS (ESI) m/z 485$(M+H)^+$;

9) Diethyl 2,6-bis((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate:b ^{1}H NMR(500 MHz, d_6-DMSO) δ (ppm) 1.14(t, 3H, J=6.64), 1.25(t, 3H, J=7.47), 2.55(s, 1H), 3.56-3.79(m, 7H), 3.86-4.05(m, 4H), 4.07-4.16(m, 1H), 4.28(d, 1H, J=16.60), 4.56-4.60(bs, 1H), 4.68(d, 1H, J=16.60), 5.88(s, 1H), 6.11(s, 1H), 6.74(d, 2H, J=8.30), 7.03(d, 2H, J=9.13), 7.68-7.88(m, 8H); ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm) 14.25, 39.22, 43.82, 55.22; 62.02, 68.09, 70.84, 99.92, 114.56, 127.82, 131.06, 132.87, 133.67, 145.36, 158.22, 166.92, 168.02; MS (ESI) m/z 738$(M+H)^+$.

III. RESULTS AND DISCUSSION

The SEM image of $NaMgBi_{0.85}Eu_{0.15}WO_6$ is shown in figure 2 which clearly indicates the nanoflake structure. To optimize the reaction conditions, we checked the four-part buildup response of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and ammonia (4 mmol) in the nearness of various reactant measures of nano $NaMgBi_{0.85}Eu_{0.15}WO_6$ at room temperature in 5 mL of EtOH, as a model response. It was found that 0.03 g of catalyst was sufficient to catalyze the response to deliver exceptional returns of dihydropyridine subsidiaries. As appeared in Table 1 (Entries 1–4), utilizing 0.03 g of the catalyst was sufficient to advance the reaction, moreover, an increase in the amount of catalysts did not make significant improvement in the yields. In the second stage the impact of solvent was examined. As can be seen from Table 1 (Entries 5–9), it was found that EtOH is the best solvent for this response to create exceptional returns in short response time in examination with other polar, non-polar, protic and aprotic solvents. To concentrate the sweeping statement of this technique, diverse sorts of beginning material were responded in the union of 1,4-dihydropyridines. As represented in Table 1, aromatic aldehydes with both electron withdrawing groups and electron donating groups respond well to give the items in great to phenomenal yields. As it is anticipated, starting from aldehyde with electron withdrawing groups reduce the yields, the electron donating groups are giving good yields in short times (for example, alkoxy). The nano flake structure and the inherent photocatalytic nature of $NaMgBi_{0.85}Eu_{0.15}WO_6$ is perhaps helpful for better yields in the multicomponent reaction.



Scheme 1: Synthesis of Dihydropyridines

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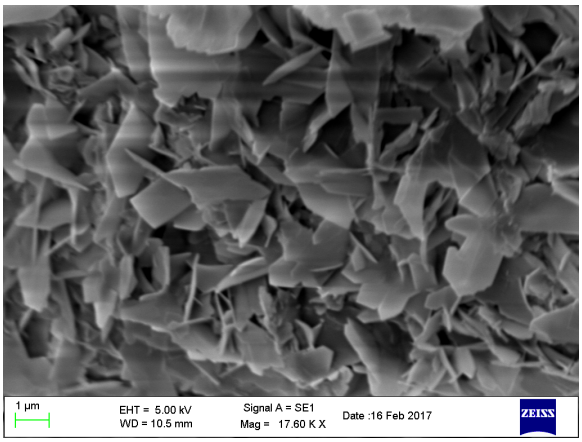
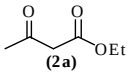
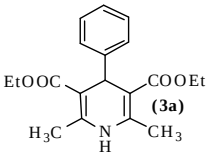
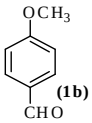
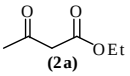
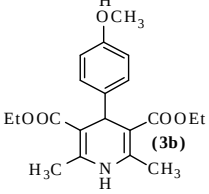
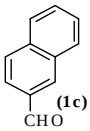
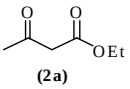
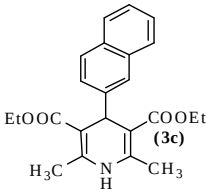
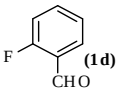
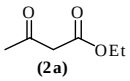
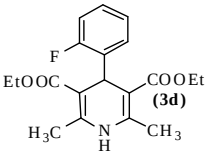
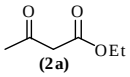
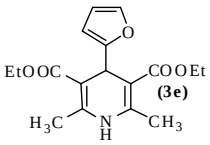
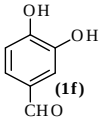
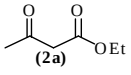
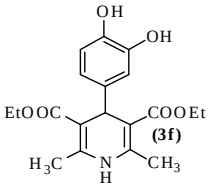
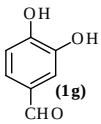
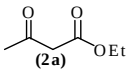
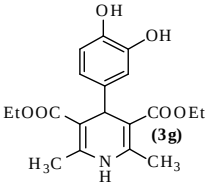


Fig. 2: SEM image of catalyst $NaMgBi_{0.85}Eu_{0.15}WO_6$

Table 1: Nano catalyzed synthesis of Dihydropyridines.

S.No.	Aldehyde	Keto Ester	Product[a]	Time(h)	Yield(%)[b]
(1)	(1a)	 (2a)	 (3a)	2.0	95
(2)	 (1b)	 (2a)	 (3b)	1.9	96
(3)	 (1c)	 (2a)	 (3c)	2.1	90
(4)	 (1d)	 (2a)	 (3d)	2.2	88
(5)	(1e)	 (2a)	 (3e)	2.3	89
(6)	 (1f)	 (2a)	 (3f)	2.2	89
(7)	 (1g)	 (2a)	 (3g)	2.2	90

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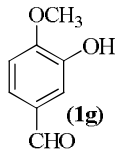
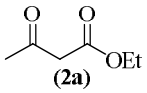
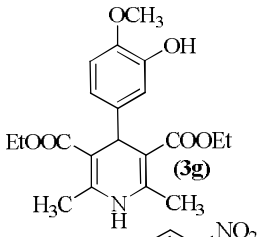
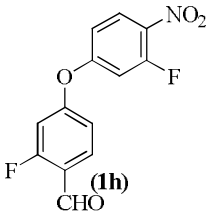
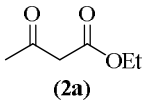
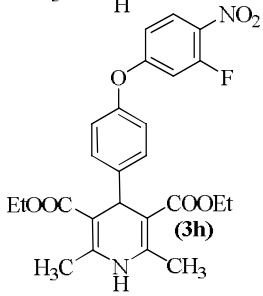
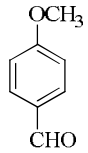
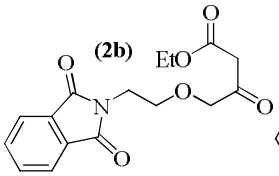
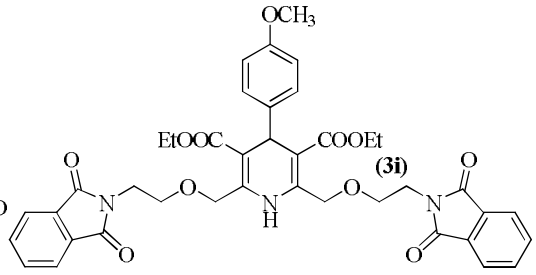
(7)	 (1g)	 (2a)	 (3g)	2.2	90
(8)	 (1h)	 (2a)	 (3h)	2.2	88
(9)		 (2b)	 (3i)	2.3	85

[a]All products were characterized by IR, 1H NMR and mass spectroscopy.
[b]Yield refers to pure products after column chromatography.

IV. CONCLUSIONS

In conclusion, a rare-earth doped double perovskite nano-material was successfully used as catalyst in the synthesis of dihydropyridine derivatives. Different aromatic aldehydes, ethylaceto acetate and ammonia could be endured in this reaction to make it cost effective and result in great yields. Reaction time perceptibly diminished from days to hours in presence of this nano catalyst. Additionally studies to extend the substrate diversity and understand detailed reaction pathway are in progress in our lab.

V. ACKNOWLEDGEMENT

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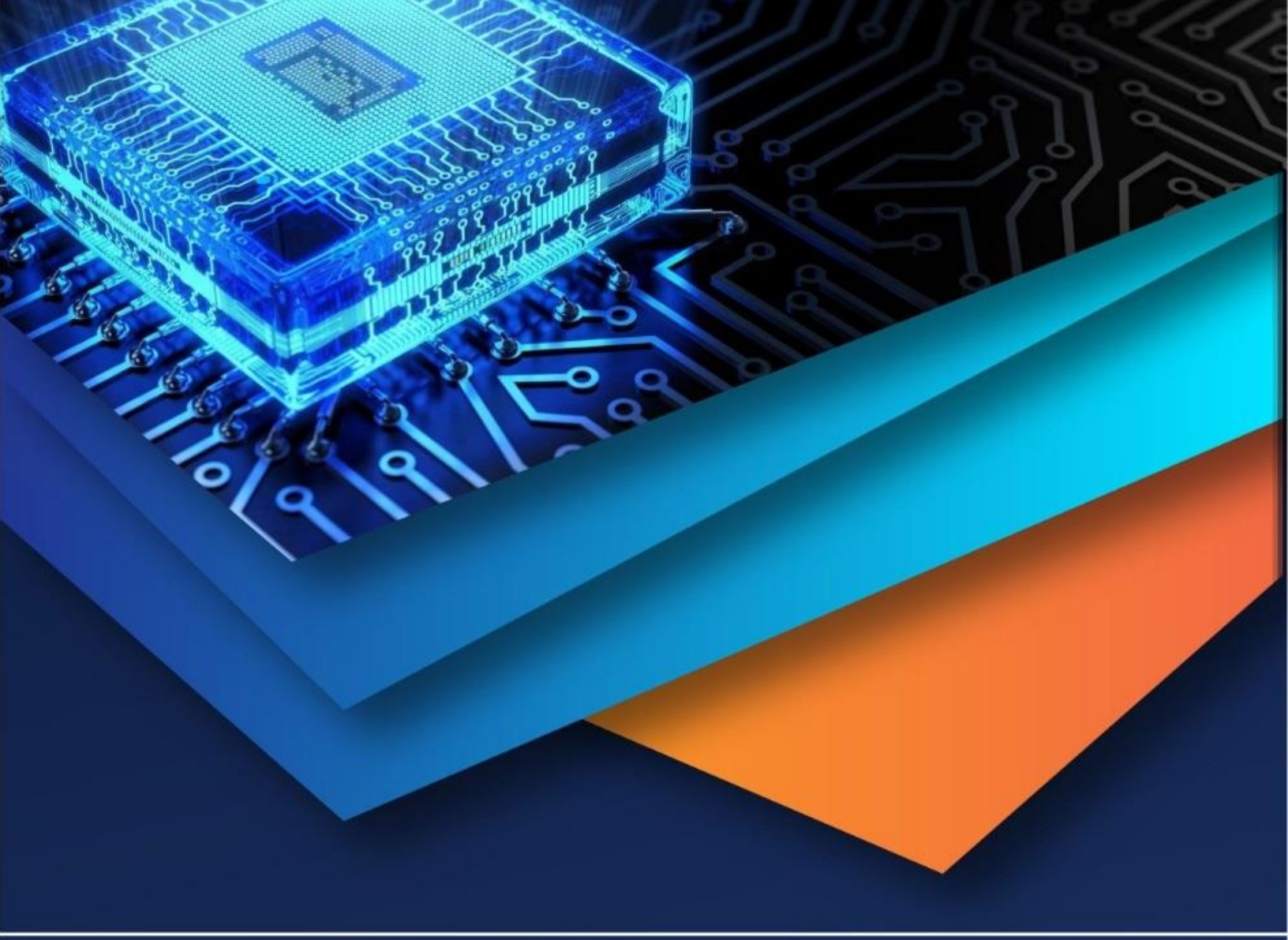

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