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Study of Additional Interactions of Heterodimeric GW7604 Derivatives at the Coactivator Binding Site through Pharmacophore Modeling

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Abstract: ***Breast cancer is still the most common cancer in women worldwide, affecting one in eight women in high-income countries, and the incidence is further increasing. Endocrine therapy, including aromatase inhibitors or selective estrogen receptor modulators (SERMs)/selective estrogen receptor down-regulators (SERDs), consequently represents an indispensable treatment opportunity. Unfortunately, acquired endocrine resistance is an inevitable issue, which manifests after prolonged therapy. Consequently, developing a novel drug for the treatment of breast cancer is need of the hour. But it is an established fact that designing or repurposing a drug using 'trial and error' approach is a tricky, long, expensive and could be a failure in clinical stage. Hence, there is a need to employ alternative approaches like computer aided drug design (CADD) to overcome these shortcomings of conventional approach. Recently, CADD has gained a high popularity among drug designers and medicinal chemists due to several advances associated with it. Pharmacophore modeling is an efficient and useful approach to identify important patterns in a series of molecules for optimizations. Hence, in this analysis, an attempt is made to develop consensus pharmacophore model of heterodimeric GW7604 derivatives using alignment approach. The dataset consists of fourteen heterodimeric GW7604 derivatives exhibiting the binding activity in a transactivation assay ERα and ERβ to the coactivator binding site. The heterodimeric GW7604 derivatives possess good variation in substation pattern like the presence of different diaminoalkane spacer and CABS binder. The consensus pharmacophore model revealed the importance of structural features and their correlation with the biological activity.***

Keywords: Heterodimeric GW7604 derivatives, Coactivator binding site, Pharmacophore modeling, Diaminoalkane spacers, Thioxo-quinazolinones scaffolds, Benzimidazole scaffolds.

I. INTRODUCTION

Worldwide, breast cancer is the most-common invasive cancer in women [1]. Along with lung cancer, breast cancer is the most commonly diagnosed cancer, with 2.09 million cases each in 2018 [2]. Breast cancer affects 1 in 7 (14%) of women worldwide [3]. The selective estrogen receptor modulators (SERMs) such as tamoxifen reduce the risk of breast cancer but increase the risk of thromboembolism and endometrial cancer [4]. There is no overall change in the risk of death [4,5]. They are thus not recommended for the prevention of breast cancer in women at average risk but it is recommended they be offered for those at high risk and over the age of 35 [5]. The benefit of breast cancer reduction continues for at least five years after stopping a course of treatment with these medications [6]. Aromatase inhibitors (such as exemestane and anastrozole) may be more effective than selective estrogen receptor (ER) modulators (such as tamoxifen) at reducing breast cancer risk and they are not associated with an increased risk of endometrial cancer and thromboembolism [7]. One possibility to impede estrogen-mediated pathways, in general, is to induce specific conformations of the estrogen receptor (ER) upon drug binding, which prevents coactivator recruitment and ultimately gene transcription in hormone dependent MC cells. The SERM tamoxifen, as the first targeted anti-breast-cancer therapeutic agent [8], acts via this mode of action. Upon attachment of an agonist at the ligand binding site (LBS), Helix 12 (H12) is oriented over the LBD. In the case of (Z)-4-hydroxytamoxifen (4-OHT), which is the active metabolite of tamoxifen, H12 is repositioned, AF2 is not formed, and interactions with coactivator peptides are blocked in hormone-dependent tumor cells, preventing their growth [9,10].

To derive an alternative after failure of tamoxifen treatment, 4-OHT was structurally modified in a way where the basic side chain was exchanged by a carboxylate bearing moiety. (E/Z)-3-(4-((E)-1-(4-Hydroxyphenyl)-2-phenylbut-1-enyl)phenyl)acrylic acid (GW7604), the cinnamic acid analogue of 4-OHT, showed diminished hormonal effects, e.g., induction of ER expression and cell-growth-stimulating effects at low concentrations [11,12].

Knox, A.K. et al used another approach and developed compounds in such a way that besides the LBS, the coactivator binding site (CABS) is targeted simultaneously. They evaluated the consequences on the receptor binding affinity and the intracellular responses [13]. In their first study, homodimers of GW7604 and of the related cyclofenil acrylic acid were designed, because an X-ray crystal structure revealed a hydrophobic groove at the CABS suitable to bind 1,1-diaryl- or 1,1,2-triarylalkenes. Alkyl spacers of different lengths between the molecules should guarantee sufficient flexibility to reach two different pockets within this exposed surface, which emerge as potential areas [13]. As proposed by them, it was possible to increase binding affinity and to inhibit ER transactivation [13]. In continuation of this structure–activity relationship (SAR) study, they tried to optimize the CABS-binding properties. 1,1-Diarylalkene derivatives can bind at the ER surface, but steric repulsion might render accessibility to the proposed binding pockets. Therefore, they selected Thioxo-quinazolinone derivatives connected via the diaminoalkane spacer to GW7604 [14]. The 5-hydroxybenzimidazole scaffold was also investigated regarding their H-bond formation within the pockets at the ER surface [14]. In this SAR study, GW7604 was linked to known CABS binders to evaluate the possibility of increasing ER binding and to inhibit coactivator recruitment. The biological activities were investigated at the isolated receptors and in cellular systems. The compounds showed the profile either of pure antiestrogens (5- methoxy/hydroxy benzimidazoles) or of pure antiestrogens with ER-degradation potency (thioxo-quinazolinones) [14].

Though, Knox, A.K. et al discussed SAR (Structure Activity Relationship), no attempt was investigated to develop a consensus pharmacophore model of heterodimeric GW7604 derivatives. This is first ever effort to develop a consensus pharmacophore model of heterodimeric GW7604 derivatives for additional interaction at the coactivator binding site (CABS) using alignment approach. The outcomes could be advantageous to chemists when developing a new drug.

Consequently, developing a novel drug for the treatment of breast cancer is need of the hour. But it is an established fact that designing or repurposing a drug using ‘trial and error’ approach is a tricky, long, expensive and could be a failure in clinical stage. Hence, there is a need to employ alternative approaches like Computer Aided Drug Design (CADD) to overcome these shortcomings of conventional approach. Recently, CADD has gained a high popularity among drug designers and medicinal chemists due to several advances associated with it. There are many examples when CADD has revealed new ideas to develop a drug. Pharmacophore modeling, molecular modeling & QSAR and other branches of CADD bas contributed successfully in developing many new block buster drugs. Pharmacophore modeling is an efficient and useful approach to identify important patterns in a series of molecules for optimizations [15,16]. Hence, in this analysis, an attempt is made to develop consensus pharmacophore model of heterodimeric GW7604 derivatives using alignment approach.

II. MATERIALS AND METHODS

A. *Selection of Dataset*

The dataset consists of fourteen heterodimeric GW7604 derivatives (thioxo-quinazolinones, 5-methoxy-benzimidazole and 5-hydroxy-benzimidazole scaffolds) exhibiting the binding activity in a transactivation assay ERα and ERβ (IC_{50} in nM range) to the coactivator binding site [14]. The thioxo-quinazolinones, 5-methoxy-benzimidazole and 5-hydroxy-benzimidazole scaffold derivatives possess good variation in substation pattern like the presence of different diaminoalkane spacer and CABS binder. Therefore, the selected dataset is wide enough to develop a consensus pharmacophore model. The dataset used in the present work has been tabulated in table 1.

TABLE 1: SMILES notation of heterodimeric GW7604 derivatives along with reported IC_{50} values of time-resolved fluorescence resonance energy transfer (TR-FRET) competitive binding assay using the isolated LBDs of ERα and ERβ.

CABS Binder	Compound	SMILES	TR-FRET ERα IC_{50} (nM)	TR-FRET ERβ IC_{50} (nM)
Thioxo-quinazolinones scaffolds	15	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCNC(CCCN(C(c(cccc2)c2N2)=O)C2=S)=O)=O)cc1)\c(cc1)ccc1O	4.01	12.6
	16	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCNC(CCCCCCCN(C(c(cccc2)c2N2)=O)C2=S)=O)=O)cc1)\c(cc1)ccc1O	1.41	0.82
	17	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCNC(c(cc2)ccc2N(CC2)CCN2C(CCCN(C(c(cccc2)c2N2)=O)C2=S)=O)=O)=O)cc1)\c(cc1)ccc1O	4.63	18.5

	18	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCNC(c(cc2)ccc2N(CC2)CCN2C(CCCCCCCN(C(c(cccc2)c2N2)=O)C2=S)=O)=O)=O)cc1)\c(cc1)ccc1O	4.23	6.81
5-methoxy-benzimidazole scaffolds	31	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCNC(CCc2nc(ccc(OC)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	2.75	4.88
	32	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCNC(CCc2nc(ccc(OC)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	4.11	3.01
	34	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCNC(CCc2nc(ccc(OC)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	2.22	5.26
	36	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCCNC(CCc2nc(ccc(OC)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	1.56	7.84
	38	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCCCNC(CCc2nc(ccc(OC)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	2.61	5.22
5-hydroxy-benzimidazole scaffolds	39	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCNC(CCc2nc(ccc(O)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	1.45	1.99
	40	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCNC(CCc2nc(ccc(O)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	2.72	3.78
	41	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCNC(CCc2nc(ccc(O)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	1.62	2.84
	42	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCCNC(CCc2nc(ccc(O)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	1.28	3.81
	43	CC/C(/c1ccccc1)=C(/c1ccc(/C=C/C(NCCCCCCNC(CCc2nc(ccc(O)c3)c3[nH]2)=O)=O)cc1)\c(cc1)ccc1O	3.41	7.80

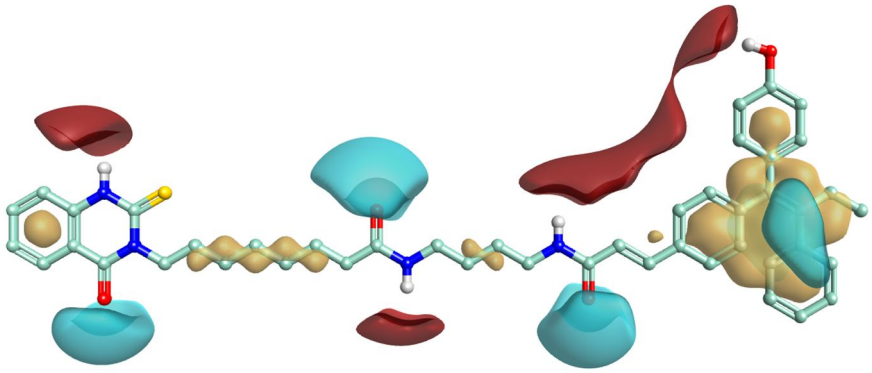
B. Developing Pharmacophore Model

The standard procedure used in the present work for developing consensus pharmacophore model involves recommended steps in the literature [17-19]. The four main steps are:

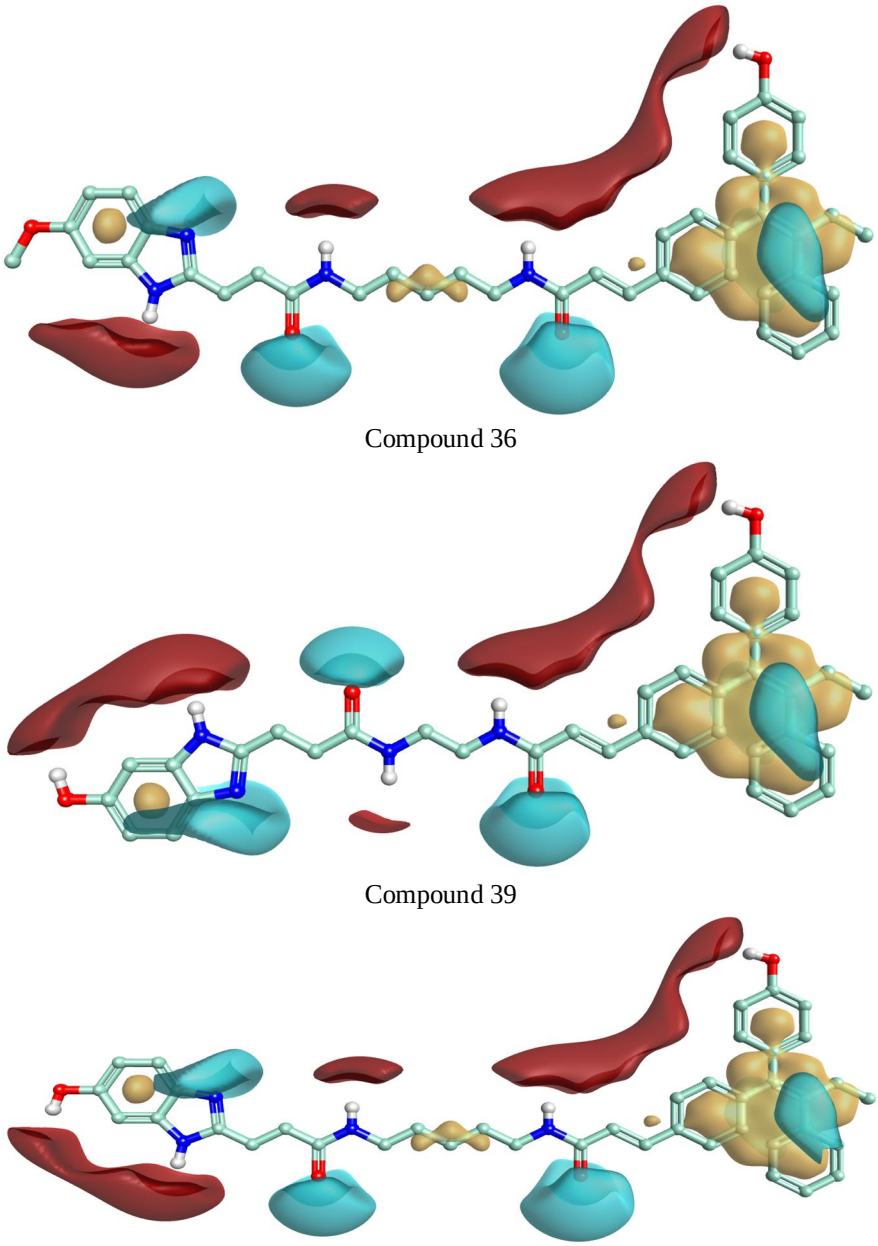
1) Drawing the structures using a software (ChemSketch 2010 freeware)
2) Optimization using a suitable method (MOPAC 2012 using AM1 method)
3) Aligning all the molecules in the dataset using suitable approach (Open3DAlign software with default setting)
4) Generation of a consensus pharmacophore model (Forge 10.0.1)

III. RESULT AND DISCUSSION

In the present work, four most active derivatives of heterodimeric GW7604 (Compound 16, 36, 39 and 42) are analysed and their pharmacophore model is represented in fig. 1. The consensus pharmacophoric pattern of different heterodimeric GW7604 derivatives is highlighted by three contour portions (Yellow: Hydrophobic/Lipophilic, Blue: Negative and Red: Positive). The present pharmacophore-oriented analysis unveils that the binding activity using the isolated LBDs of ERα and ERβ to the coactivator binding site has good correlation with these three contour portions.



Compound 16



Compound 36

Compound 39

Compound 42

Fig. 1 – 3D- representation of consensus pharmacophoric pattern for (most active heterodimeric GW7604 derivatives) Compound 16, 36, 39 and 42.

From fig. 1, it is found that, there are three types of positive contour regions (red colour portion) present in compound 16, 36, 39 and 42. This indicate that, these compounds have three types of different ligand moieties attached to it. One type of positive charge region (red colour portion) is present over the –OH and –NH ligand which is attached to aromatic moiety of GW7604 scaffold. Both the ligand –OH and –NH are conjugated with double bond of aromatic ring and aliphatic chain respectively. Hence, they occupy the same type of positive charge region. Second type of positive charge region (red colour portion) is present over –NH ligand of amide which is attached to aliphatic chain moiety. Both –NH ligand of diaminoalkane spacers (linkers) molecule shows remarkable variation correspond to positive charge region. Third type of positive charge region (red colour portion) is present over –NH group of thioxo-quinazolinones scaffold in compound 16, also present over –NH and $–OCH_3$ group of 5-methoxy-benzimidazole scaffold in compound 36 and in compound 39 and 42 it is present over –NH and –OH group of 5-hydroxy-benzimidazole scaffold. This third type of positive charge region (red colour portion) shows notable variation with respect to first type of positive charge region (red colour portion) even though they contain –NH and –OH ligand combination.

It is observed from fig. 1 that, all compounds show four types of negative charge region (blue colour portion). One type of negative charge region is due to presence of alkene hydrocarbon of GW7604 scaffold in which three aromatic rings are attached to it. All compounds have such type of same region. Second and third type of negative charge region is shown by diaminoalkane spacers (linkers) molecule and is appeared due to oxygen atom of carbonyl group in amide. This pattern is same in all compounds. Fourth type of negative charge region shows remarkable variation between compound 16 and compound 36, 39, 42. In compound 16, this type of negative charge region is obtained due to oxygen atom of carbonyl group present in thioxo-quinazolinones scaffold while in compound 36, 39 and 42 it is due to presence of nitrogen atom in benzimidazole scaffold.

All compounds show two types of hydrophobic/lipophilic region (yellow colour portion), which is the most common feature in them. One type of common hydrophobic/lipophilic region is shown due to presence of three aromatic moiety of GW7604 scaffold in all compounds. Second type of common hydrophobic/lipophilic region is observed due to aromatic ring of thioxo-quinazolinones and benzimidazole scaffold. The most comparatively remarkable difference shown by all compounds is related to hydrophobic/lipophilic nature and it is directly corelated with alkyl chain of both diaminoalkane spacers and thioxo-quinazolinones and benzimidazole scaffold. As compared to compound 36, 39 and 42, compound 16, shows increase in hydrophobic/lipophilic nature due to increase in alkyl chain moiety of diaminoalkane and thioxo-quinazolinones scaffold. This indicate that, in compound 16, GW7604 is linked by diaminoalkane spacers to thioxo-quinazolinones scaffold is favourable to hydrophobic/lipophilic nature. As a result, additional interaction is present in heterodimeric GW7604 derivative (compound 16) at the coactivator binding site. In future, optimizations of these regions (Yellow: Hydrophobic/Lipophilic; Blue: Negative and Red: Positive), should be advantageous to chemists while developing a new drug design.

IV. CONCLUSION

The present analysis reveals important pharmacophoric patterns of additional interactions of heterodimeric GW7604 derivatives at the coactivator binding site. It unveils the importance of attachment of –OH, –NH and $–OCH_3$ ligand to aromatic ring, diaminoalkane chain and thioxo-quinazolinones or benzimidazole scaffold. It also highlights the importance of oxygen atom of carbonyl group in amide, nitrogen atom in benzimidazole scaffold and oxygen atom in thioxo-quinazolinones scaffold. It is also revealing the importance of alkyl chain of diaminoalkane linker, thioxo-quinazolinones and benzimidazole scaffold and their correlation with binding at the coactivator binding site and their biological activity. Hence such a combination of these moieties must be retained in future optimization to have good activity. The present study is effective in discovering useful structural features for future optimizations.

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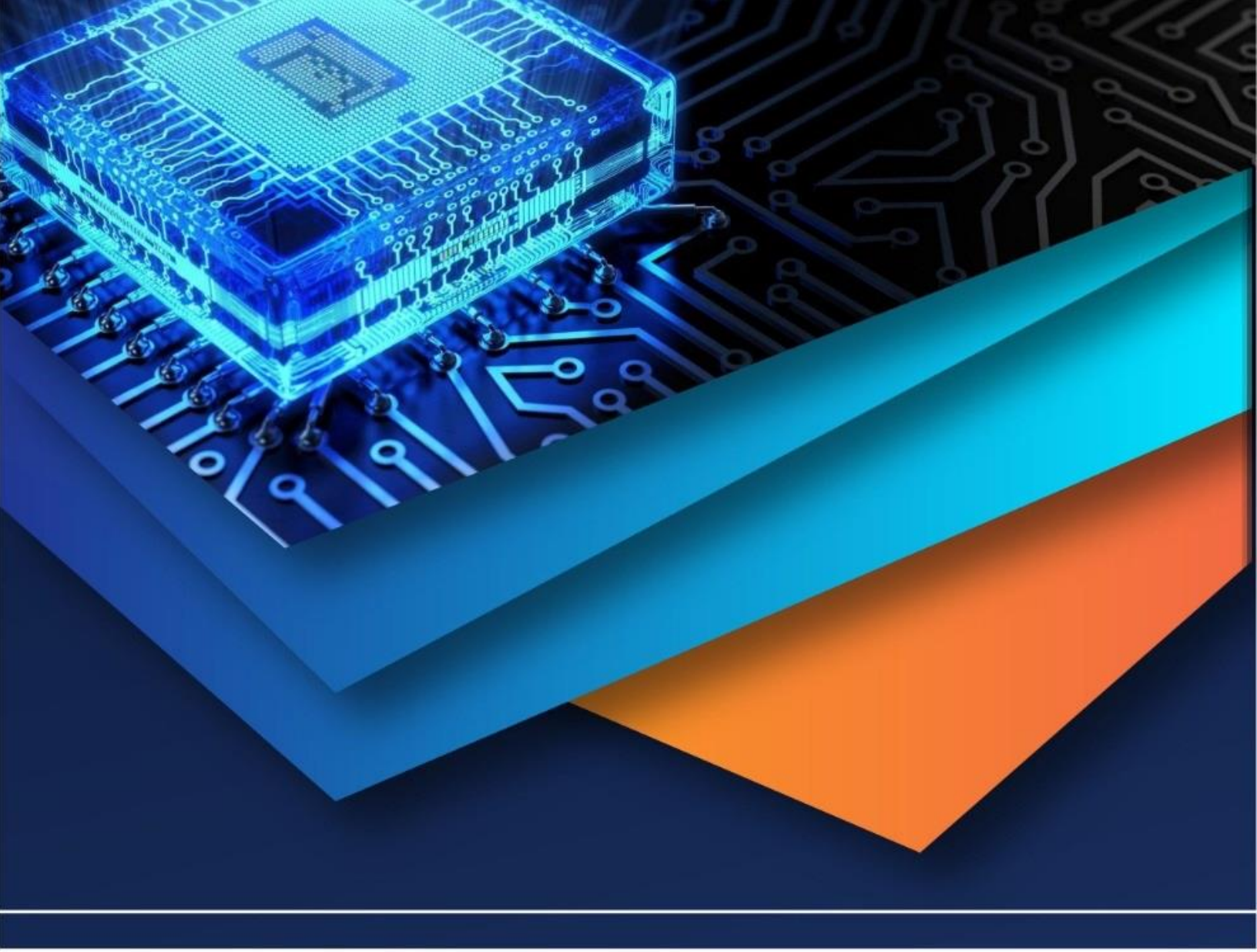

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