A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF ÇANKIRI KARATEKİN UNIVERSITY

MOLECULAR DOCKING STUDY OF SOME MODIFIED NATURAL PRODUCTS AS POTENTIAL ANTICANCER AGENTS

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

BY

MARWAN ADNAN AHMED AL-JANABI

ÇANKIRI

2023

MOLECULAR DOCKING STUDY OF SOME MODIFIED NATURAL PRODUCTS AS POTENTIAL ANTICANCER AGENTS

By Marwan Adnan Ahmed AL-JANABI

February 2023

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

Advisor : Prof. Dr. Volkan EYÜPOĞLU
Co-Advisor : Asst. Prof. Dr. Ahmed MAHAL

Examining Committee Members:

Chairman : Assoc. Prof. Dr. Şevki ADEM
Chemistry
Çankırı Karatekin University

Member : Asst. Prof. Dr. Ümit YIRTICI
Medical Laboratory
Kırıkkale University

Member : Prof. Dr. Volkan EYÜPOĞLU
Chemistry
Çankırı Karatekin University

Approved for the Graduate School of Natural and Applied Sciences

Prof. Dr. Hamit ALYAR
Director of Graduate School

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Marwan Adnan Ahmed AL-JANABI

ABSTRACT

MOLECULAR DOCKING STUDY OF SOME MODIFIED NATURAL PRODUCTS AS POTENTIAL ANTICANCER AGENTS

Marwan Adnan Ahmed AL-JANABI

Master of Science in Chemistry

Advisor: Prof. Dr. Volkan EYÜPOĞLU

Co-Advisor: Asst. Prof. Dr. Ahmed MAHAL

February 2023

The current work comprised the prediction of a few tetrahydrocurcumin derivatives (1-6) that Docking and DFT investigations suggest may be anti-breast cancer. The Autodock technique was carried out by MGL (Molecular Graphic Laboratory) and Discovery Studio Visualizer (DSV). Total Electron Density (TED) measurements were used to identify the adsorption sites for molecules . To identify which compounds were more effective than others, numerous factors were taken into consideration. In order to examine the inhibitory potential of tetrahydrocurcumin derivatives, the binding energy (Eb) of these compounds was used in docking simulations. DFT and docking revealed that C, THC, and $THCN_3$ were the most effective inhibitory positions, and the least effective inhibitory positions it is THCN,$THCN_1$ and $THCN_2$.

2023, 42 pages

Keywords: Curcuminoids, Tetrahydrocurcumin, Docking, DFT, Breast cancer

ÖZET

BAZI DEĞİŞTİRİLMİŞ DOĞAL ÜRÜNLERİN POTANSİYEL ANTİKANSER AJANLAR OLARAK MOLEKÜLER YERLEŞTİRME ÇALIŞMASI

Marwan Adnan Ahmed AL-JANABI

Kimya, Yüksek Lisans

Tez Danışmanı: Prof. Dr. Volkan EYÜPOĞLU

Eş Danışman: Dr. Öğr. Üyesi Ahmed MAHAL

Şubat 2023

Bu araştırma, göğüs kanserine karşı önerilen bazı tetrahidrokurkumin türevlerinin (1-6) Docking ve DFT çalışmaları ile öngörülmesini içermektedir. Discovery Studio Visualizer (DSV) ve MGL (Moleküler Grafik Laboratuvarı) Autodock işlemini gerçekleştirmiştir. Moleküllerin adsorpsiyon alanları, Toplam Elektron Yoğunluğu (TED) ölçülerek ortaya çıkarılmıştır. Hangi moleküllerin diğerlerinden daha verimli olduğunu saptamak için kullanılan çok daha fazla değişken bulunmaktadır. Tetrahidrokurkumin türevlerinin bağlanma enerjisi (Eb), tetrahidrokurkumin türevlerinin inhibitör kabiliyetini araştırmak için docking simülasyonlarında kullanılmıştır. DFT ve docking, C, THC ve $THCN_3$ en etkili inhibitör pozisyonları olduğunu göstermiştir, ve en az etkili inhibitör pozisyonlar THCN,$THCN_1$ and $THCN_2$.

2022, 42 sayfa

Anahtar Kelimeler: Kurkuminoidler, Tetrahidrokurkumin, Docking, DFT, Meme kanseri

PREFACE AND ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Prof. Dr. Volkan EYÜPOĞLU and co-advisor, Asst. Prof. Dr. Ahmed MAHAL, for their patience, guidance and understanding.

Marwan Adnan Ahmed AL-JANABI

Çankırı-2023

CONTENTS

LIST OF SYMBOLS

μ	Dipole moment
S	Chemical softness
χ	Electronegativity

LIST OF ABBREVIATIONS

^{1}HNMR	Proton nuclear magnetic resonance
ADT	Autodock tools
ARG	Arginine
ASN	Asparagine
DFT	Density functional theory
DSV	Discovery studio visualizer
EA	Electron affinity
GW 09	Gaussian 09
HOMO	Highest occupied molecular orbital
IP	Ionization potential
LUMO	Lowest unoccupied molecular orbital
MGL	Molecular graphic laboratory
PDB	Protein data bank
SER	Serine
TED	Total electron density

LIST OF FIGURES

LIST OF TABLES

1. INTRODUCTION

Curcumin is a phytochemical of the *Zingiberaceae* family isolated from the rhizome of turmeric *Curcuma longa (*Lakhan *et al*. 2015). Turmeric that contains 2% to 5% curcumin is a result of the treatment of the rhizome or root (Wilken *et al*. 2011).The three major structures of turmeric extract are curcumin (1, 60–70%), demethoxycurcumin (2, 20–27%), and bisdemethoxycurcumin (4, 10–15%), along with other few secondary metabolites as shown in (Figure 1.1) (Nelson *et al.* 2017). *Curcuma longa* species are forming bright yellow curcumin. Curcumin is used in the market as herbal medicine, food flavoring, coloring agents, and cosmetics ingredient. A diarylheptanoid of curcumin that belongs to the curcuminoids family of phenolic pigments that give turmeric its yellow color. Although a lot of studies done but investigating no evidence for its therapeutic activity (Baker 2017). Although a lot of studies done but investigating no evidence for its therapeutic activity due to its both instability and poor bioavailability and therefore, it is unlikely to be drug development (Manolova *et al.* 2014).

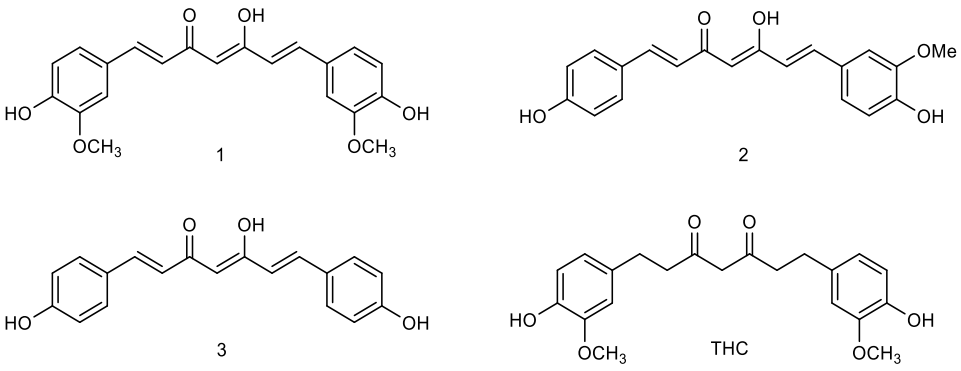

Figure 1.1 The major structures of turmeric extract and THC (Nelson *et al.* 2017)

The reduction of curcumin (Pari *et al.* 2005) leads to the preproduction of another curcuminoid of turmeric so called tetrahydrocurcumin (THC) (Figure 1.1) which is isolated from *Curcuma wenyujin* (Song *et al.* 2018) as traditional Chinese medicine. Phase I metabolism is producing THC by hepatic reductases as a curcumin major metabolite (Esatbeyoglu *et al.* 2012). On the other hand, the hydrogenation of curcumin

is producing THC (white color) in the laboratory and investigated its bioactivity as an anti-inflammatory, antioxidant, and anticancer agent (Song *et al*. 2018). The findings show the potent cytotoxic activity of THC as a cancer-fighting agent (Mahal *et al.* 2017) and colon carcinogenesis as an effective chemopreventive treatment (Kim *et al.* 1998). THC shows the potent inhibitory activity as *P-glycoprotein* (P-gp) inhibitors *against* Multidrug Resistance in cancer diseases (Limtrakul *et al.* 2007). Clinical trials utilizing the three curcuminoids known as curcumin, bisdemethoxycurcumin, & demethoxycurcumin at doses of up to 12,000 mg/day of 95 percent content indicated that FDA-approved curcuminoids had good toleranc and safety (Mahady *et al.* 2002). Although curcumin is thought to possess anti-inflammatory and antioxidant properties, it appears to possess a restricted bioavailability due to its low absorption, fast metabolism, and rapid elimination (Gupta *et al.* 2013) . These and other ways for increasing curcumin's bioavailability have been studied extensively. A number of these compunds have been created to block curcumin's metabolic route in an effort to increase the bioavailability of curcumin. Curcumin's bioavailability increases by 2000% when piperine, a well-known bioavailability booster, makes an appearance in the black pepper extract. As a result, the problem of low curcumin bioavailability seems to be overcome by adding bioavailability-improving drugs like piperine (Aggarwal *et al.* 2003). In *our continuous attempts* to develop novel potent bioactive agents (Zinad *et al.* 2020a, Zinad *et al.* 2020b, Zinad *et al.* 2020c, Mohapatra *et al*. 2021, El-ajaily *et al.* 2019, Mahal *et al.* 2015a, Mahal and A. 2015 , Abdel-Jalil *et al.* 2015, Mahal *et al.* 2011, Ibad *et al.* 2011, Eleya *et al.* 2011, Salman *et al.* 2011, Mahal *et al.* 2010, Hussain *et al.* 2008, Mahal *et al.* 2015b, Salman *et al.* 2020, Zinad *et al*. 2021a, Ali Salman *et al.* 2022, Marzano *et al.* 2022, Zinad *et al.* 2020d, Zinad *et al.* 2021b, Yang *et al*. 2017, El-Barasi *et al.* 2020, Yang *et al.* 2018), we aim at this study to investigate the molecular docking and DFT calculation of potent anticancer agents of tetrahydrocurcumin.

1.1 Aim of Study

To predict some tetrahydrocurcumin derivatives that are suggested as anti-brest cancer by Docking and DFT studies.

2. LITERATURE REVIEW

Turmeric has drawn significant interest from the scientific and medical professions, as well as from the culinary community. One of the ginger family members, Curcuma longa, is a rhizomatic perennial herbaceous perennial plant (Curcuma longa). Although the major component of turmeric, curcumin, has long been known to offer medicinal benefits, Researchers have just lately been able to pinpoint the exact mechanism or mechanisms of action and pinpoint the bioactive components. One of the principal polyphenols present in the rhizomes of Curcuma longa (turmeric) and other Curcuma spp. is curcumin (1,7-bis(4hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). Curcuma longa has a long history of usage as a medicinal herb in Asia owing to its potent antioxidant, anti-inflammatory, anti-mutagenic, anti-bacterial, and anti-cancer effects (Priyadarsini 2014).

Researchers have discovered that polyphenol curcumin targets a wide range of signaling molecules and also acts on cells, providing evidence of its many health advantages. It has been shown to help with metabolic syndrome and inflammatory illnesses.Inflammatory and degenerative eye disorders, as well as pain relief. The kidneys also seem to benefit from it. Curcumin supplementation seems to provide several therapeutic advantages, however, The majority of these benefits are attributable, in large part, to the anti-inflammatory and antioxidant properties that it possesses.Curcumin is said to have antioxidant and anti-inflammatory effects, despite the fact that its bioavailability is low. This seems to be mostly the result of inadequate absorption, a rapid metabolism, and rapid excretion (Gupta *et al.* 2013)

Clinical tests employing the three curcuminoids curcumin, bisdemethoxycurcumin, & demethoxycurcumin at doses between 4,000 and 8,000 mg/day and up to 12,000 mg/day of 95 percent concentration indicated that the curcuminoids approved by the FDA have outstanding tolerance and safety properties (Mahady *et al.* 2002).

The vast majority of studies on curcumin in humans have been conducted on participants who already had one or more medical problems. If the biomarkers in the

trials being done on healthy adults are normal at the beginning of the study, which may be difficult, the effects may not be as rapid and noticeable. To get the most out of long-term research, it's important to follow patients for a long period to see whether there are any health advantages. As a result of the varied dosages utilized in the few studies that have been conducted, it might be difficult to conduct cross-comparisons (Reddy *et al.* 2005).

Investigated the targeting activities of curcumin and its derivatives against epidermal growth factor receptor (EGFR), further the structure–activity relationship was examined. In their study, It was demonstrated that the diversity in the structures of curcumin and its derivatives caused the binding stabilities between EGFR and curcumin and its derivatives to differ from one another. Interestingly, both hydrogen bonds and hydrophobic interactions play vital roles in the binding of curcumin and its derivatives with EGFR. They further asserted that the methoxyl and 3,5-dione groups had a significant influence on their electrostatic interactions with EGFR.They concluded that curcumin and its derivatives can act as promising tyrosine kinase inhibitors (Liang *et al.* 2021).

To develop better treatment against cancer, (Saeed *et al.* 2022) In order to examine the potential of curcumin compounds as anti-cancer medicines, Saeed and his team employ a technique known as molecular docking to target the cancer-related target proteins of curcumin, including EGFR and nuclear factorκB (NF-κB). Additionally, they used the annexin V/propidium iodide assay, lactate dehydrogenase assay, resazurin cell viability assay, and flow cytometric measurement of reactive oxygen species to validate the docking results for locating a curcumin-based drug against cancer.

performed molecular docking to show that potential of 22 selected food-derived compounds as hyperglycemia reducers. They found that curcumin is a dual inhibitor of DPP-4 and α-glucosidase, two enzymes important for glycemic control. Based on the docking results, they examined the enzymatic evaluation via *in vitro* studies. Cao and his team discovered that curcumin dramatically alleviated the diet-induced hyperglycemia (such as fasting plasma glucose levels and glycogen storage in muscle or

liver) in mice. This condition was brought on by a change in the mice's diet. Curcumin is highlighted as a potential component of foods with functional qualities that are utilized to manage diet-induced hyperglycemia in a study that was conducted by (Cao *et al.* 2022).

In scopolamine-induced amnesia, the behavioral mice models of elevated plus maze (EPM) and novel object recognition (NOR) were employed to study five mono-carbonyl curcumin analogs for their possible neuroprotective or memory-improving properties in vivo. The inhibitory mechanism of cholinesterase by synthetic curcumin analogs was also investigated using molecular docking. They stated that curcumin analogs have the potential to improve memory and function as an efficient neuroprotective agent (Hussain *et al.* 2021).

The DFT analyses of synthesized curcumin analogues were studied by (Ahsan *et al.* 2022), where the HOMO/LUMO configuration of the compounds lies between the energy levels E = 3.55 and 3.35 eV. In addition, the antiproliferative efficiency of produced curcumin analogues (3a-c) was evaluated using a total of fifty dozen distinct cancer cell lines in both a single dosage experiment (10 M) and five dose assays (0.001 to 100 M). Both 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(phenoxy) ethanone (3b) and 3,5-bis(4-hydroxy-3-methoxystyryl)-3C demonstrated the most encouraging antiproliferative activity against the cancer cell lines, with growth inhibitions of 92.41% and 87.28%, respectively. In addition to this, it demonstrated significant antiproliferative activity (%GIs > 68%) against 54 of the The use of curcumin analogues as a therapeutic intervention may prove to be advantageous in the fight against cancer, as suggested by the findings of (Ahsan *et al.* 2022).

In an investigation into the inhibition of aldose reductase (rate-limiting enzyme of progression of diabetic complications), (Kondhare *et al.* 2019) synthesized of novel series of curcumin analogues and biological activity studies implemented. The biological activity revealed that, in comparison to the quercetin standard, all curcuminoids had AR inhibitory (ARI) activities that ranged from moderate to good. They reported that 5 compounds of newly synthesized have IC_{50} values less than 5.95

μM. Moreover, binding mode of most active compounds were subjected to molecular docking. The newly synthesized series of curcumin analogues may be of use to the researchers in the development of novel medicines for the treatment of diabetic problems.

(Elengoe *et al.* 2020) The most lethal disease impacting women globally is breast cancer. The search for a cancer cure is never-ending. Plant compunds with anti-cancer potential have been discovered. As a result, phytocompounds may hold the potential to pave the way for the development of brand-new pharmaceuticals. The three-dimensional (3-D) structures of the tumor suppressor gene p53, caspase-3, and retinoblastoma-1, as well as proteins derived from breast cancer cell lines, were constructed in this study. Docking with plant chemicals (respectively garcinone E, triterpenoid, or gallic acid) was also investigated. Throughout the entirety of the process of building three-dimensional representations of the proteins, the SWISS model was consistently put to use. After that, the ExPASy-ProtParam program was used in order to analyze the various physical and chemical properties of the protein models that had been created. After that, several validation programs such as PROCHECK, ProQ, ERRAT, or Verify 3D were applied in order to examine the proteins. This was done. The findings, which demonstrate that the proteins are stable, are reported in the following paragraphs. In the conclusion, the BSP-slim server was utilized to achieve a successful docking of the protein models with garcinone E, triterpenoid, and gallic acid in the appropriate manner. The protein-phytocompound complexes of p53-garci-none E, caspase-3-triterpenoid, & Rb1-gallic acid were each given a docking score of 3.873, 4.321, and 3.051, respectively.The proteins were able to form a secure link with the phyto-compounds. Research on the interaction between proteins & phytocompounds will be beneficial to the development of novel pharmaceutical drugs, as stated in the conclusion of the preceding paragraph.

According to the findings of a number of investigations, the curcumin analogues have demonstrated antiviral effectiveness against SARS CoV-2. Take, for example, (Gonzalez-Paz *et al.* 2020, Sherif *et al.* 2021) conducted molecular docking for phytochemical compounds against 3CL-Protease of COVID19, and they found

curcumin had best docking score. Furthermore, (Bhaliya *et al.* 2020) screened the series of curcumin analogues against 3CL-Protease of COVID19 to identify potent treatment against COVID19 (Rampogu *et al.* 2022). Other researchers attempted to evaluate the impact of curcumin against to a variety of SARS-CoV-2 proteins. They suggested that curcumin has the potential as an antiviral against COVID-19 via running the docking and simulation studies (Suravajhala *et al*. 2021).

3. MATERIALS AND METHODS

3.1 Calculations Models

3.1.1 Ground state predications

It was suggested that the compunds in Figure 3.1 could prevent cancer. In this work, Gaussian 09 was utilized in conjunction with density functional theory (DFT) (Plata *et al.* 2015). The 6-311G* basis set was used, and the B3LYP function was used as the exchange-correlation function (Salman *et al.* 2019). The energy of the highest occupied molecular orbital (EHOMO), the energy of the lowest unoccupied molecular orbital (ELUMO), Egap = EHOMO- ELUMO, global hardness (η), global softness (η), electrophilicity index (ω), and dipole moment (μ) were computed, among other chemical parameters (Lee *et al.* 1988).

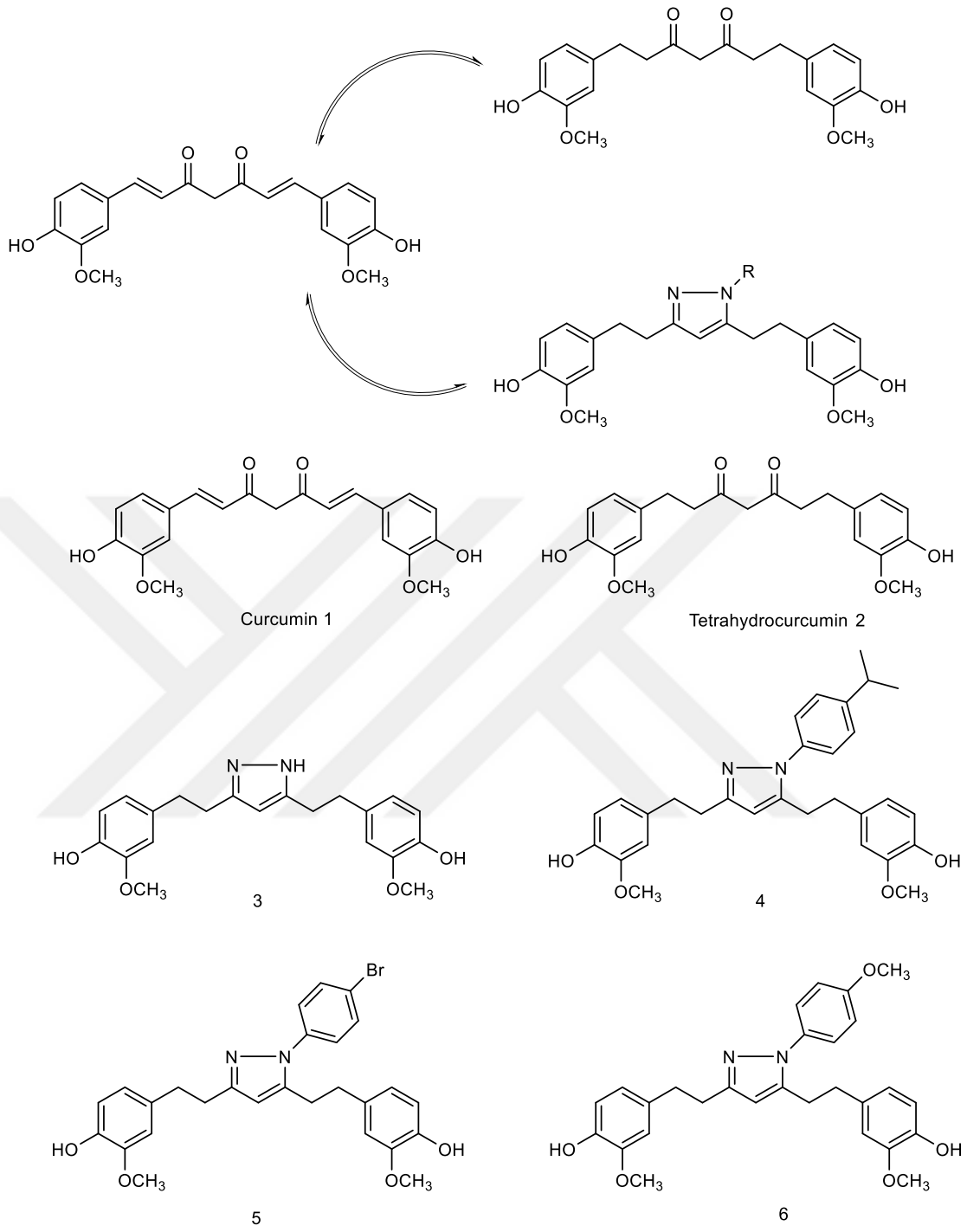

Figure 3.1 The basic mechanisms and 2D structures for the studied chemicals

3.1.2 Physical properties

- Charge of the atom

Electrostatic (polar) or orbital cooperation in chemistry (covalent). Electrostatic collaboration is made possible by the presence of electric charges inside the particle. Many chemical reactions and the physical characteristics of substances are influenced by the local electron density or charge density. The densities of local electrons or charges are necessary and respond to the physical and chemical properties of compounds. Along these lines, depending on the parameters of charge for measuring molecular activity. As an outcome, there are numerous techniques for calculating the partial charges. Mulliken populace investigation (Sayin *et al.* 2019) was utilized for the count of the charge distribution in a particle. In addition, the subatomic polarity is described using atomic charges.

- Orbital energies of the molecule

The highest occupied molecular orbital energy (E_{HOMO}) is the orbital that has an electron to contribute to bonds. On the other hand, the lowest unoccupied molecular orbital energy (E_{LUMO}) is the deepest (lowest energy) orbital that may take electrons, making it a potential electron acceptor. According to the border molecular orbital theory, the interaction between the two orbitals (HOMO and LUMO) of reactants determines the structure of a transition state. The design of a transition state is the result of this collaboration (Radhi *et al.* 2020). Both the ionization potential of the HOMO and the electron affinity of the LUMO can be identified based on their respective energies. The HOMO–LUMO gap, also known as the difference in energy between the HOMO and LUMO states, is an essential indicator of dependability. High chemical stability is indicated by a significant HOMO–LUMO gap. The HOMO–LUMO energy hole has also been used to measure activation hardness. Because a smaller energy gap often causes a more straightforward polarization of the molecule, the subjective sense of hardness is inextricably linked with polarizability (Becke 1993).

- Dipole moment (μ)

The Net molecule polarity, or charge, is measured by the dipole moment. The product of the atom's charge and the distance between the two bound atoms is called the bond strength. A polar covalent bond's dipole moment serves as a gauge for its polarity (Lestari *et al.* 2014). The absolute value of the molecular dipole moment can be determined by adding up the dipole moments of the various bonds in the molecule (Lee *et al.* 1988).

- Ionization potential (IP)

Definition: The amount of energy needed to remove electrons from molecules or atoms in order to an anion (cation) is known as the ionization potential (Yaqo *et al.* 2020).

X + energy= X+ + e

The EHOMO's ionization potential may be calculated using the following Equation (3.1).

$$IE\ (Ionization\ potential) = -EHOMO \quad (3.1)$$

The ionization energy of atoms and molecules is a measure of their chemical reactivity. Atoms and molecules with high ionization energy are more stable, whereas those with low ionization energy are more reactive (Yaqo *et al*. 2020). Higher activity is from low ionization energy.

- Electron affinity (EA)

When an electron is brought into a system and an antimatter particle is produced, the amount of energy released is referred to as electron affinity (EA) (Yaqo *et al.* 2020).

X + e- = X - + energy

Electron affinity related to ELUMO is shown in Equation (3.2).

$$EA\ (Electron\ affinity)\ =\ -ELUMO \tag{3.2}$$

When reacting with electrophiles, the more reactive molecule has greater HOMO energy, whereas nucleophiles need a lower LUMO energy (Khadom *et al.* 2021).

- Chemical hardness (η)

The resistance of an atom to a charge transfer is measured by chemical hardness (η) (Peters *et al.* 1998). Hardness is an imperative property to quantify molecular stability and reactivity. A hard particle has a considerable energy gap (Khadom *et al.* 2021). It can be calculated by utilizing the Equation (3.3):

$$\eta(Hardness) = (IE - EA)/2 \tag{3.3}$$

- Chemical softness (S)

Chemical softness (S) is the ability of an atom or group of atoms to accept electrons, and it is the inverse of global hardness (Khadom *et al.* 2021). Softness is a measure the molecular reactivity and stability. Molecules with high values of softness have a small energy gap (Hussein *et al.* 2020). It calculates by Equation (3.4).

$$S\ (global\ softness)\ =\ 1/\eta \tag{3.4}$$

- Electronegativity (χ)

In the theory of chemical reactivity, electronegativity is advantageous. Definition: It is the capacity to attract electrons from atoms or a collection of them (Khadom *et al.* 2021). It is calculated by the following Equation (3.5):

$$\chi(electronegativity) = (IE + EA)/2 \quad (3.5)$$

The higher the electronegativity, the less active it is (Hussein *et al.* 2020).

3.2 Autodock Calculations

In the present investigation, software programs such as Molecular Graphic Laboratory (MGL) and Gaussian View were utilized. (09). The geometrical optimization of the compounds using the (6-311G) basis set was proposed by the Density Functional Theory (DFT) (Becke 1993). LDH-5 cancer cells were identified as a prospective target for inhibition by the complexes that are the subject of this study. (Research Collaboratory for Structural Bioinformatics) RCSB (Berman *et al.* 2000) The information necessary to determine the protein's structure was obtained by employing (5NQR). Through the use of autodock tools, Each component's LDH-5 and drug locations have been established. (ADT, version 1.5.6). ADT (files with the extension *.pdbqt) can be used to determine the structure of proteins or their complexes. During the process of computing, both polar hydrogen atoms or Gasteiger charges are taken into consideration. In the event that the user does not specify the root of the molecule, It will be determined by the Autodock on its own. Autodock used an automated procedure to choose the root (Radhi *et al.* 2020) correctly calculated the atomic affinity maps and electrostatics for every single ligand atomic group using Autogrid (version 4.2.6). Displaying the interactions that take place between the cell & its complexes is the job of the DSV program.

4. RESULTS AND DISCUSSION

4.1 Converge Theoretical and Experimental Results

This part inserts to improve the theoretical values from experimental according to reference (Radhi *et al.* 2020). Compound 3 was used as the standard in this study. DFT method and (6-311G) basis set were used to estimate the nuclear magnetic resonance (NMR). The prediction results with experimental shown in Table 1. Whereas Figure 2 included values of R^2 (coefficient of determination). R^2 explains the convergence in two values groups and the best convergence when going to number (1). From this experiment, the R2 value is (0.9992) Figure 4.1 and Table 4.1. As result, the theoretical part of the current study approved the correct estimations.

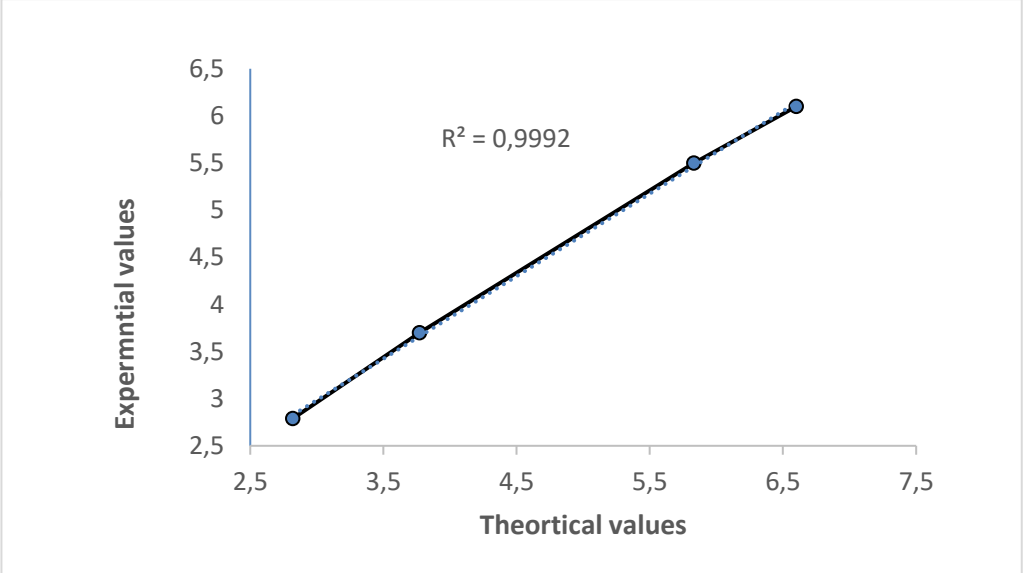

Figure 4.1 NMR values in theoretical and experimentally studies

Table 4.1 ^{1}H-NMR theoretically and experimentally values of compound 3

Functional groups	Theoretical values	Experimental values OF H-NMR
m, 4H, ArH	6.10	6.60
s, 1H, C4-H	5.5	5.83
s, 6H, OMe	3.70	3.77
bs, 8H, 4CH2	2.79	2.82

m, multi, s, single,

4.2 Activity and Molecular Orbitals

These chemicals' action (Khazaal *et al.* 2020) within the context of the physical characteristics that they possess in this section Table 4.2. The value of ELUMO drops from 2 to 1, then from 5 to 1 to 5, then from 3 to 4, then ultimately from 5 to 6. The energy gap between the HOMO and LUMO orbitals was discovered to follow the order 1 > 2 > 5 > 3 > 4 > 6, which emphasizes the pattern of activity even more. Ionization energy, or IE, is the amount of energy needed to rip an electron out of an atom. To optimize activity, ionization energy has to be below (Allouche 2011).

$$IE = -E_{HOMO} \quad \text{.....(1)}$$

The compounds under investigation are ordered in order of action by the IE: 3 > 6> 4 > 5 > 1> 2.

Hardness (η) (Radhi *et al.* 2020) is a measure of a molecule's reactivity and stability that is represented as the second derivative from the molecule's energy.

$$\eta = \frac{IE-EA}{2} \quad \text{....(2)}$$

The sequence is as follows, according to η:

1 > 2> 5 > 3 > 4> 6

The global softness (S) (Radhi *et al.* 2020) is the quality that opposes the global toughness. The degree of a molecule's softness is one of the most important factors in influencing both its stability and its reactivity.

$$S = \frac{1}{\eta} \quad \text{.....(3)}$$

The sequence, according to S, is:

6 > 4> 3 > 5 > 2> 1

When inhibition has a large value, it is more effective for the dipole moment (μ) (Khadom *et al.* 2021). Hence, the correct series of events is as follows:

2 > 1> 6 > 3 > 5> 4

Compounds C and THC were the most active after these circumstances, followed by compounds $THCN_3$ and THC. They will thus consider this in the following section.

Table 4.2 The DFT method was used to estimate the quantum chemical characteristics of the inhibitor molecules while they were in a vacuum

Comp.	**E_{HOMO}[a]**	**E_{LUMO}[a]**	**IE[a]**	**E_{gap}[a]**	**η[a]**	**S[b]**	**μ[c]**
C	-5.63125	-1.67381	5.631251	3.957441	1.978721	0.505377	6.9638
THC	-8.26727	-3.81131	8.267278	4.455965	2.227983	0.448837	7.1497
THCN	-5.42634	-0.31103	5.426345	5.115312	2.557656	0.390983	5.8587
THCN1	-5.50580	-0.22123	5.505804	5.28457	2.642285	0.37846	4.9986
$THCN_2$	-5.57465	-0.59158	5.57465	4.983061	2.491531	0.40136	5.3485
$THCN_3$	-5.47423	-0.08190	5.474238	5.39233	2.696165	0.370897	6.2059

a: in eV, b: in eV^{-1}, c: in Debye.

This is illustrated in Figure 4.2, which depicts the optimization of molecule morphologies in the gas phase, as well as the distribution of LUMO and HOMO density. The color green represents a low electron density, whereas the color red represents an electron density that is elevated (Berman *et al.* 2000). Metal surfaces with a high electron density have the ability to absorb electrons from atoms in close proximity to them. Electrons are amassed in the Green area of the spectrum. In other words, the division of labor between these two areas is of the utmost importance. The presence of an oxygen atom in the ring is responsible for the increased electron density found at the receptor site for compound THC. On the other hand, chemical 1 appears to attach itself to O atom receptors while simultaneously giving the cell C atoms. In

compound $THCN_3$, The oxygen atom has a similarly high electron density. The receptor site is mainly composed of atoms of carbon and nitrogen.

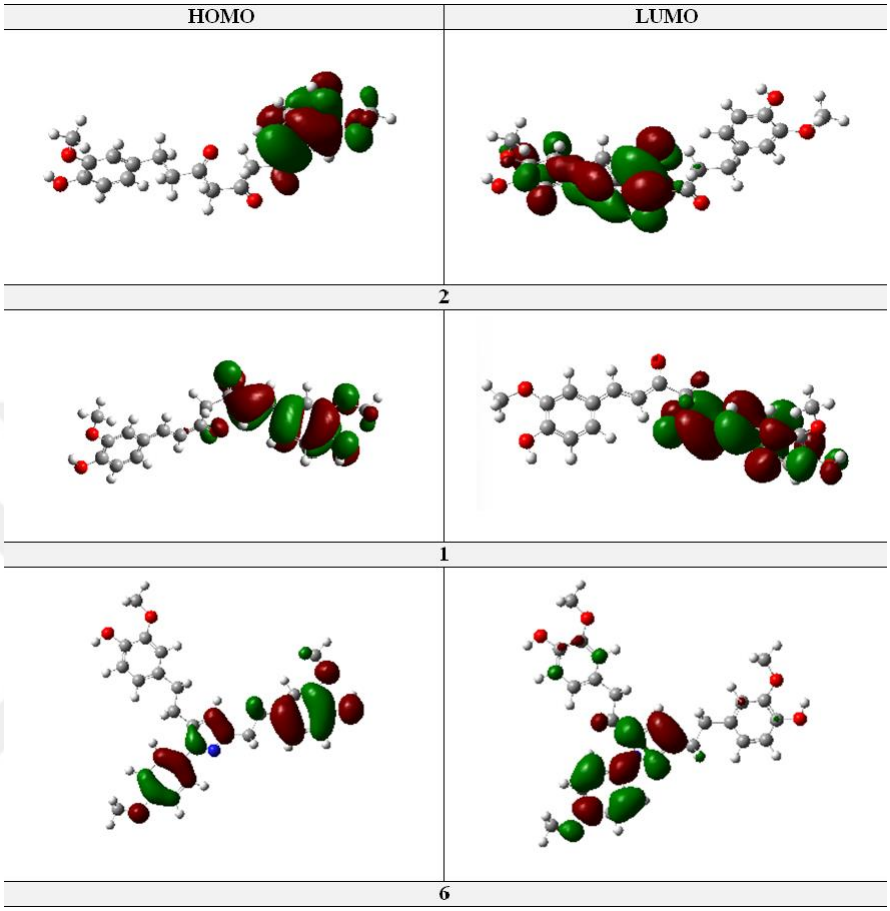

Figure 4.2 Energy levels Orbitals of the most researched inhibitors in the HOMO and LUMO shells (C, THC and $THCN_3$)

4.3 TED Map of the Studies Compounds

The inhibitors that were discussed in sections THC, C, and $THCN_3$ are the ones that are most likely to be found in this area. The total electron density (TED) can be approximated by calculating the number of electrons that are present in a given area. The atoms C and O, which are represented by the color red, are shown to be the most electronegative in the molecules shown in Figure 4.3. The color blue comprises a greater number of positive sites, each of which has the ability to take an electron from the donor (Khazaal *et al.* 2020). The presence of charges has an effect on the physicochemical properties that are exhibited by the reactions (Yaqo *et al.* 2020,

Khadom *et al.* 2021). The electrophilic attack on compounds C, THC, and $THCN_3$ showed that the carbon of carbonyl groups, the carbon atom, and the hydrogen atom were the most reactive sites that were able to accept electrons Figure 4.3 and Figure 4.4.

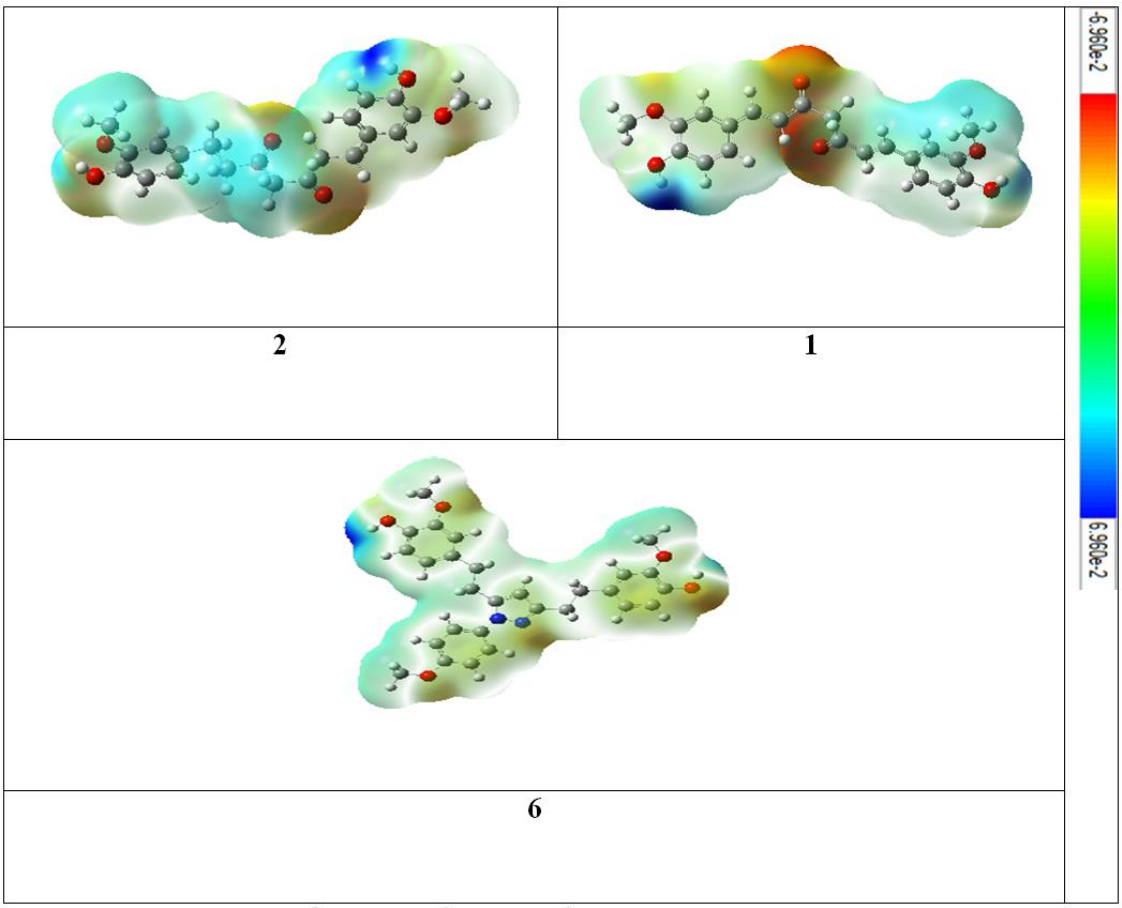

Figure 4.3 TED maps of compounds THC, C, and $THCN_3$

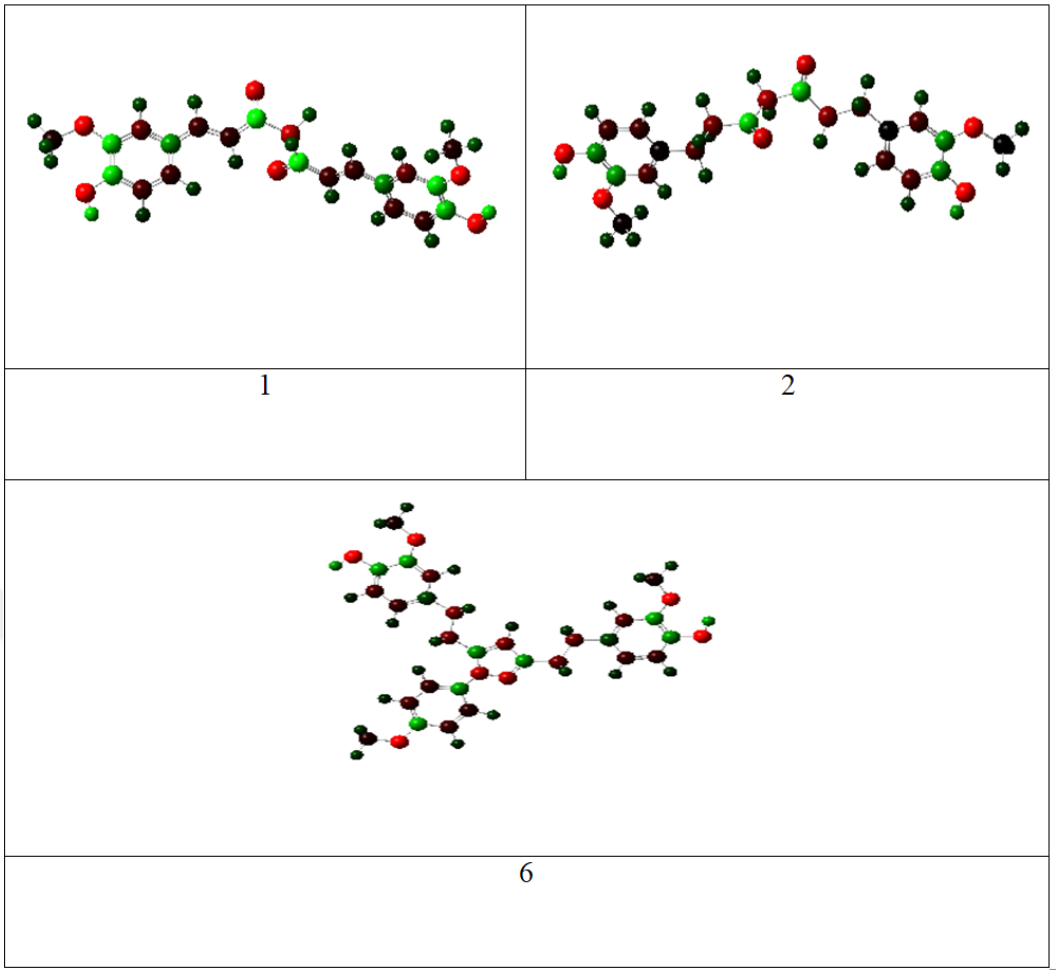

Figure 4.4 Distribution of Millikan charges on compounds structures

4.4 Docking Results

Evaluation of the cancer-fighting capabilities of compounds one through six has been completed. Because of the diverse array of substrates that are amenable to being processed by NUDIX hydrolases, this family of nucleotide-metabolizing enzymes has recently been recognized as a significant contributor to the field.NUDT5, often referred to as NUDIX5, has been shown to play a role in the metabolic processes involving ADP-ribose and 8-oxa-guanine. This activity of the protein functions as a rheostat, regulating the expression of hormone-dependent genes and the proliferation of breast cancer cells. In this work, researchers are looking into known NUDT5 substrates to learn more about how NUDT5 influences gene expression and how it helps breast cancer cells grow and spread. This study reveals that NUDT5 is involved in the

metabolic process of ADP-ribose, but, it does not show any link to the elimination of oxidized nucleotides from the cell. The finding of potent NUDT5 inhibitors has led to a significant improvement in CETSA's ability to bind to NUDT5 cellular targets. This improvement was made possible as a direct consequence of the discovery of NUDT5 inhibitors. Compounds known as curcuminoids are capable of suppressing the ability of breast cancer cells to create progestin-dependent, PAR-derived nuclear ATP and the processes of chromatin transformation, gene regulation, and proliferation that are directly related to this ability. Our disclosed curcuminoids extract is a highly selective inhibitor of NUDT5 activity and ADP-ribose metabolism that may be used in future studies.

(Berman *et al.* 2000) The Protein Data Bank was utilized so that the crystalline form could be found in order to make the discovery. (5NQR). Binding energy Eb and ligand efficiency LE are two parameters that can be used to describe NUDT5 function in relation to inhibitors. Each of these measurements evaluate a substance's affinity for a receptor protein (receptor) binding energy per atom of ligands. Compounds 1, 2, and 6 have a larger ability to inhibit NUDT5 than the other chemicals do. This can be deduced from the values of their Eb, which are expressed in Kcal/mol Table 4.3.

There is a preferred receptor binding site (L=1–10) for each of the three substances (C, THC, and $THCN_3$), with L2 and L10 being the most prevalent Figure 4.5. The list of substances that follow is presented in the order in which they are most effective at inhibiting LDH-5: 1> 6 > 2

Table 4.3 Values for the binding energy and ligand efficiency of the substances under study

Comp.	E_b	L_E	Best local	RMS
C	-4.24	-0.16	2	13.04
THC	-2.86	-0.11	10	14.10
$THCN_3$	-3.52	-0.10	4	12.46

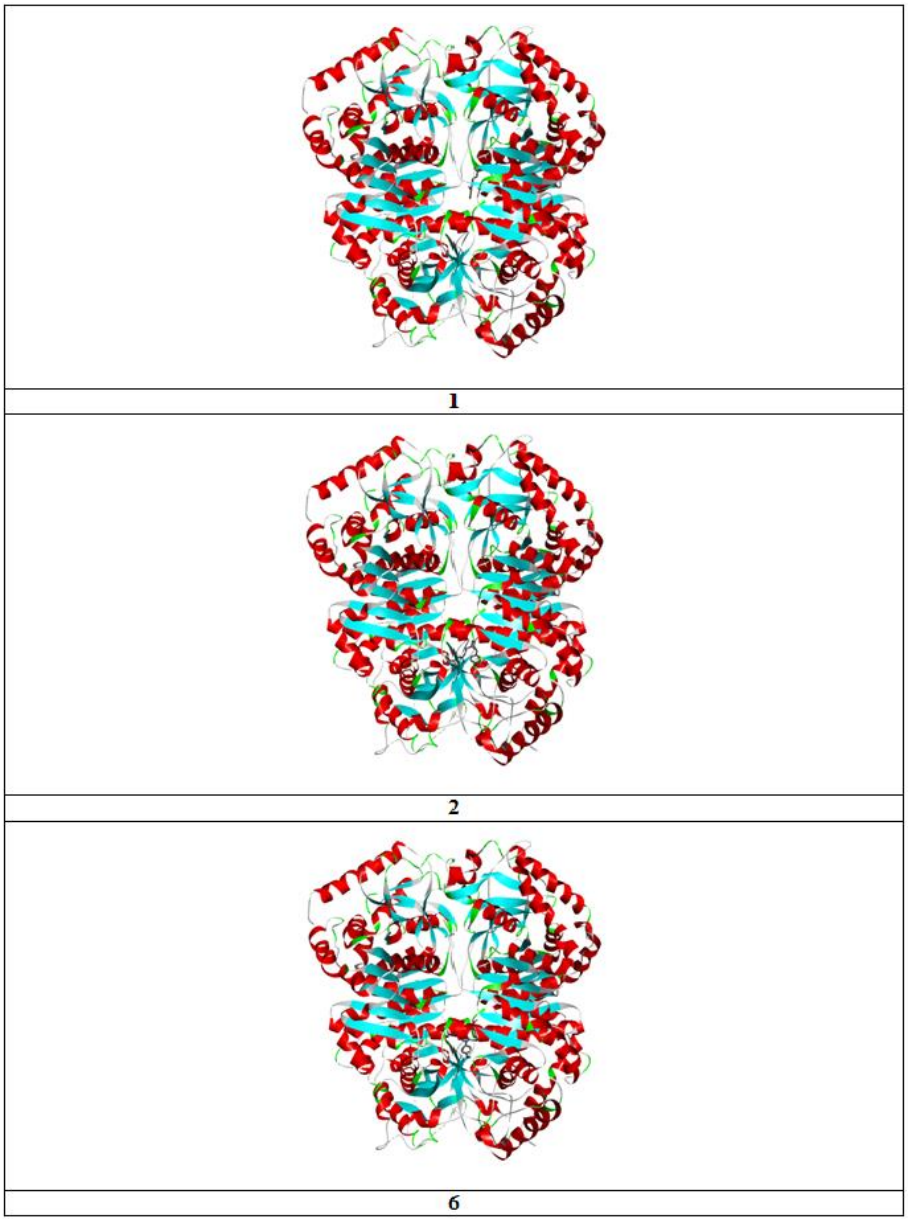

Figure 4.5 Compounds C, THC, and $THCN_3$ interacting with the receptor

4.5 The Molecules Interactions

It has been demonstrated that receptors have active areas that are able to both take in and give out hydrogen bonds. The compounds that were studied Figure 4.6 contain C atoms that have a donor density of electrons. These electrons are responsible for the formation of hydrogen bonds. The density, on the other hand, is typically accepted by the other atoms. In addition, the substances that were studied have both hydrophilic and hydrophobic characteristics. Figure 4.7 demonstrates that the hydrophilic, represented

by the color blue, and the hydrophobic, depicted by the color white, each have unique values Figure 4.7.

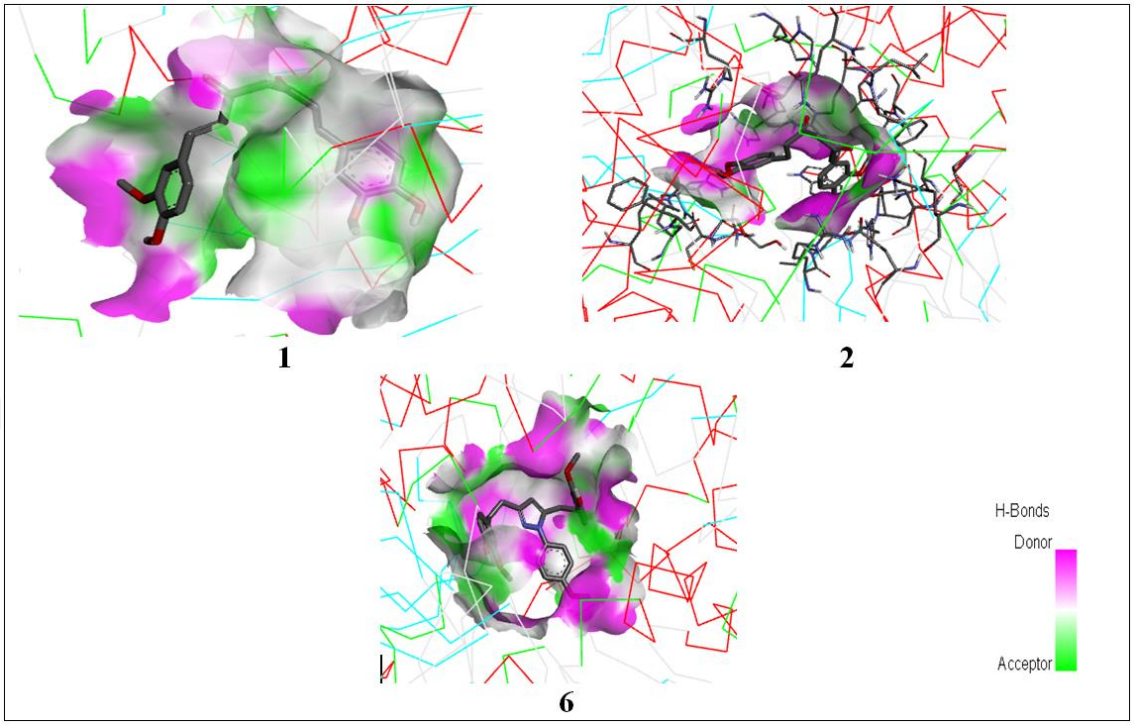

Figure 4.6 Sites for forming and accepting H bonds in the spikes' structure

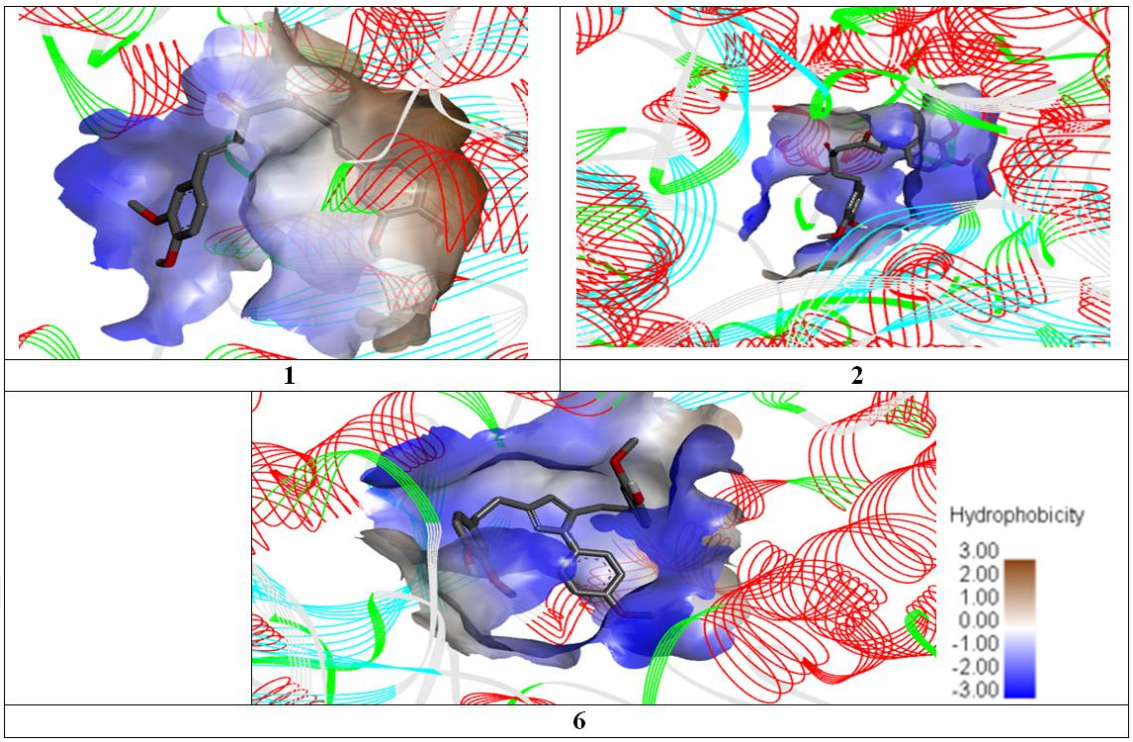

Figure 4.7 The connecting region of inhibitors and spikes, respectively, contains hydrophilic and hydrophobic sites

4.6 Two Dimension Structres

The most effective compounds C, THC, and $THCN_3$ were investigated. Compound C contains four different interaction sites when it comes to protein. The linking of the oxygen and hydrogen atoms by a hydrogen bond with (SER, and SYR). In addition, alkyl types, Vander vals, and amide-pi stacking bonds can be discovered Figure 4.8.

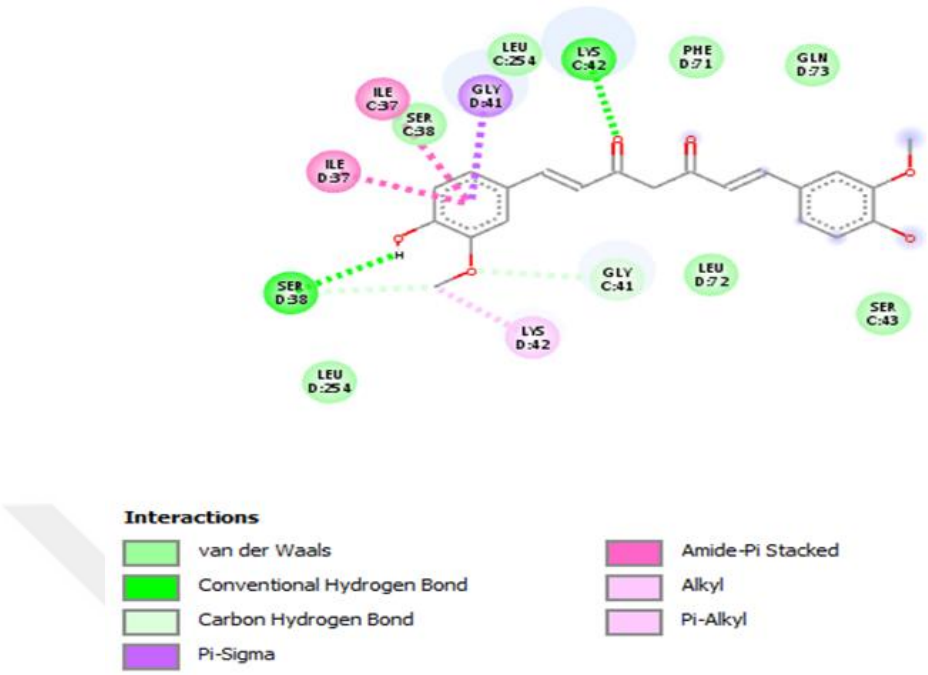

Figure 4.8 Two dimensions structures of the studied compound C

Whereas compound THC may have any of the four possible forms of linkages to its constituent parts. Hydrogen bonds between (ASN, SER, and ARG), in addition to a carbon-hydrogen relationship with SER, but the contact with the HIS amino acid is a Vander Waals force Figure 4.9.

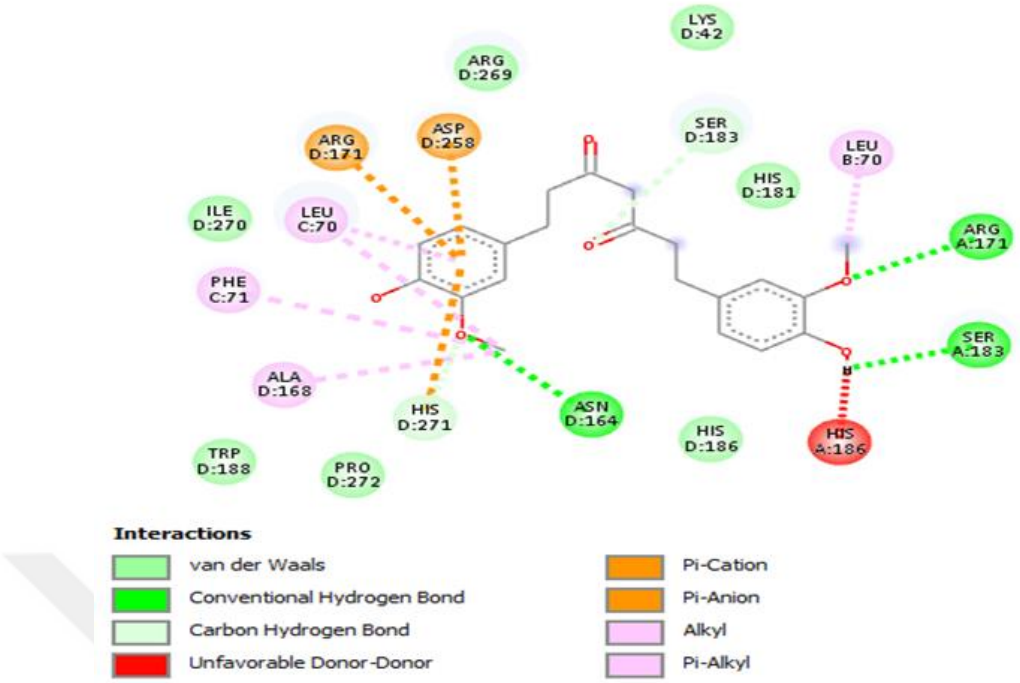

Figure 4.9 Two dimensions structures of the studied compound THC

Furthermore, the linkages in the structures of compounds $THCN_3$ and THC are identical, making them structurally equivalent. By three hydrogen bonds with (LYS, GLN, LEU). As can be observed in Figures, respectively, the number of linkages in compound 2 is quite high, whereas the number of linkages in compound $THCN_3$ is not quite as high Figure 4.10 (Khadom *et al.* 2021, Al-Janabi *et al.* 2021, Kadhim *et al.* 2021).

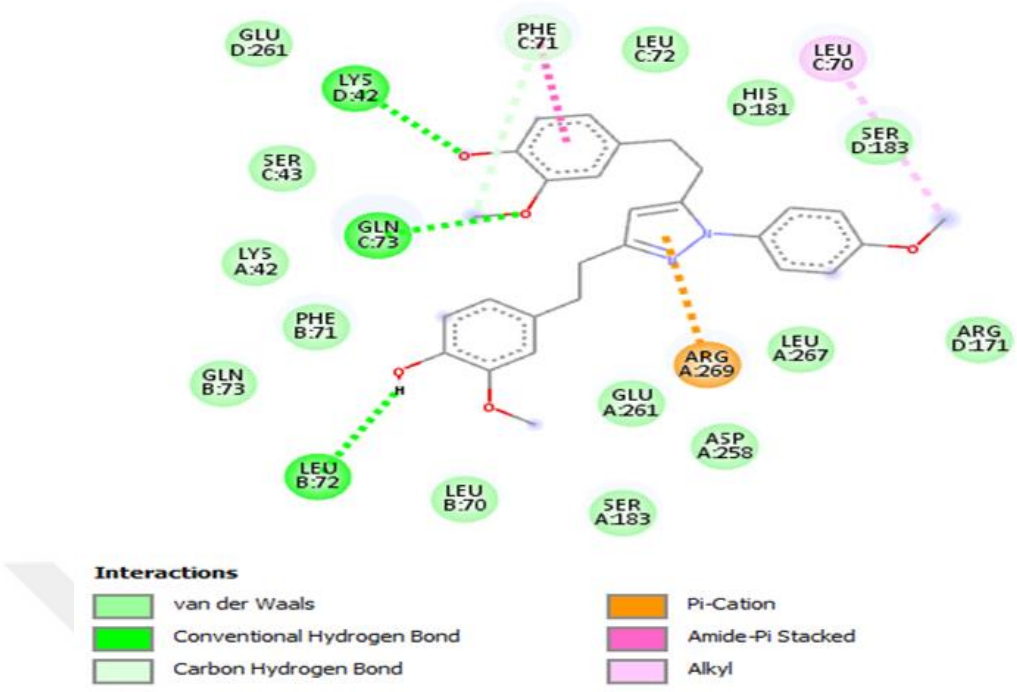

Figure 4.10 Two dimensions structures of the studied compound $THCN_3$

4.7 Less Effective Compounds

The compounds have a lower level of action (THCN, $THCN_1$, and $THCN_2$). In the field of computational chemistry, two of the most significant challenges are the optimization of gas-phase molecule morphologies and the estimation of LUMO or HOMO density distributions. These tasks are often performed using quantum chemical methods. A number of different approaches, including as density functional theory (DFT), ab initio methods, or semi-empirical approaches, can be utilized in order to achieve the goal of optimizing the form of a molecule that exists in the gas phase. These methods take into account the electronic structure of the molecule, as well as its geometry, and attempt to find the most stable configuration. n some cases, red is indeed used to represent high electron density, while blue or green is used to represent low electron density. However, in other cases, the colors are reversed or a different color scheme is used altogether Figure 4.11.

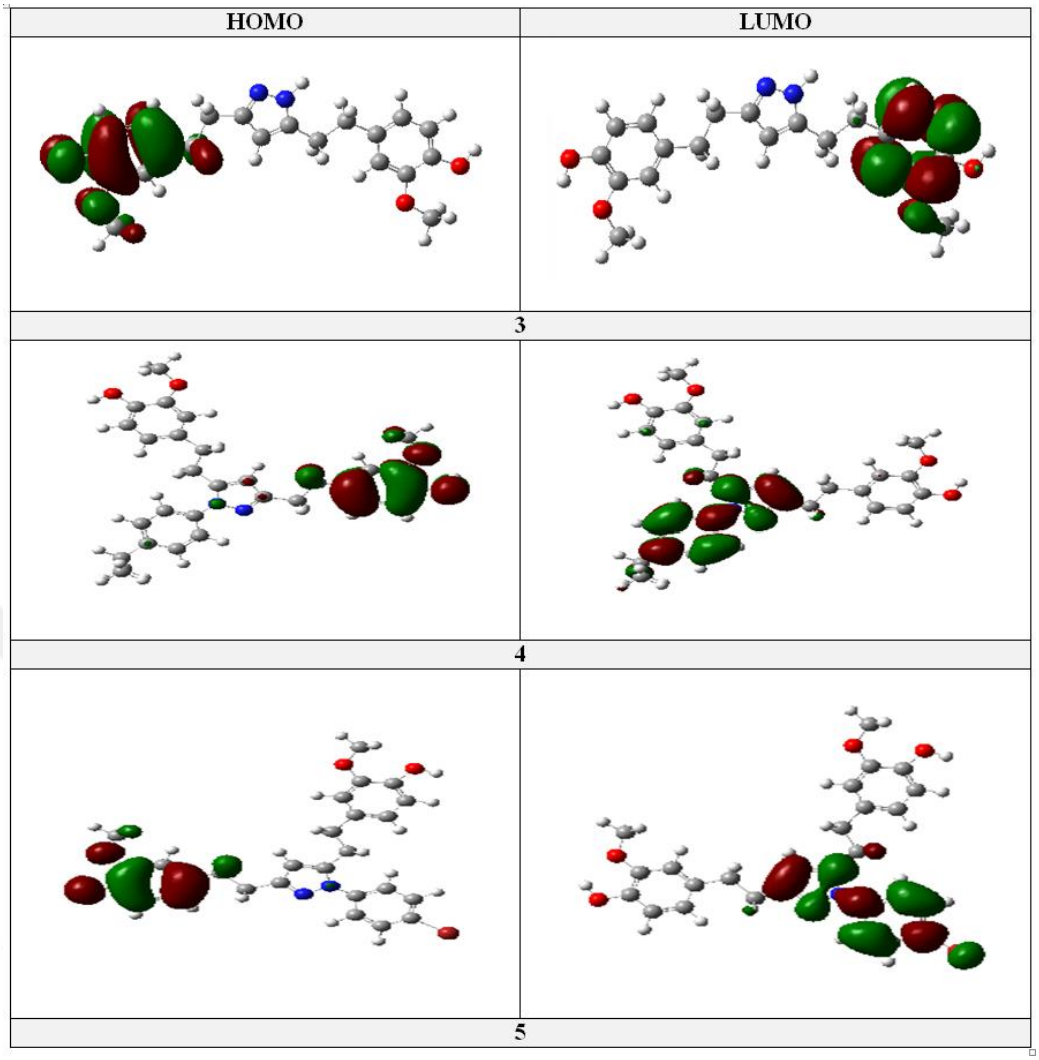

Figure 4.11 HOMO-LUMO orbitals of (THCN, $THCN_1$, and $THCN_2$) compounds

Now the TED of (THCN, $THCN_1$, and $THCN_2$) compounds in Figure 4.12. Some Carbone and Oxygen atoms, The atoms in the molecules with the highest electronegative charge are represented by the color red. In addition, blue contains a greater number of positive sites, which have the potential to absorb donor electrons. It predicat in DFT as in Table 4.2 and docking models.

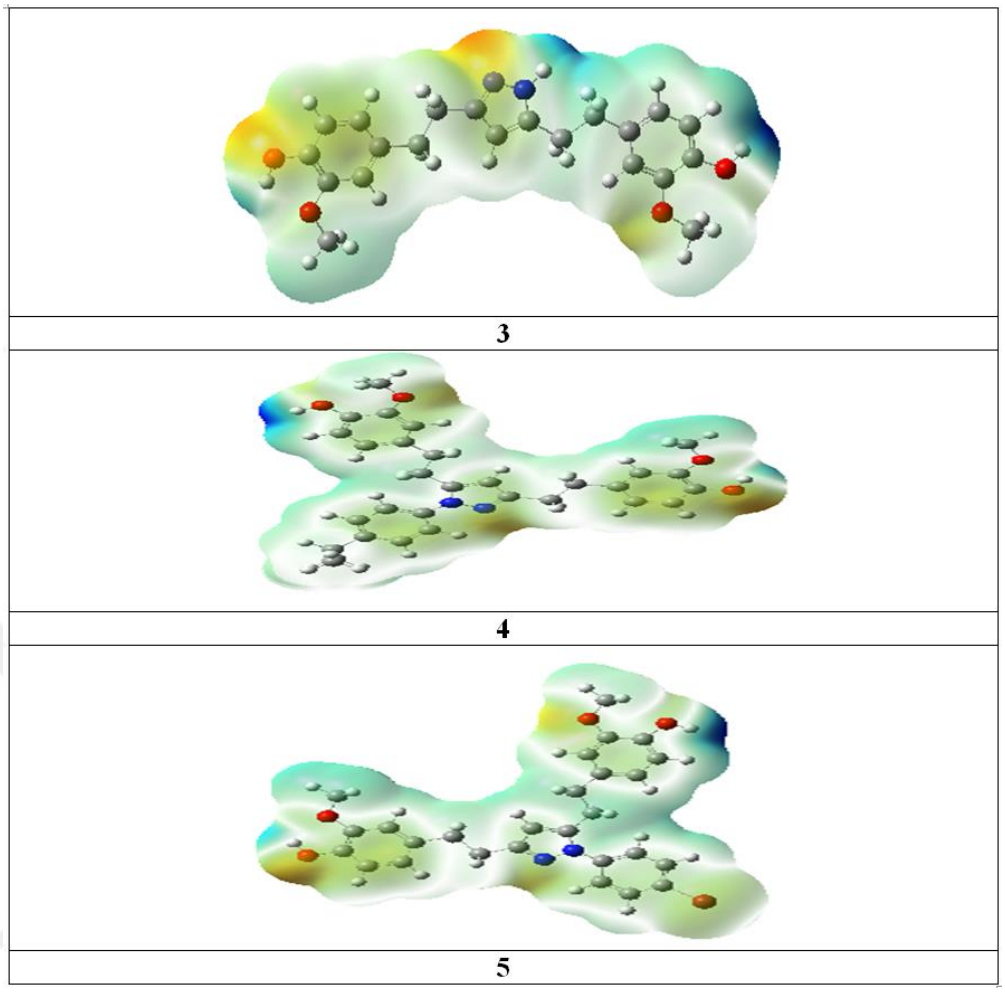

Figure 4.12 TED map of (THCN, $THCN_1$, and $THCN_2$) compounds

Table 4.4 present the values of the Eb and LE of the compounds (THCN, $THCN_1$, and $THCN_2$). Accordind to Eb values, its from docking models It has shown that the harmful compounds act as anti-cancer compounds, as shown in Figure 4.13 respectively. The most effective compounds C, THC, and $THCN_3$ were investigated. Compound C contains within it four interaction sites for protein.

Table 4.4 The amounts of ligand efficiency or binding energy that were measured for the compounds that were looked at (THCN, $THCN_1$, and $THCN_2$)

Comp.	E_b	L_E	Best Local	RMS
THCN	-1.59	-0.06	2	11.07
$THCN_1$	-1.89	-0.05	7	17.10
$THCN_2$	-1.46	-0.04	4	13.48

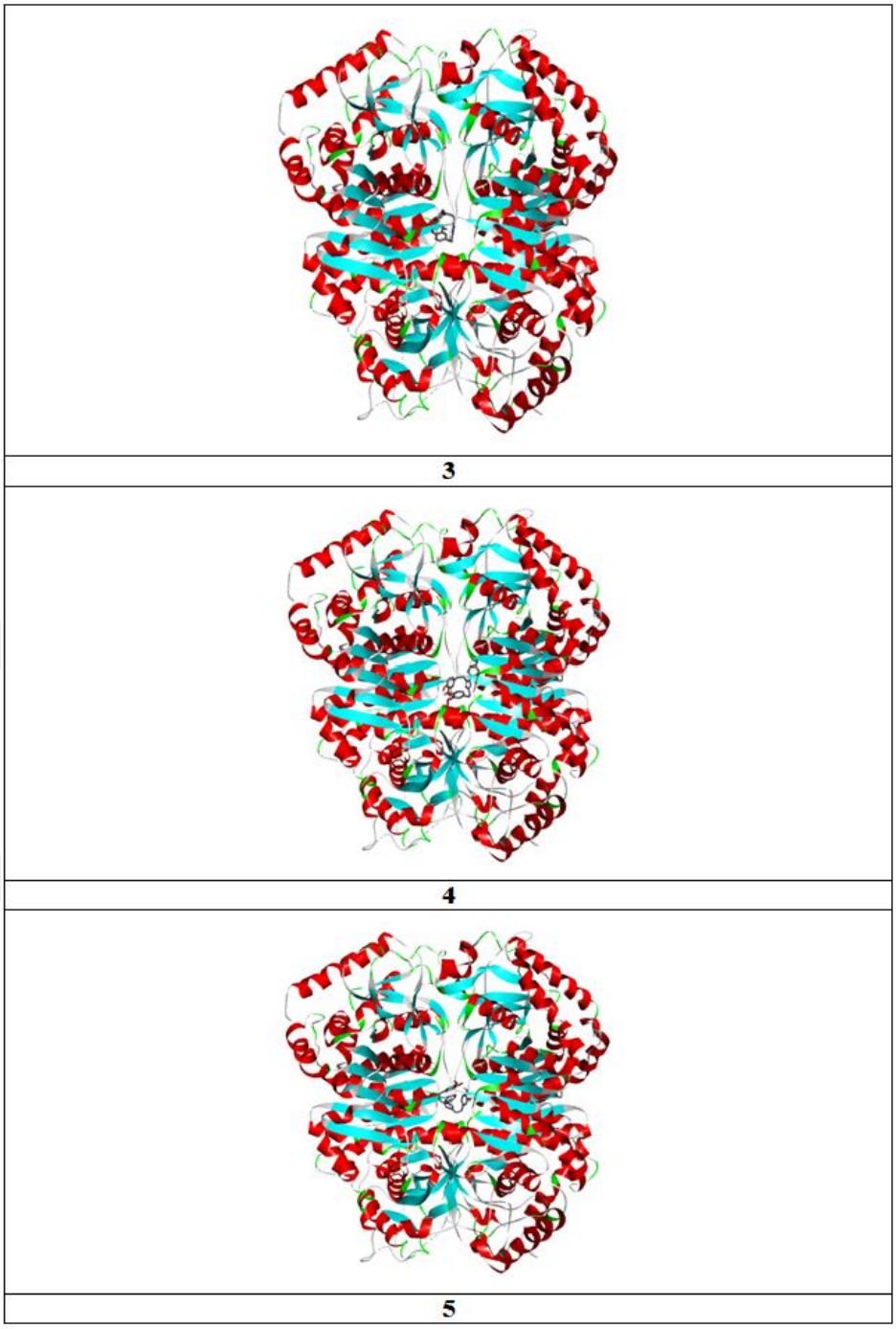

Figure 4.13 Interactions of compounds THCN, $THCN_1$, and $THCN_2$ with the receptor

The two dimension intractions of protien with ligand (THCN, $THCN_1$, and $THCN_2$). The N and H atom linkage by a hydrogen bond with (LYS and GLY) and Pi-cation with (LYS) of compund THCN Figure 4.14.

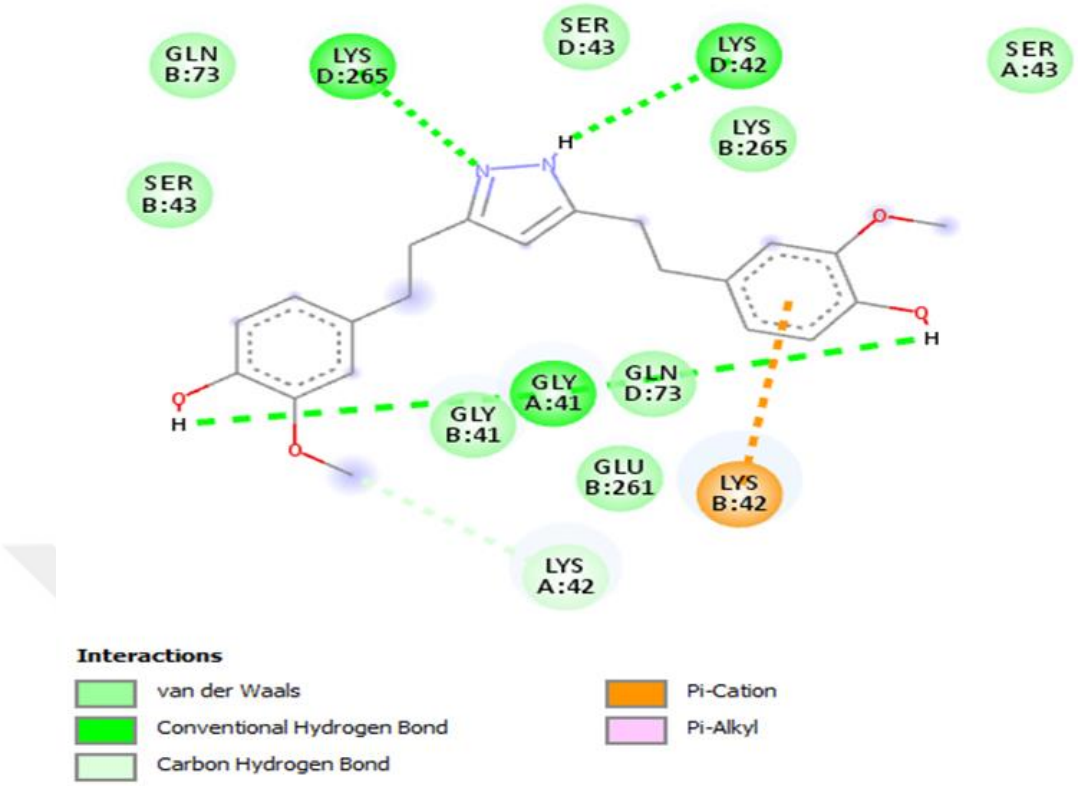

Figure 4.14 Tow dimensions structure with intreactions of compound THCN

While compound $THCN_1$ can be found to exist in three different linking forms. Hydrogen bonds to (GLY, LYS), as well as carbon-hydrogen interaction with LYS, whereas LYS is involved in Pi-cation interactions Figure 4.15.

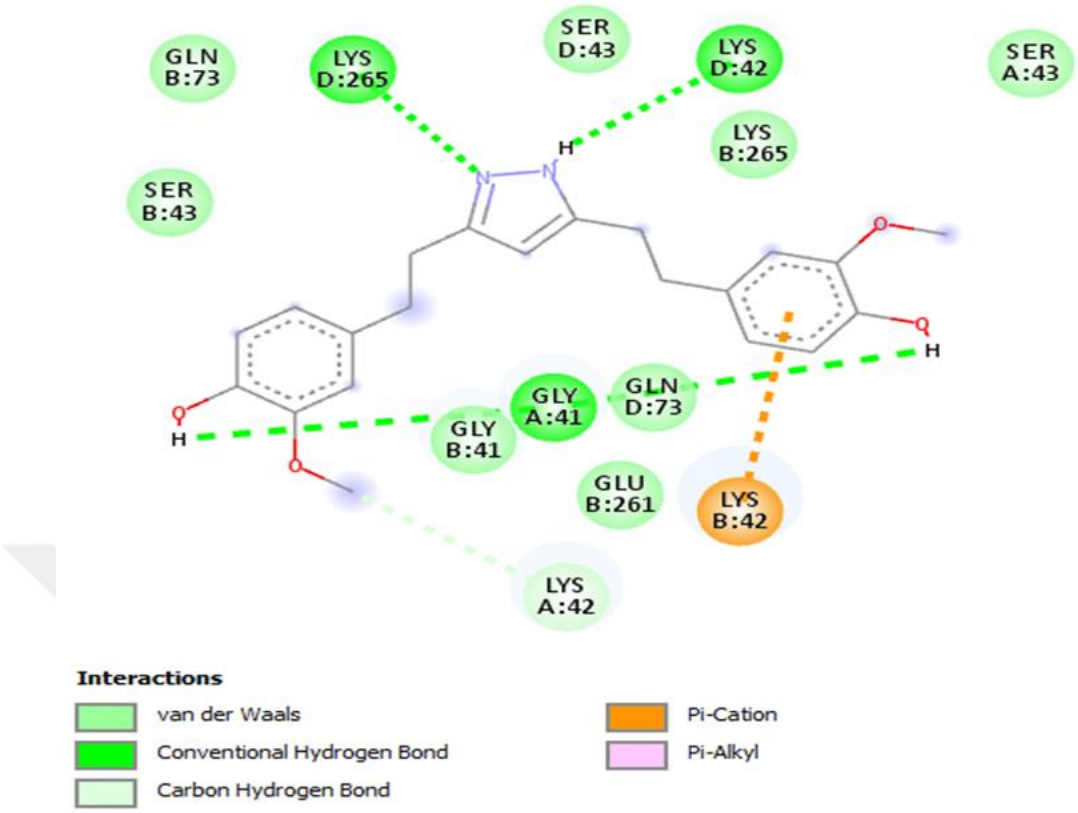

Figure 4.15 Tow dimensions structure with intreactions of compound $THCN_1$

In addition to this, the structure of compound $THCN_2$ features a coupling of hydrogen via LYS that has been seen. Also, the Vander Vales with GLN Figure 4.16.

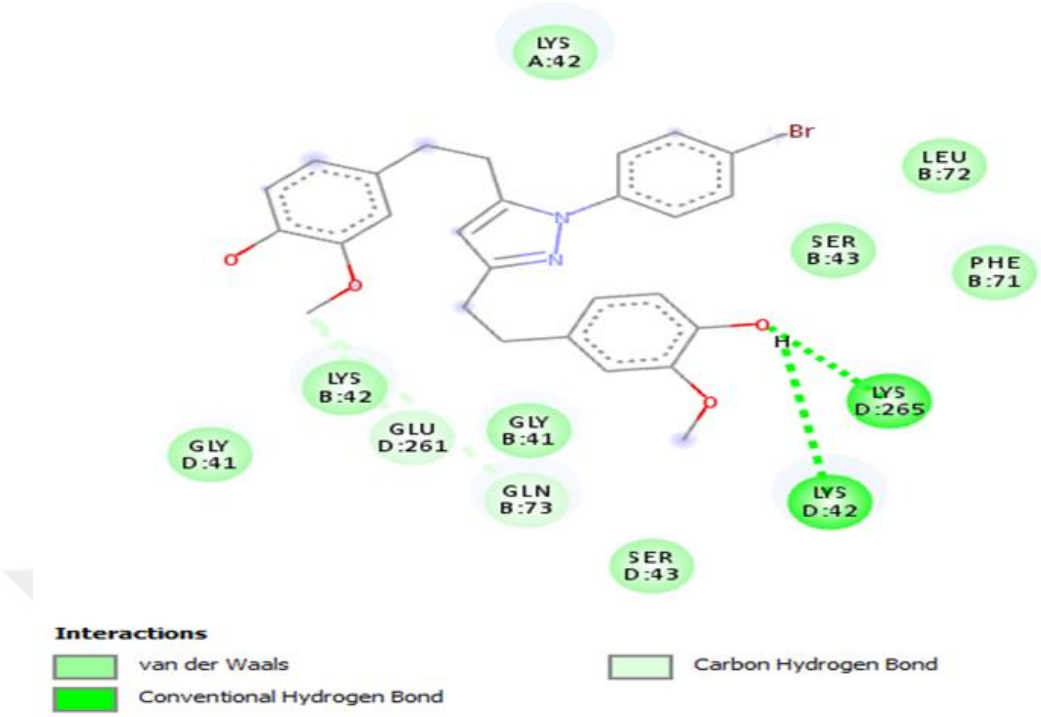

Figure 4.16 Tow dimensions structure with intreactions of compound $THCN_2$

5. CONCLUSIONS AND RECOMMENDATION

5.1 Conclusions

An anticancer (breast cancer) role for new compounds 1-6 is proposed . Results from ^{1}HNMR validated R^{2}'s docking values. DFT studies were carried out to investigate some of the physical properties of the compounds. They proved the high level of activity of Compounds C, THC, and $THCN_3$. Based on TED and ESP maps, theoretical simulations predicted that oxygen, nitrogen, and chloride atoms in all of the compounds studied would have the highest electron densities. The Autodock study discusses the compounds' potential as anticancer medications as well as the superior efficacy of the identical molecules C, THC, and $THCN_3$, and the least effective inhibitory positions it is THCN, $THCN_1$, and $THCN_2$.

5.2 Recommendation

Based on the obtained results from this study, there is ongoing research aim at the development of potent anticancer agents based on the modification of the natural products and study the binding affinity using the molecular docking and employing the DFT calculations to predict the activity stability and electron properties of these compounds leading to more understand the structure of these.

REFERENCES

Abdel-Jalil, R. J., Steinbrecher, T., Al-Harthy, T., Mahal, A., Abou-Zied, O. K. and Voelter, W. 2015. Stereoselective synthesis and molecular modeling of chiral cyclopentanes. Carbohydrate Research, 415: 12-16.

Aggarwal, B. B., Kumar, A. and Bharti, A. C. 2003. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Research, 23(1/A): 363-398.

Ahsan, M. J., Choudhary, K., Ali, A., Ali, A., Azam, F., Almalki, A. H. and Tahir, A. 2022. Synthesis, DFT Analyses, Antiproliferative Activity, and Molecular Docking Studies of Curcumin Analogues. Plants, 11(21): 2835.

Ali Salman, G., S. Zinad, D., Mahal, A., Rizki Fadhil Pratama, M., Duan, M., Alkhouri, A. and Alamiery, A. 2022. Synthesis, Antibacterial Activity, and Molecular Docking Study of Bispyrazole-Based Derivatives as Potential Antibacterial Agents. Chemistry Select, 7(4): e202103901.

Al-Janabi, A. S., Kadhim, M. M., Al-Nassiry, A. I. and Yousef, T. A. 2021. Antimicrobial, computational, and molecular docking studies of Zn (II) and Pd (II) complexes derived from piperidine dithiocarbamate. Applied Organometallic Chemistry, 35(2): e6108.

Allouche, A. R. 2011. Gabedit—A graphical user interface for computational chemistry softwares. Journal of Computational Chemistry, 32(1): 174-182.

Baker, M. 2017. Deceptive curcumin offers cautionary tale for chemists. Nature, 5(41): 7636.

Becke, A. D. 1993. Density-Functional Thermochemistry. III. The Role of Exact Exchange. Journal Chemical Physics, 98: 5648-5652.

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H. and Bourne, P. E. 2000. The protein data bank. Nucleic Acids Research, 28(1): 235-242.

Bhaliya, J. and Shah, V. 2020. Identification of potent COVID-19 main protease (Mpro) inhibitors from curcumin analogues by molecular docking analysis. International Journal Advantage Research Ideas Innovation Technology, 6: 664-672.

Cao, W., Chen, X., Chin, Y., Zheng, J., Lim, P. E., Xue, C. and Tang, Q. 2022. Identification of curcumin as a potential α-glucosidase and dipeptidyl-peptidase 4

inhibitor: Molecular docking study, in vitro and in vivo biological evaluation. Journal of Food Biochemistry, 46(3): e13686.

El-ajaily, M. M., Sarangi, A. K., Mohapatra, R. K., Hassan, S. S., Eldaghare, R. N., Mohapatra, P. K. and Al-Noor, T. H. 2019. Transition Metal Complexes of (E)-2 ((2-Hydroxybenzylidene) Amino-3-Mercaptopropanoic Acid: XRD, Anticancer, Molecular Modeling and Molecular Docking Studies. Chemistry Select, 4(34): 9999-10005.

El-Barasi, N. M., Miloud, M. M., El-ajaily, M. M., Mohapatra, R. K., Sarangi, A. K., Das, D. and Azam, M. 2020. Synthesis, structural investigations and antimicrobial studies of hydrazone based ternary complexes with Cr (III): Fe (III) and La (III) ions. Journal of Saudi Chemical Society, 24(6): 492-503.

Elengoe, A. and Sundramoorthy, N. D. 2020. Molecular docking of curcumin with breast cancer cell line proteins. Pharmaceutical and Biomedical Research, 6(1): 27-36.

Eleya, N., Mahal, A., Hein, M., Villinger, A. and Langer, P. 2011. Synthesis of Arylated Quinolines by Chemo-and Site-selective Suzuki–Miyaura Reactions of 5, 7-Dibromo-8-(trifluoromethanesulfonyloxy) quinoline. Advanced Synthesis and Catalysis, 353(14-15): 2761-2774.

Esatbeyoglu, T., Huebbe, P., Ernst, I. M., Chin, D., Wagner, A. E. and Rimbach, G. 2012. Curcumin—from molecule to biological function. Angewandte Chemieical International Edition, 51(22): 5308-5332.

Gonzalez-Paz, L. A., Lossada, C. A., Moncayo, L. S., Romero, F., Paz, J. L., Vera-Villalobos, J. and Alvarado, Y. J. 2020. Theoretical molecular docking study of the structural disruption of the viral 3CL-protease of COVID19 induced by binding of capsaicin, piperine and curcumin part 1: A Comparative Study with Chloroquine and Hydrochloroquine Two Antimalaric Drugs, 2: 34-36.

Gupta, S. C., Patchva, S. and Aggarwal, B. B. 2013. Therapeutic roles of curcumin: lessons learned from clinical trials. The AAPS Journal, 15: 195-218.

Hussain, H., Ahmad, S., Shah, S. W. A., Ghias, M., Ullah, A., Rahman, S. U. and Alghamdi, S. 2021. Neuroprotective potential of synthetic mono-carbonyl curcumin analogs assessed by molecular docking studies. Molecules, 26(23): 7168.

Hussain, I., Yawer, M. A., Appel, B., Sher, M., Mahal, A., Villinger, A. and Langer, P. 2008. Synthesis of 4-hydroxy-and 2, 4-dihydroxy-homophthalates by [4+ 2] cycloaddition of 1, 3-bis (silyloxy)-1, 3-butadienes with dimethyl allene-1, 3-dicarboxylate. Tetrahedron, 64(34): 8003-8009.

Hussein, E. A., Shaheed, I. M., Hatam, R. S., Kadhim, M. M., Al-Kadhum, D. T. and Abd AL-kareem, E. 2020. Adsorption, thermodynamic and DFT studies of removal RS dye on the Iraqi's clay from aqueous solutions. Systematic Reviews in Pharmacy, 11(3): 495-502.

Ibad, M. F., Eleya, N., Obaid-Ur-Rahman, A., Mahal, A., Hussain, M., Villinger, A. and Langer, P. 2011. Site-Selective Suzuki-Miyaura Reactions of 1, 4-and 3, 5-Bis (trifluoromethylsulfonyloxy)-2-naphthoates. Synthesis, 2011(13): 2101-2116.

Kadhim, M. M., Salman, A. W., Zarzoor, A. M. and Kadhum, W. R. 2021. Inhibition of SARS-CoV-2 reproduction using Boswellia carterii: A theoretical study. Journal of Molecular Liquids, 337: 116440.

Khadom, A. A., Kadhim, M. M., Anaee, R. A., Mahood, H. B., Mahdi, M. S. and Salman, A. W. 2021. Theoritical evaluation of Citrus Aurantium leaf extract as green inhibitor for chemical and biological corrosion of mild steel in acidic solution: Statistical, molecular dynamics, docking, and quantum mechanics study. Journal of Molecular Liquids, 343: 116978.

Khazaal, F. A., Kadhim, M. M., Husseein, H. F., Abbas, Z. M., SHamzah, M., Khudhair, I. A. and Saieed, H. S. 2020. Electronic transfers and (nlo) properties predicted by ab initio methods with prove experimentally. Neuro Quantology, 18(1): 46.

Kim, J. M., Araki, S., Kim, D. J., Park, C. B., Takasuka, N., Baba-Toriyama, H. and Tsuda, H. 1998. Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1, 2-dimethylhydrazine initiation. Carcinogenesis, 19(1): 81-85.

Kondhare, D., Deshmukh, S. and Lade, H. 2019. Curcumin analogues with aldose reductase inhibitory activity: synthesis, biological evaluation, and molecular docking. Processes, 7(7): 417.

Lakhan, S. E., Ford, C. T. and Tepper, D. 2015. Zingiberaceae extracts for pain: a systematic review and meta-analysis. Nutrition Journal, 14(1): 1-10.

Lee, C., Yang, W. and Parr, R. G. 1988. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Physical Review, 37(2): 785.

Lestari, M. L. and Indrayanto, G. 2014. Curcumin. Profiles of Drug Substances, Excipients and Related Methodology, 39: 113-204.

Liang, Y., Zhao, J., Zou, H., Zhang, J. and Zhang, T. 2021. In vitro and in silico evaluation of EGFR targeting activities of curcumin and its derivatives. Food and Function, 12(21): 10667-10675.

Limtrakul, P., Chearwae, W., Shukla, S., Phisalphong, C. and Ambudkar, S. V. 2007. Modulation of function of three ABC drug transporters, P-glycoprotein (ABCB1): mitoxantrone resistance protein (ABCG2) and multidrug resistance protein 1 (ABCC1) by tetrahydrocurcumin, a major metabolite of curcumin. Molecular and Cellular Biochemistry, 296, 85-95.

Mahady, G. B., Pendland, S. L., Yun, G. and Lu, Z. Z. 2002. Turmeric (Curcuma longa) and curcumin inhibit the growth of Helicobacter pylori, a group 1 carcinogen. Anticancer Research, 22(6C): 4179-4181.

Mahal, A. 2015. Oxetanes as versatile building blocks in the total synthesis of natural products: An overview. European Journal of Chemistry, 6(3): 357-366.

Mahal, A., Abu-El-Halawa, R., Zabin, S. A., Ibrahim, M., Al-Refai, M. and Kaimari, T. 2015. Synthesis, characterization and antifungal activity of some metal complexes derived from quinoxaloylhydrazone. World Journal of Organic Chemistry, 3(1): 1-8.

Mahal, A., D'Errico, S., Borbone, N., Pinto, B., Secondo, A., Costantino, V. and Piccialli, G. 2015. Synthesis of cyclic N1-pentylinosine phosphate, a new structurally reduced cADPR analogue with calcium-mobilizing activity on PC12 cells. Beilstein Journal of Organic Chemistry, 11(1): 2689-2695.

Mahal, A., Villinger, A. and Langer, P. 2010. Synthesis of 1, 2-diarylanthraquinones by site-selective Suzuki-Miyaura reactions of the bis (triflate) of alizarin. Synlett, 2010(07): 1085-1088.

Mahal, A., Villinger, A. and Langer, P. 2011. Site-Selective Arylation of Alizarin and Purpurin Based on Suzuki–Miyaura Cross-Coupling Reactions. Sciences, 1: 13.

Mahal, A., Wu, P., Jiang, Z. H. and Wei, X. 2017. Synthesis and cytotoxic activity of novel tetrahydrocurcumin derivatives bearing pyrazole moiety. Natural Products and Bioprospecting, 7: 461-469.

Manolova, Y., Deneva, V., Antonov, L., Drakalska, E., Momekova, D. and Lambov, N. 2014. The effect of the water on the curcumin tautomerism: A quantitative approach. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 132: 815-820.

Marzano, M., Terracciano, M., Piccialli, V., Mahal, A., Nilo, R. and D'Errico, S. 2022. O6-[(2 ″, 3 ″-O-Isopropylidene-5 ″-O-t butyldimethylsilyl) pentyl]-5′-O-t butyldiphenylsilyl-2′, 3′-O-isopropylideneinosine. Molbank, 2022(1): M1345.

Mohapatra, R. K., El-ajaily, M. M., Alassbaly, F. S., Sarangi, A. K., Das, D., Maihub, A. A. and Al-Noor, T. H. 2021. DFT, anticancer, antioxidant and molecular docking investigations of some ternary Ni (II) complexes with 2-[(E)-[4-(dimethylamino) phenyl] methyleneamino] phenol. Chemical Papers, 75: 1005-1019.

Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F. and Walters, M. A. 2017. The essential medicinal chemistry of curcumin: miniperspective. Journal of Medicinal Chemistry, 60(5): 1620-1637.

Pari, L. and Amali, D. R. 2005. Protective role of tetrahydrocurcumin (THC) an active principle of turmeric on chloroquine induced hepatotoxicity in rats. Journal Pharm Pharma Science, 8(1): 115-23.

Peters, J. W., Lanzilotta, W. N., Lemon, B. J. and Seefeldt, L. C. (1998). X-ray crystal structure of the Fe-only hydrogenase (CpI) from Clostridium pasteurianum to 1.8 angstrom resolution. Science, 282(5395): 1853-1858.

Plata, R. E. and Singleton, D. A. 2015. A case study of the mechanism of alcohol-mediated Morita Baylis–Hillman reactions. The importance of experimental observations. Journal of the American Chemical Society, 137(11): 3811-3826.

Priyadarsini, K. I. 2014. The chemistry of curcumin: from extraction to therapeutic agent. Molecules, 19(12): 20091-20112.

Radhi, A. H., Du, E. A., Khazaal, F. A., Abbas, Z. M., Aljelawi, O. H., Hamadan, S. D. and Kadhim, M. M. 2020. HOMO-LUMO energies and geometrical structures

effecton corrosion inhibition for organic compounds predict by DFT and PM3 methods. Neuro Quantology, 18(1): 37.

Rampogu, S., Lee, G., Park, J. S., Lee, K. W. and Kim, M. O. 2022. Molecular docking and molecular dynamics simulations discover curcumin analogue as a plausible dual inhibitor for SARS-CoV-2. International Journal of Molecular Sciences, 23(3): 1771.

Reddy, R. C., Vatsala, P. G., Keshamouni, V. G., Padmanaban, G. and Rangarajan, P. N. 2005. Curcumin for malaria therapy. Biochemical and Biophysical Research Communications, 326(2): 472-474.

Saeed, M. E., Yücer, R., Dawood, M., Hegazy, M. E. F., Drif, A., Ooko, E. and Efferth, T. 2022. In Silico and In Vitro Screening of 50 Curcumin Compounds as EGFR and NF-κB Inhibitors. International Journal of Molecular Sciences, 23(7): 3966.

Salman, A. W., Haque, R. A., Kadhim, M. M., Malan, F. P. and Ramasami, P. 2019. Novel triazine-functionalized tetra-imidazolium hexafluorophosphate salt: Synthesis, crystal structure and DFT study. Journal of Molecular Structure, 1198: 126902.

Salman, G. A., Mahal, A., Shkoor, M., Hussain, M., Villinger, A. and Langer, P. 2011. Regioselective Suzuki–Miyaura reactions of the bis (triflate) of 1, 2, 3, 4-tetrahydro-9, 10-dihydroxyanthracen-1-one. Tetrahedron Letters, 52(3): 392-394.

Salman, G. A., Zinad, D. S. and Mahal, A. 2020. Design, synthesis, and biological evaluation of new quinoline-based heterocyclic derivatives as novel antibacterial agents. Monatshefte Chemical Monthly, 151: 1621-1628.

Sayin, K., Kariper, S. E., Taştan, M., Sayin, T. A. and Karakaş, D. 2019. Investigations of structural, spectral, electronic and biological properties of N-heterocyclic carbene Ag (I) and Pd (II) complexes. Journal of Molecular Structure, 1176: 478-487.

Sherif, Y. E., Sayed, A. H. and Lotfy, M. 2021. Antiviral Effect of Curcuminoids and Curcumin Derivatives Against Coronavirus (Sars-Cov-2) Predicted Using Molecular Docking Approach. Egyptian Academic Journal of Biological Sciences. C, Physiology and Molecular Biology, 13(2): 47-62.

Song, G., Lu, H., Chen, F., Wang, Y., Fan, W., Shao, W. and Lin, B. 2018. Tetrahydrocurcumin-induced autophagy via suppression of PI3K/Akt/mTOR in

non-small cell lung carcinoma cells. Molecular Medicine Reports, 17(4): 5964-5969.

Suravajhala, R., Parashar, A., Choudhir, G., Kumar, A., Malik, B., Nagaraj, V. A. and Kishor, P. K. 2021. Molecular docking and dynamics studies of curcumin with COVID-19 proteins. Network Modeling Analysis in Health Informatics and Bioinformatics, 10(1): 44.

Wilken, R., Veena, M. S., Wang, M. B. and Srivatsan, E. S. 2011. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Molecular Cancer, 10(1): 1-19.

Yang, L., Li, H., Wu, P., Mahal, A., Xue, J., Xu, L. and Wei, X. 2018. Dinghupeptins a–d, chymotrypsin inhibitory cyclodepsipeptides produced by a soil-derived streptomyces. Journal of Natural Products, 81(9): 1928-1936.

Yang, L., Mahal, A., Liu, Y., Li, H., Wu, P., Xue, J. and Wei, X. 2017. Two new 2, 5-diketopiperazines produced by Streptomyces sp. SC0581. Phytochemistry Letters, 20: 89-92.

Yaqo, E. A., Anaee, R. A., Abdulmajeed, M. H., Tomi, I. H. R. and Kadhim, M. M. 2020. Electrochemical, morphological and theoretical studies of an oxadiazole derivative as an anti-corrosive agent for kerosene reservoirs in Iraqi refineries. Chemical Papers, 74(6): 1739-1757.

Zinad, D. S., Mahal, A. and Al-Amiery, A. 2020. An efficient synthesis of novel imidazo-aminopyridinyl derivatives from 2-chloro-4-cyanopyridine. Organic Preparations and Procedures International, 52(4): 361-367.

Zinad, D. S., Mahal, A. and Salman, G. A. 2021. Synthesis and antibacterial activity of novel 1, 3-oxazine derivatives. Organic Preparations and Procedures International, 53(6): 578-584.

Zinad, D. S., Mahal, A. and Shareef, O. A. 2020. Antifungal activity and theoretical study of synthesized pyrazole-imidazole hybrids. In IOP Conference Series: Materials Science and Engineering. IOP Publishing, 770(1): 012053.

Zinad, D. S., Mahal, A., Mohapatra, R. K., Sarangi, A. K. and Pratama, M. R. F. 2020. Medicinal chemistry of oxazines as promising agents in drug discovery. Chemical Biology and Drug Design, 95(1): 16-47.

Zinad, D. S., Mahal, A., Siswodihardjo, S., Pratama, M. R. F. and Mohapatra, R. 2021. 3D-Molecular Modeling, Antibacterial Activity and Molecular Docking Studies of Some Imidazole Derivatives. Egyptian Journal of Chemistry, 64(1): 93-105.

Zinad, D. S., Shareef, O. A. and Mahal, A. 2020. Theoretical investigation for synthesis and characterization of two novel disubstituted imidazoles using microwave. In AIP Conference Proceedings. AIP Publishing LLC, 2213(1): 020188.