IMAGE: A MAP OF THE STARS OF THE ORION CONSTELLATION

Print ISSN: 2631-8490 Online ISSN: 2631-8504

JournalPreview

London Journal of Research in Science: Natural and Formal
Volume 24 | Issue 7 | Compilation 1.0

Great Britain Journals Press

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Journal Content
In this Issue

Great Britain Journals Press

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ABSTRACT

Based on the study of the current-voltage dependences during the joint electroreduction of rhenium and molybdenum ions from sulfate electrolytes on the nickel electrode, the conditions for the deposition of alloy nanocoatings in the Re-Mo system were established. The influence of various factors on the composition and quality of coatingswas studied: the content of components in the electrolyte, current density, temperature, acidity of solutions, etc., It has been established that, with an increase in the content of rhenium in the electrolyte and current density, the content of rhenium in the alloy increases. Based on the experimental data, the following electrolyte composition (mol/l) is recommended to obtain semiconductor rhenium-molybdenum alloys containing 35-50% Re: electrolyte (mol/l): 1.5 10^{-3} Na_2MoO_4 + 3.5 10^{-3} $KReO_4$ + 2.0 H_2SO_4 ; pH=0.4; Ev=0.005 Vs^{-1} t=75°C, electrode – Pt..

Keywords: rhenium alloys; molybdenum; thin coatings; electrochemical deposition; binary alloys; current density.

Classification: LCC Code: QD181

Language: English

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LJP Copyright ID: 925681
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ABSTRACT

Based on the study of the current-voltage dependences during the joint electroreduction of rhenium and molybdenum ions from sulfate electrolytes on the nickel electrode, the conditions for the deposition of alloy nanocoatings in the Re-Mo system were established. The influence of various factors on the composition and quality of coatingswas studied: the content of components in the electrolyte, current density, temperature, acidity of solutions, etc., It has been established that, with an increase in the content of rhenium in the electrolyte and current density, the content of rhenium in the alloy increases. Based on the experimental data, the following electrolyte composition (mol/l) is recommended to obtain semiconductor rhenium-molybdenum alloys containing 35-50% Re: electrolyte (mol/l): 1.5 10^{-3} Na_2MoO_4 + 3.5 10^{-3} $KReO_4$ + 2.0 H_2SO_4 ; pH=0.4; Ev=0.005 Vs^{-1} t=75°C, electrode – Pt.

Keywords: rhenium alloys; molybdenum; thin coatings; electrochemical deposition; binary alloys; current density.

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I. INTRODUCTION

Recently, rhenium alloys, which are used in aviation and space technology, have shown great interest all over the world [1-4].

The combination of unique physical and chemical properties of rhenium makes this metal promising for use in high-tech industries such as aviation, rocket engine manufacturing, nuclear power engineering, electronics, biomedicine, and heterogeneous catalysis.

Because both molybdenum and rhenium are refractory metals, the mixing of the two elements as alloys provides the double advantage of both the high temperature physical properties of rhenium and the excellent mechanical properties of molybdenum; thus, the overall characteristics of the alloy are markedly improved. Rhenium is a strong, ductile, refractory metal with a hexagonal close-packed crystal structure. It has the second highest melting point of all metals. Compared to other refractory metals, Re has a higher ultimate tensile strength. Molybdenum, in turn, is a very versatile refractory metal that is easy to machine, has a high melting point, high heat resistance, high thermal conductivity, and reduced neutron swelling.

Being in an alloy with other metals, Mo can impart various properties to the resulting coating. As you know, molybdenum is a refractory metal with low ductility. The addition of the rare earth element rhenium (8-47%) significantly increases ductility and makes it possible to create alloys with properties such as refractoriness, heat resistance, high corrosion resistance, and good electromotive force.

Molybdenum-rhenium alloy is one of the advanced developments of the metallurgical industry, which was introduced to the world quite recently. Due to the presence of rhenium in the alloy, molybdenum becomes ductile. This, in turn, allows it to be used to obtain alloys endowed with such unique qualities as: resistance to high temperatures; resistance to corrosion; infusibility.

The electrodeposition of alloys is one of the effective methods for improving the quality of metal coatings. Alloy coatings often have high anti-corrosion properties, greater hardness, wear resistance and heat resistance compared to individual metal coatings.

The purpose of this work is the electrochemical synthesis of new nanomaterials based on Re-Mo alloys on nickel substrate. For this purpose, we studied the cathodic processes during the reduction of molybdenum with rhenium in a sulfate electrolyte on a Ni electrode. This work was carried out to determine the possibility of obtaining thin coatings of molybdenum with rhenium by the electrochemical method by electrolysis from a sulfate electrolyte. The studies were carried out in solutions of composition (mol/l): Electrolyte composition (mol/l): $1{,}5{\cdot}10^{-3}Na_2MoO_4$+ $3{,}5{\cdot}10^{-3}KReO_4$+2,0 H_2SO_4 ; pH=0,4 ; Ev=0,005Vs^{-1}t=75°C.

II. EXPERIMENTAL

Nickel electrode with a visible surface of 0.07 cm^2 is used as the working electrode. The three-electrode cell contained the electrode under study, an auxiliary platinum electrode with an area of 4 cm^2, and a silver chloride reference electrode.To study the structure and composition film deposition was carried out on Ni substrate with an area of 2.0 cm^2. Working temperature during electrodeposition 75°C, deposition time 60 min. The kinetics of the processes was controlled using measurements by the method of cyclic voltammetry on IVIUMSTAT. To study the morphology of films nickel substrate, the electrode surface was examined on a JEOL JSM7600F scanning electron microscope at various magnifications, and, accordingly, was subjected to elemental analysis using an Oxford X-MAX 50 detector. X-ray diffraction analysis of the obtained films was carried out on a DRON- 5 with Cu K α-radiation. The films were obtained in the galvanostatic mode without electrolyte stirring. For analysis, the cathode deposit was dissolved on heating in concentrated HNO_3 acid. The amount of rhenium and molybdenum was also determined separately by the thiourea complex by the colorimetric method on a SPECORD 50 PlUS instrument.

III. RESULTS AND DISCUSSION

This work was carried out with the aim of finding the possibility of obtaining nanocoatings based on Re-Mo alloys from sulfate electrolyte. The research was carried out in the following main stages:

1. electrodeposition of molybdenum and rhenium separately.
2. joint electrodeposition of the molybdenum rhenium alloy.

Molybdenum and rhenium in pure form at the cathode can only be obtained with a low current efficiency [12-19]

Rhenium has a unique effect on lowering the transition temperature of tungsten and molybdenum in a brittle state. The mechanism of action of rhenium on these metals has not yet been fully elucidated. Alloys of rhenium with molybdenum and tungsten are of great practical interest, since rhenium has an exceptional effect on their deformability and mechanical properties. A sharp increase in the plasticity of tungsten and molybdenum occurs when they are alloyed with rhenium. We have studied the kinetics of cathodic reactions in sulfate solutions proposed for the electrodeposition of metallic molybdenum. By taking cyclic polarization curves using the potentiodynamic method on Pt and Ni electrodes, the mechanism, kinetics of the process and the potential range of joint electrodeposition of these

components are determined. It has been established that the reduction of molybdenum compounds in the +6 oxidation state proceeds stepwise according to the scheme Mo(VI) → Mo(V) → Mo(III); observed on the polarization curves. The reduction of molybdenum to the metallic state is possible only at very negative cathode potentials. The deposit formed on the surface of a solid cathode under cathodic polarization (i = 0.5 A cm^{-2}) contains both molybdenum in the metallic state and molybdenum oxides.

In this work, the choice of sulfate electrolyte is due to the fact that it is possible to obtain high-quality deposits of molybdenum and rhenium from this electrolyte, while it is not always possible to obtain high-quality rhenium films from an alkaline electrolyte. Also, it was established by preliminary experiments that high-quality films can be obtained from sulfate electrolyte even at very low concentrations of molybdenum in the electrolyte. This is very important in the co-deposition of molybdenum with more electronegative metals, such as bismuth, antimony, cadmium, and rhenium. At low concentrations of molybdenum in the electrolyte, its deposition is accompanied by high polarization, which causes a shift in the deposition potential of molybdenum to the deposition potentials of a more electronegative metal and, at the same time, favorable conditions are created for the joint deposition of these metals.

As is known, the standard electrode potential of molybdenum is +0.56 V, and that of rhenium is +0.36 V. Usually, the joint deposition of rhenium with molybdenum occurs under the conditions of the limiting current of the more noble metal. However, it is known that the convergence of the deposition potentials can be achieved by changing the activity of ions in the solution. Therefore, in this case, when studying the kinetics and mechanism of molybdenum deposition, the main attention was paid to those factors that contribute not only to obtaining high-quality deposits, but also significantly shift the potential of more noble metal in the negative direction (or the deposition of a more noble metal is accompanied by high polarization).Therefore, a more detailed study of the patterns of molybdenum electrodeposition from the selected electrolyte was necessary, the knowledge of which would help to choose the optimal conditions for the joint deposition of molybdenum with rhenium. For this purpose, a study of cathodic processes during the reduction of molybdenite ions in sulfate electrolyte on Pt and Mo electrodes was performed. Taking into account the fact that during the deposition of molybdenum and rhenium from sulfate solutions on the cathode, benign deposits are obtained, in this work, a sulfate electrolyte is used. Figure 1 shows the cyclic polarization curves of molybdenum taken from sulfate solutions. As can be seen from Fig. 1, the forward and reverse polarization curves differ significantly. Since with an increase in cathodic polarization, a gradual reduction of oxide compounds of molybdenum occurs. As a result, the discharge of molybdenum ions at the cathode becomes more difficult, the rate of the process drops sharply, and the polarization curve shifts towards negative potentials. Later, in order to identify the reasons hindering the electrode process of molybdenum deposition in the studied electrolytes, the effect of temperature on the cathode process was studied.

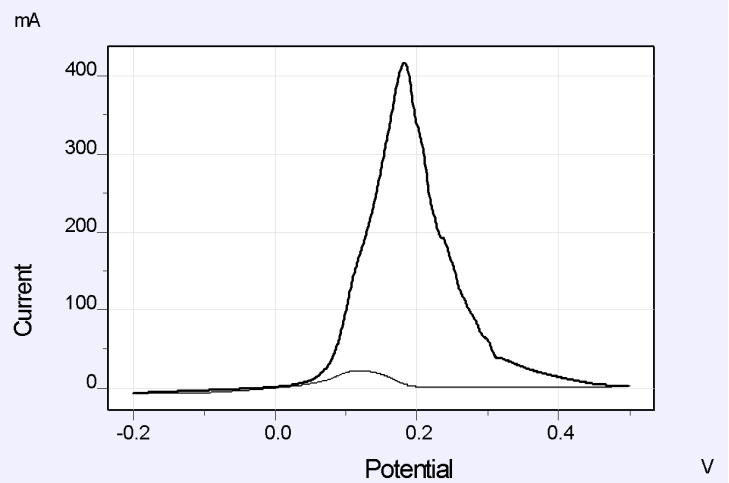

Figure 1: Polarization curves of molybdenum from sulfate electrolyteson a nickel electrode. Electrolyte composition (mol./l): 1,5·10^{-3}Na_2MoO_4 +2,0 H_2SO_4 ; pH=0,4 ; Ev=0,005Vs^{-1}t=75^{0}C.

Figure 2 shows the polarization curves of the rhenium reduction on a nikel cathode, The recording of polarization curves during the reduction of rhenium in the absence of molybdenum showed that the reduction of rhenium in acidic electrolytes occurs stepwise, through the formation of rhenium oxides and is accompanied by the reduction of hydrogen, which is in good agreement with theliterature data [5-8]

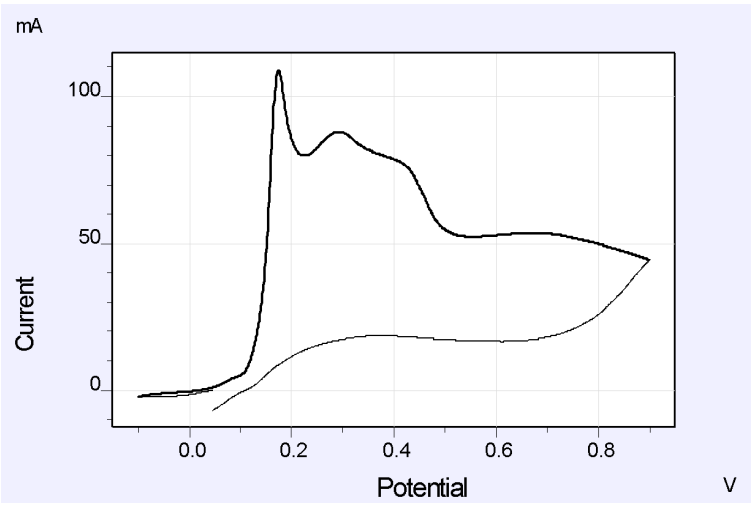

Figure 2: Polarization curves of rhenium from sulfate electrolyteson a nickel electrode. Electrolyte composition (mol./l): 3.5 10^{-3}$KReO_4$ + 2.0 H_2SO_4; pH=0.4; Ev=0.005 Vs^{-1} t=75^{0}C.

On the polarization curves of rhenium, one clear wave is observed: at a potential of +0.45 V. The presence of these waves can be explained by the stepwise mechanism of perrhenate ion reduction, with intermediate stages of the rhenium oxides formation and their further reduction by evolving hydrogen to metallic.We believe that the cathode process is described as the reduction of the perrhenate ion to metallic rhenium through the stages of formation of ReO_3 and ReO_2, as evidenced by the presence of red and blue precipitates in the resulting film.

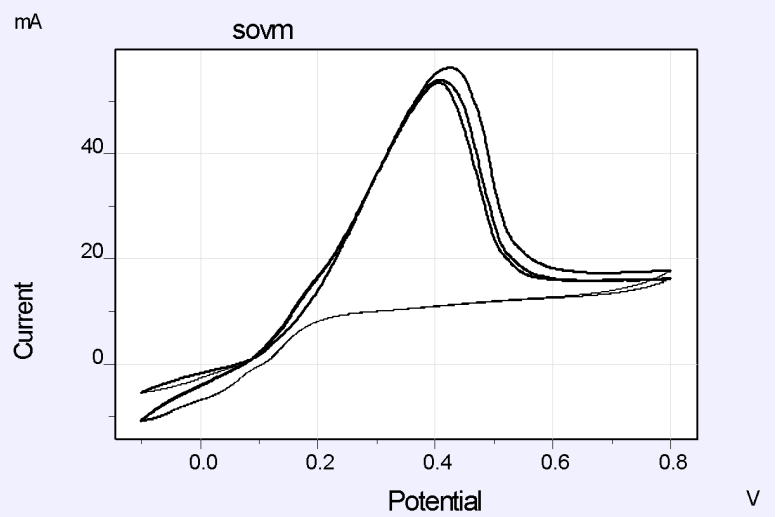

Figure 3: Polarization curves of molybdenum-rhenium alloy from sulfate electrolytes on a nickel electrode. Electrolyte composition (mol/l) Electrolyte composition (mol./l): 1,5·10^{-3}Na_2MoO_4 +3,5·10^{-3}$KReO_4$ + 2,0 H_2SO_4 ; pH=0,4 ; Ev=0,005Vs^{-1}t=75°C

The polarization curves of Re–Mo alloys are presented in fig 3. As can be seen from the figure, the cathodic reduction of the Re–Mo alloy is located in the region of more positive potentials than the potentials of deposition of individual elements. With the shift of the cathode curve to the region of more positive potentials, the value of the limiting current increases. A similar effect is explained by the release of energy during the formation of a chemical compound. Chemical and X-ray diffraction analysis established that at a potential of –0.1 V, an alloy is obtained on the cathode, the composition of which corresponds to the $ReMo_2$. The electrochemical process of its formation is described by the equation:

$$Re^o + 2Mo \rightarrow ReMo_2.$$

The effect of temperature on the co-deposition of rhenium with molybdenum from a sulfate electrolyte was also studied. Figure 4 shows the cyclic current-voltage dependencies of the cathodic polarization on temperature. As can be seen from figure 4, the cathodic polarization strongly depends on the temperature of the electrolyte. As the temperature increases, the polarization curves shift in the positive direction, i.e. cathodic polarization decreases. Polarization curves are characterized by limiting currents, which increase with increasing temperature and concentration. On the polarization curves obtained at temperatures of 60 and 80°C, the anodic oxidation waves decrease, and the rhenium oxidation wave increases. High-quality coatings of the rhenium-molybdenum alloy are obtained at a temperature of 75 °C. Therefore, further experiments were studied at a temperature of 75 °C. The potential region was also found at which high-quality coatings of rhenium molybdenum alloys are obtained.

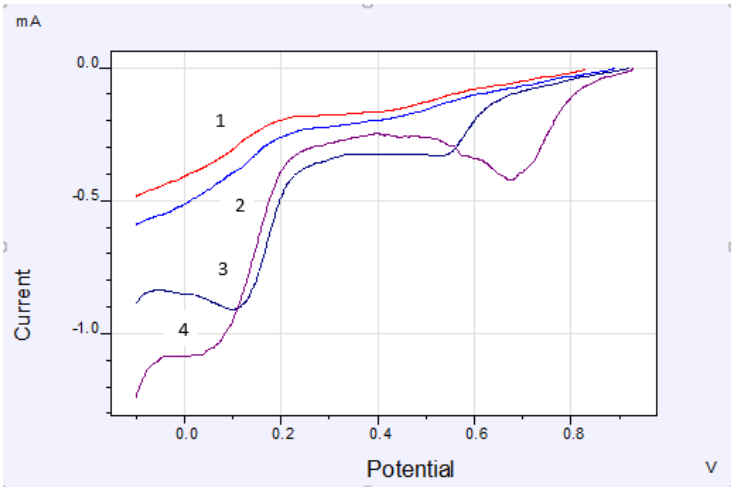

Figure 4: Effect of temperature on the co-deposition of molybdenum-rhenium alloy from sulfate electrolytes on a nickel electrode. Electrolyte composition (mol/l): 1.5 10^{-3} Na_2MoO_4 +3.5 $10^{-3}KReO_4$ 2.0 H_2SO_4 ; pH=0.4; Ev=0.005 Vs^{-1}, t ^oC-1-25, 2-45, 3-65,4-85.

The effect of the substrate on the co-deposition of molybdenum with rhenium was studied. The cyclic polarization curves of the rhenium-molybdenum alloy from a sulfate electrolyte on a nickel electrode were presented in fig 3.

The composition and morphology of thin Re-Mo films electrodeposited on a platinum electrode were analyzed. The phase composition of the obtained films was determined by XRF on a diffractometer (Fig. 5). The study of the morphology of Re-Mo films on platinum and nickel substrates was performed on a scanning electron microscope. It follows from the SEM data that the film consists of 76.9% at, Re, 23.1% at. Mo (Fig. 6).

Thus, on the basis of experimental data, the following electrolyte composition (mol/l) is recommended for obtaining thin coatings of molybdenum with rhenium: 1.5 10^{-3} Na_2MoO_4 +3.5 $10^{-3}KReO_4$ 2.0 H_2SO_4 ; pH=0.4; Ev=0.005 Vs^{-1} t=75^oC.

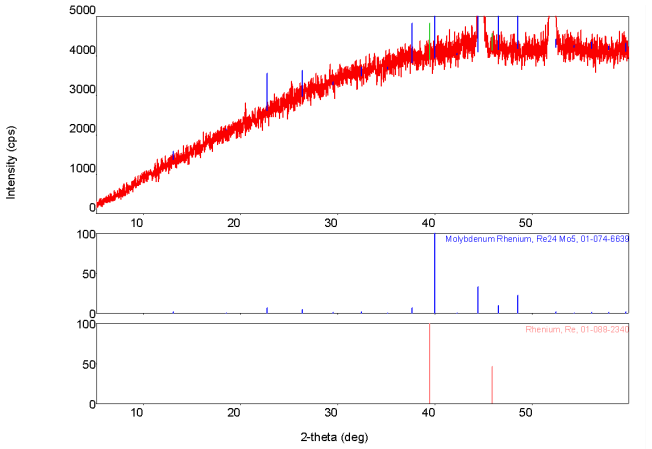

Figure 5: X-ray diffraction analysis of thin Re-Mo coatings obtained by electrochemical method from sulfate electrolyte

Element	Weight %	Atomic%
Ni K	76.62	90.66
Mo L	1.77	1.28
Re M	21.62	8.06
Results	100.00	

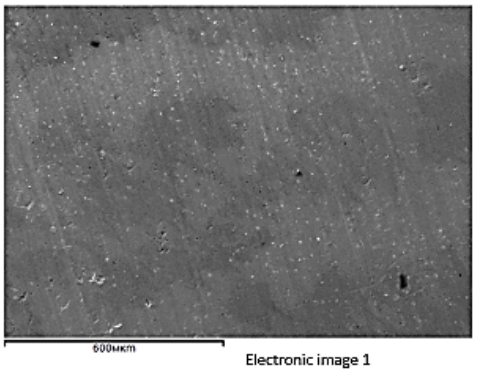

Figure 6: Morphology of thin Re-Mo coatings obtained by electrochemical method.

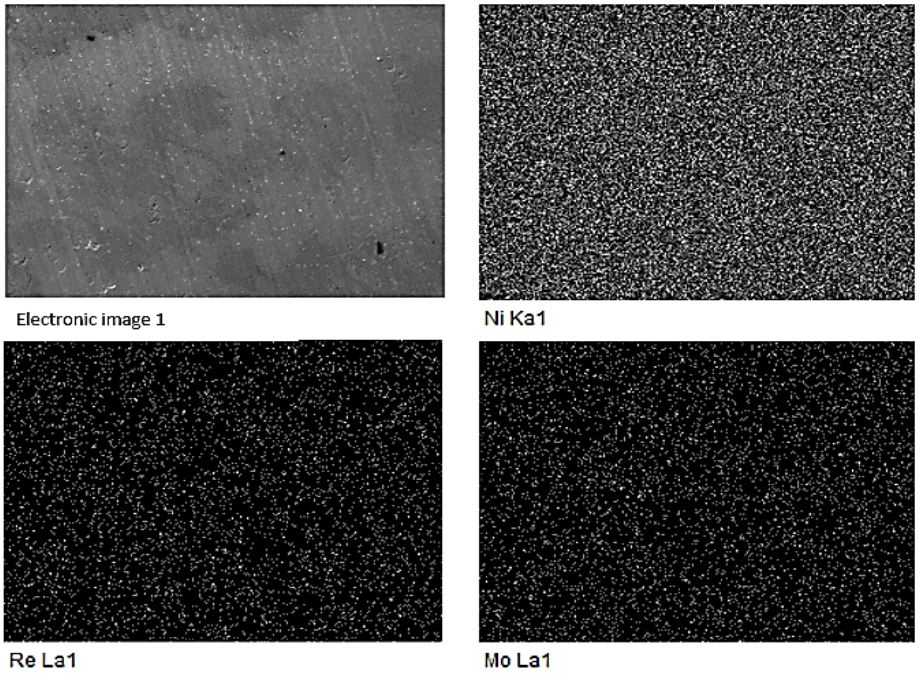

Figure 7: SEM image of Re-Mo thin film deposited on Ni electrode (production of rhenium-molybdenum alloys containing 45-80 wt.% Re from 0,0015 M Na_2MoO_4 + 0,0035 M $KReO_4$ + 2M H_2SO_4; pH 0,4; t=75°C)

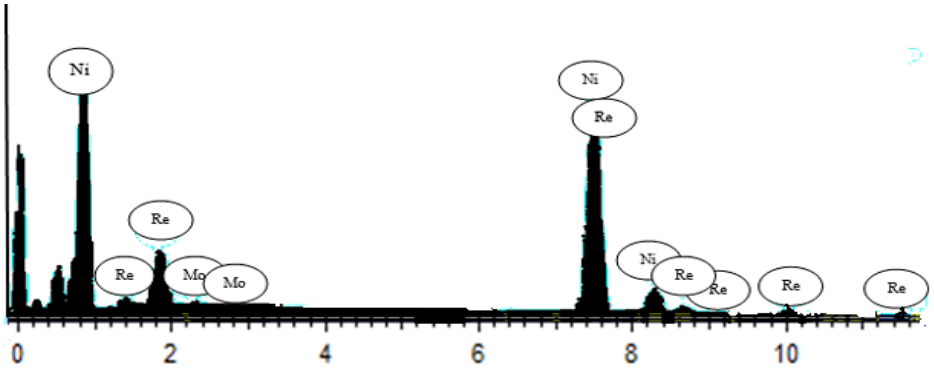

Figure 8: Elemental analysis of Re-Mo thin film deposited on Ni electrode (production of rhenium-molybdenum alloys containing 45-80 wt.% Re from 0,0015 M Na_2MoO_4 + 0,0035 M $KReO_4$ + 2M H_2SO_4; pH 0,4; t=75°C)

IV. CONCLUSION

1. Analysis of the results of measurements of the cathode and anodic polarization curves during the joint electrodeposition of rhenium with molybdenum shows that the process of joint deposition is accompanied by depolarization, which proves the formation of a chemical compound or a solid solution based on these compounds, and the potential range at which compounds of stoichiometric composition are formed on the cathode is determined.
2. Based on experimental data, the optimal composition of the electrolyte and the electrolysis mode were developed to obtain high-quality semiconductor coatings of molybdenum with rhenium from sulfate electrolyte.

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A Letter to the Scientific Community

Samo Liu

ABSTRACT

During the era of Aristotle, understanding of the cosmos was insufficient, leading Western philosophical thought to pivot entirely toward the philosophy of cosmic material, abandoning the philosophy of cosmic origin and the existence of divinity within space, relegating these inquiries to theology. The debate between Newton and Leibniz over absolute space left physics with inadequate information, subject to skepticism and lacking conclusion. Today, modern physics, systems science, physical cosmology, and other scientific disciplines provide information on time, mechanics, the composition of cosmic space—both material and immaterial. Based on the philosophical thoughts of Daoism, Buddhism, and dialectical materialism, there may now exist an opportunity to investigate the existence of divinity within space and to study the cosmic origin. It is hoped that scientists will reconsider and investigate the issue of immaterial existence within space, and reevaluate absolute space (Liu,"0-Dimensional Universe - Absolute space test绝对空间考", liu (2021), liu (2020)). This may be the key to resolving the contradictions between quantum mechanics and relativity, and I request your Consider publishing the letter.

Keywords: space absolute space relative space basic energy intelligence energy matter energy information.

Classification: LCC Code: BD311

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During the era of Aristotle, understanding of the cosmos was insuficient, leading Western philosophical thought to pivot entirely toward the philosophy of cosmic material, abandoning the philosophy of cosmic origin and the existence of divinity within space, relegating these inquiries to theology. The debate between Newton and Leibniz over absolute space left physics with inadequate information, subject to skepticism and lacking conclusion. Today, modern physics, systems science, physical cosmology, and other scientific disciplines provide information on time, mechanics, the composition of cosmic space—both material and immaterial. Based on the philosophical thoughts of Daoism, Buddhism, and dialectical materialism, there may now exist an opportunity to investigate the existence of divinity within space and to study the cosmic origin. It is hoped that scientists will reconsider and investigate the issue of immaterial existence within space, and reevaluate absolute space (Liu, "0-Dimensional Universe - Absolute space test绝对空间考 ", liu (2021), liu(2020)). This may be the key to resolving the contradictions between quantum mechanics and relativity, and I request your Consider publishing the letter.

In order to investigate this issue, I have consulted numerous works, published six books, Wroted afew articles.(Liu(2020)(2021)(2024.5)(2024.8)(2024.8a)) and derived some insightful conclusions for the scientific community 's consideration, which may provide some inspiration.

The foundation of this contemplation lies in the Daoist theory of Yin-Yang and the Five Elements(阴阳五行) from the "I Ching(易经）, " as well as the Buddhist philosophy doctrine of the emptiness(空) of causality(因果关系). It is believed that both material and immaterial existences coexist within cosmic space as manifestations of Yin(因) and Yang(阳). The law of conservation of energy suggests that matter is the variable material energy that perceives both force and time (Liu 's "Reflection and research on the origin of the universe, 宇宙本原考" and "Thinking and research on the Human origin 人类本原考 "); matter and energy possess spirituality and perception (Liu 's "Survival test of all things 万物生存考 "). In the process of perceiving information, there is motion and change within matter, energy, and information. Force, time, particle-wave , fields, etc., are all factors of immaterial emptiness, information in nature, without of material dimension, directing the motion and change of energy with balance as the goal, perpetually circulating.

Inspired by Jeremy Webb 's "Void, " Leibniz 's "Monadology, " and Einstein 's four-dimensional spacetime, energy and information are conceived as basics energy (基础能量, factors因素, Yang阳) and intelligent energy (智慧能量, causes因, Yin 阴) that exist without material presence in a 0-dimensional space. This is akin to the Eastern concepts of Yin-Yang Qi and causality, equivalent to the energy (Yang阳), force causal causes, and causal causes of time (Yin 因) in physics. The form of existence determines the description of space, with the absolute space of cosmic origin existing in a 0-dimensional form. The relative space of material existence can be termed as three-dimensional, but it is not the primordial space of the universe (Liu 's "Reflection and research on the origin of the universe "刘, (2021)). Therefore, I Earnestly hope the scientific community to criticize empirically and Verify these notions.

London Journal of Research in Science: Natural and Formal

The Zero-Dimensional Universe's Thought Experiment
— An Appeal to the Scientific Communityfor Empirical Evidence of Space and Its Contents

Executive summary:
Science, perhaps, is caught up in material philosophical thinking, is bounded by materialistic philosophy.

Keywords: space absolute space relative space basic energy intelligence energy matter energy information.

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I. ESTEEMED MEMBERS OF THE SCIENTIFIC COMMUNITY

I am a Doctor of Engineering, a Professor-level Senior Engineer. Through study and research, it has become apparent that the development of science over the past 500 years has been rooted in materialistic philosophy. It has detached itself philosophically from the essence and reality of the universe. Boldly speaking, the progress of science over these 500 years has occurred without a clear understanding of the true foundation of space.

I am writing this letter, to be published in journals such as "Nature," or "Science" to convey a message to scientists worldwide. The content of this letter is open for publication.

The main purpose of this letter is to Earnestly hope the scientific community to pay attention to the issue of space and to request mathematicians, physicists, systems scientists, and others to prove the existence of space and its contents. Over 2500 years ago, the ancient Greek philosophers, along with Eastern Daoist and Buddhist philosophers, continuously inherited and addressed this issue in their respective ideologies. They believed that the universe is composed of both material and immaterial elements within space, with the immaterial being the primordia of matter and the divine presence within emptiness. The expressions of ancient Greek philosophers regarding space and its contents were not systematic, often leaning towards materiality. The issue of cosmic origin and the existence within space was shelved by Aristotle. Despite attempts by subsequent philosophers such as René Descartes, Immanuel Kant, Isaac Newton, Gottfried Leibniz, Fichte, Schelling, Hegel, and Feuerbach to salvage this issue, the lack of scientific information prevented success. While the existence of natural divinity within the universe was acknowledged, its nature remained unknown. Science has thrived without a clear understanding of the issue of space and the existence within space, considering materialistic relative space and place as space. The immaterial primordial space has been overlooked (Liu, "宇宙 本原考", liu,(2024.5)(2024.8).

Newton discovered the primary force of the material universe, universal gravitation, and once proposed the issue of absolute space (Newton's" Mathematical Principles of Natural Philosophy"). Leibniz, from a theological perspective, opposed Newton's formulation of absolute space. Although he disagreed, Leibniz used the methods of scientific philosophy to demonstrate the existence of absolute space, stating that where there is no matter, there is no distance or other material parameters, hence absolute space ("Leibniz and Clarke Correspondence"). If the great Leibniz had lived longer and if there had been relativity and quantum mechanics at that time, he could have proven it mathematically. This remains a great regret in the history of philosophy and physics. Analyzing absolute space through the philosophical thoughts of Daoism and Buddhism regarding the origin of the universe, it is likely

equivalent to Daoism's concept of Wuji(无极)("Tao Te Ching") and Buddhism's concept of Sunyata(空性)("Diamond Sutra"), representing the 0-dimensional universe.(liu(2020)(2021)(2024.5)(2024.8))

Later, Mach opposed Newton's proof of absolute space in his "The History of Mechanics," rightly so, as the existence of absolute space cannot be proven through materiality physics. However,Influenced by the philosophy of material, Mach did not conclude what absolute space is. Analyzing it from the viewpoint of Eastern Philosophy (liu"道德经.宇宙本原的宣言" , "宇宙本原经典考"), absolute space could serve as a philosophical framework and approach to resolve the contradictions between quantum mechanics and relativity. The current state of science indicates that materiality philosophical thought has its limitations, and the scientific information now potentially provides the conditions and opportunities to prove the origin of the universe. We are compelled to once again face the issue of space and emptiness shelved by Aristotle, and confront the issue of absolute space. After the development of quantum mechanics and relativity, the problem of the existence of “immaterial entities” within space and absolute space has inevitably emerged in science. When contradictions arise between quantum mechanics and relativity, analyzing these contradictions through the philosophical thoughts of Daoism andBuddhism regarding the origin of the universe with dialectical materialism can provide a solution. This is not a problem of science but a problem arising from flaws in our philosophical thinking.(liu(2024.5)(2024.8)) The existence of matter has led us to overlook the immaterial origin space(Liu's "0-Dimensional Universe - 绝对空间考", Liu (2024.5)). Because our philosophical thinking is rooted in materialistic rationality, it has not resolved the issue of information in space,hence the focus of debate and contradictions arise from the lack of empirical evidence of the existence of immaterial entities within space. Therefore, the empirical proof of Newton's concept of absolute space has become an inevitable and unavoidable major issue for the scientific community, as well as what was said by the Buddha Sakyamuni in the sixth chapter of the"Diamond Sutra," a problem of human mental contemplation to be resolved 2500 years later(now).This is the essential attribute of space and the problem of existence in space.

Buddhist philosophy holds that after the departure of the Buddha, humanity will undergo five periods of 500 years of development and change. The last 500 years, known as the "latter 500 years," or today's era 2500 years later, is termed the turning times of the Dharma(末法时代)(liu"宇宙本原经典考")..

In terms of time, the "latter 500 years" roughly refers to the period from the 16th century to the present day. According to the "Diamond Sutra," the period of the "latter 500 years" can be understood as follows: during this period, humanity will scientific empirically demonstrate the essential attribute of space and the immaterial factors(因素) and cause(因) within space. In this era, humanity will develop into a highly advanced scientific period, where humans may possess the ability to destroy themselves. This period may represent a turning point or era in human development. Humanity is its own savior (liu" 宇宙本原经典考").

II. PLEASE CONVEY TO PROFESSOR EDWARD WITTEN

Through contemplation on the philosophical thoughts of Daoism and Buddhism regarding the origin of the universe, it is understood that "Relativity" studies the relative changes in the shape、movement and mass of matter, not changes on space. However, four-dimensional spacetime has opened the door to the study of space. Time is not equal to zero; it studies materiality. Only When time equals zero can we study space. Time is specifically a measure of the existence of matter and energy. Similarly, Professor Witten's research on multi-dimensional universe theory is not about space theory but about material science theory. The dimensions studied by ProfessorWitten are the material dimensions of physics. It is believed that Professor Witten's M-theory will greatly benefit the development of material science and may lead to breakthroughs in materialscience. However, it is not about space theory.

For example, the concepts of point, string, and brane, whether material or immaterial, must be clear. Otherwise, it will bring about the confusion of scientific concepts in philosophical thinking.(Liu,《宇宙本原考》)

If it is physical, in space, the point can be an Earth or a galaxy; It can be an atom or a particle. String, can be a very thick rope; It can also be a very thin line. Film, can be a very thick board; It can also be a very thin cloth. Etc.(Liu,《人类本原考》)

If it is immaterial, it is a wrong concept. Or something that doesn't exist.

But it does exist. Judging by the thought of the origin of the universe, it is the energy that the material dimension is 0 and the time is not 0. Furthermore, there is information in which the physical dimension is zero and time is zero.Further, there also is the existence of absolute zero degrees.

All are in space, and the form of existence determines the artificial description of the occupied space. (Liu (2024.5) (2024.8)) Either 0 or other numerical dimensions can be related to the existence in space. But you can't be place in space, you have to respect space. (Liu (2024.8) (2024.8a))

Through the analysis of the thought of the origin of the universe, judging from the current information, (Liu, (2024.5) (2024.8)) there are only three types of space, please judge the scientific community.

One is the existence of matter, and the existence, movement and change of its external dimension can be judged by three dimensions.

One is the existence of energy, which cannot be used in three dimensions, and can be used to judge the changes and movements of its existence in zero dimensions.

One is the existence of information, which is neither matter nor energy, but is both matter and energy, allowing matter and energy to exist, move, change, and disappear.

The three co-exist, so that the universe and all things are alive and exist.（Liu (2024.5) (2024.8)）

Space has no dimensions; there is a 0-dimensional non-material existence in space that can give birth to three-dimensional material or exist without material and material dimensions. Time and space do not curved. Quantum mechanics has already scientifically told us that the creation of matter comes from the energy sea of nothingness. Professor Lawrence M. Krauss's book "A Universe from Nothing" is excellent, stating that matter comes from the 0-dimensional energy and information of non-material. It can becalled the great god of the universe. Western philosophy is based on materialistic logical philosophy, rational scientific philosophy, not the philosophy of the origin of the universe, but materialistic philosophy. The philosophy of the origin of the universe must wait for the development of modern physics to determine and wait for empirical evidence of non-material existence in space and space to determine (Liu, " 0-Dimensional Universe - 绝对空间考", liu,(2021)).

From Aristotle to Newton, Leibniz to Ernst Mach, and then to Albert Einstein, they were great.They used rational scientific thinking to consider the material world but never thought clearly about what non-material existence in space and space is.Because there is no information on this subject; Think about this information in terms of our ancestors' cosmic origin thoughts. Quantummechanics and relativity tell us that it should be 0-dimensional energy and information,non-material existence. A group of great quantum physicists such as Max Planck, Einstein, NielsBohr, and Paul Dirac solved this information problem. They tell us that both humanity and all things come from energy and

information. Fermions are energy bodies, and bosons are information bodies, coming from the great yin(阴) and yang(阳) of information and energy. Strong and weak forces are interactions and causal factors between particles. If gravitational and electromagnetic forces represent the order of motion and change between matter, then strong and weak forces represent the aggregation and dispersion of energy. Strong forces polymerization, weak forces radiate. Eastern philosophy calls it yin-yang dual gas (阴阳二炁),cause and factor(因和因素). Please count the abundant of works and practices recorded inBuddhist and Daoist doctrines. The philosophical thought of the origin of the universe has been fully explored and understood; for example, the expression of space is called elastic bag withgreat emptiness (其大无外) and small emptiness(其小无内), called Wuji(无极), without dimensions. The expression of all existence is called yin and yang, macroscopically called non-material and material; non-material gas concept(炁)of yin (阴)and yang(阳); The concept of interactions(因缘) of causal (因)and factors(因素);let matter exist and change, calledyin and yang five elements(阴阳五行); the creation of the universe is called non-action butaction(无为而为);five aggregates are empty(五蕴皆空), etc. They all talk about the relationship between matter, energy, and information (Liu, "道德经.宇宙本原的宣言", liu,“宇宙本原经典考”).

Our ancestors had a complete philosophical rational framework for quantum mechanics and relativity. When science developed to quantum mechanics and relativity, especially when quantum mechanics and relativity had contradictions, when physical cosmology told us that material energy accounts for only about 4.9% of relative space, and dark matter and dark energy account for about 95.1%, the category we think about should shift from materialistic philosophy to the dialectics of the origin of the universe in Daoist and Buddhist philosophy. According to the thoughts of Daoism and Buddhism, 95.1% of existence should be non-material existence. Theabout 4.9% material existence comes from there and finally must return there (Liu, "道德经.宇宙本原的宣言", “宇宙本原经典考”, liu, (2024.5)).

Quantum mechanics and relativity have answered the precious thoughts of the ancient ancestors about the origin of the universe. Matter exists, but its origin comes from the yin and yang dual gas(阴阳二炁) of non-material emptiness, energy, and information. They have given us opportunities and opportunities to rethink space and the non-material existence in space. Ourancestors' understanding of the origin of the universe is a scientific and rational thought. They Explored our universe and the origin of the universe with another scientific and rational method,telling us that the universe is not purely material but a collections of matter, energy, and information. That is to say, matter is a kind of existence named by humans as a three-dimensional existence, and the origin of matter is the 0-dimensional existence of non-material, the balanceand change of yin and yang dual gas(阴阳二炁)in Daoism; the causal change of cause(因)andfactor(因素) in Buddhism。In the"Reflection and research on the origin of the universe(宇宙本原考)"、"Thinking and research on the Human origin(人类本原考)"、" 0-DimensionalUniverse - Survival test of all things(万物生存考)"、" 0-Dimensional Universe-Absolute spacetest(绝对空间考)"、"Tao Te Ching- Universal Declaration(道德经宇宙本原的宣言)" and "Textual research of the universe original classic(宇宙本原经典考)" are referred to as basic energy (factors, yang 阳) and intellectual energy (cause, yin 阴); and according to the multi-dimensional universe ranking, named as four-dimensional universe existence,five-dimensional universe existence, not space. In the four-dimensional spacetime coordinate system, time is designed as 0, and two virtual dimensions are added, called disappearing dimensions and changing dimensions; they are gods of the universe, all exist in the 0-dimensional space, create matter and coexist with material energy. It is hoped that the scientific community will empirically or empirical research it using scientific and mathematical rational methods.

I am a Doctor of Mineral Processing Engineering, a believer and thinker of Daoist and Buddhist Philosophy, and a fan of physics and systems science. The "Diamond Sutra" says that we should pay attention. Focus on the material, do not study the external phase of the material, the shape is always changing. Study the natural endowment of matter, study the causal changes of the causes and the factors of emptiness of matter. Physics have already done.(liu,"0-Dimensional Universe -万物生存考", liu,(2021))

Physics has discovered universal gravitation, electromagnetism, dynamics, and thermodynamics, which are the causes of motion and change in matter perceived by each other. Quantum mechanics has been developed, discovering strong and weak forces, which are the causes of aggregation and dispersion of material energy, including the cause of time. Chemistry has discovered chemical bonds, the cause of material formation. All mechanics are what Buddhism and Daoism call cause（因缘） of causes 因 (yin 阴) and factors 因素 (yang 阳), the causality（因果关系）of the five elements' generation and restraint（五行生克）." 宇宙本原考" and "人类本原考" believe that force is the intellectual energy of the cause of information, the soul of matter. All matter is perceptible. Action at a distance exists. Five hundred years of scientific development has brought about earth-shaking changes for humanity; the three industrial revolutions are revolutions created by humanity's understanding and mastery of mechanics, energy, and information, revolutions in the material world, bringing material enjoyment to humanity. However, it has overlooked the existence of non-material divinity in space and the void within space. Although scientists have discovered this, human philosophical thinking is bounded（囿）by materialistic philosophy.

Time is also a cause（因）,The time "Second" defined by the International Committee of Weights and Measures（CIPM）(13th CGPM. (1969)), which is consistent with the judgment on the Relationship between Time and Material Created of the "He Guanzi《鹖冠子》" in Daoist philosophy that time is related to material quality and weak forces. So, judged by Buddhist thought, scientists are great bodhisattvas. Time is the numerical process of material and energy existence and has perception of time (Liu, "万物生存考").

I hope the scientific community will not blame or attack religion. The great thoughts of religion, God, deities, are all subjects and topics that our scientific community is always committed to exploring and pursuing. If exploration is not thorough, it is our scientific responsibility, and we are not qualified to attack or blame religion (Liu, " 宇宙本原考").

We should not blame philosophy either because Aristotle has turned philosophy into scientific philosophy, the second philosophy, classifying and dividing, and handing over the main responsibility of philosophical thinking to science. In fact, scientists are the great philosophers who discovered classical mechanics and quantum mechanics. Quantum mechanics discovered that everything in our universe comes from energy and information, from the great basic energy,which is Einstein's four-dimensional spacetime, the existence of the universe when time equals zero, the existence of 0-dimensional existence in 0-dimensional space, the existence of the vacuum energy sea. Using the thinking of Daoist and Buddhist philosophy, it is discovered thatthe great universe is alive, （liu, ɣ 2024.5"）Tan(惚) is the god of the universe, Tan（惚） is the great God of space. Look at the orderly movement and change of everything, planets, galaxies, everything, and humans, are they created by humans? The god of the universe used the thought of "non-act but action 无为而为"("Tao Te Ching"), the consciousness of "the five aggregates are empty 五蕴皆空" ("Heart Sutra"),without subjective consciousness, without human feelings, but used the non-material existence of infinite space, in infinite time, to create planets, galaxies, everything, and humans by trial and error.(Liu, "人类本原考") believes that space is the mother of our humanity and all things (Liu, "宇宙本原考").

The ancestral thoughts on the origin of the universe tell us: the universe is alive, everything isalive. From the big bang of the universe, planets, galaxies, to the process of black holes, it is thelife span of material existence, just like living people. The cause of time is given by the universe.Humans are even more alive, but humans have two souls. One is the life given by the universe with feelings and subjective consciousness; when we die, the soul of feeling and subjective consciousness leaves us, and we are still ordinary material, our body still exists like everything else, until it returns to energy completely. So, "Zhuangzi《庄子》" believes that humans and allthings are "Qi Yi"（万物齐一）(Liu, "Thinking and research on the Human origin").

Humanity has entered the realm of science with the information tools of language, writing, andnumbers, and has come to know the material universe, material philosophy, and material science.Let us understand that the universe is material, defined as a three-dimensional universe with coordinates. So, have we grasped the information of the entire universe? What is the information of the entire universe? The philosophy of the origin of the universe believes it is the existence of the basics energy and intellectual energy of "non-act but action（无为而为）"and "the fiveaggregates are empty（五 蕴皆空）", the universe of information and energy. It is information that has enabled us to understand the material universe, and with the development of materialscience, we are increasingly clear about the material universe. Why has science developed in this way? What is the relationship with mechanics, energy, and information? Is mechanics a concept of 0-dimensional void or a concept of material 3-dimensionality? What are the concepts of energy and information? Regardless of what concepts they are, have we all treated them as concepts of material? Science, why do we treat all matter as dry corpses, as purely material to study? Is there no soul? Why is the universe changing? Why is all matter in motion? Are only humans alive? I remember a scientist saying in a book that the terrifying thing about science is the loss of the soul.

Science, do not sleep in the zombie of material, everything has a spirit, the universe is alive,matter is alive! And this problem, you have discovered it. I hereby extend my highest respect to the great scientific community through "science" magazines. Scientists are the great bodhisattvas of humanity.

Dear Editor:

Today's scientific information presents a moment for investigating the true cosmos. The contradictions within modern physics necessitate an examination of the fundamental issue of space, a question that has been deferred for over 2500 years.

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Time Has Two Dimensions-Exploring Coordinate Connotation of Five-Dimensional Space

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ABSTRACT

For purpose of further quantifying and perfecting the theory of five-dimensional space, and building upon the ideas of Theodor Kaluza, Itzhak Bars and David Bohm, as well as recognizing the validity of B. Feng's new physics theory for deeper understanding particle physics and astrophysics, the corresponding coordinate connotation representation has been determined through reasoning, repressed in form (x, y, z, ict, iat^2). Here, a represents the curvature acceleration of light, equal to $1.627746473 \times 10^{31}$ m/s^2. This is believed to be the maximum possible acceleration in the universe, beyond which nothing can exceed. It currently has no prospects for practical application, except for theoretical supplementation. The essence of the two time dimensions is special relativity and general relativity.

Keywords: NA

Classification: LCC Code: QC173.6

Language: English

Great Britain Journals Press

LJP Copyright ID: 925683
Print ISSN: 2631-8490
Online ISSN: 2631-8504

London Journal of Research in Science: Natural and Formal

Volume 24 | Issue 7 | Compilation 1.0

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I. BACKGROUND

Itzhak Bars, an American theoretical physicist, was the first to propose the concept of *two dimensions of time*. He introduced this idea in 2001[1]. Bars' proposal builds on ideas from string theory and aims to provide a framework for understanding the fundamental nature of spacetime and its relationship to particle physics. His work has stimulated further research and discussions within the theoretical physics community (His work was followed by Penrose Roger (2004), McDonald John Q (2006), Marcus Chown (2007), Weinstein Steven (2009, 2013) and Dinov Ivo; Velev Milen (2021) *et al.* scientists).

Itzhak Bars discovered that incorporating a second dimension of time could help resolve specific issues and provide a deeper understanding of fundamental physical phenomena. In Bars' framework, the second dimension of time is conceptualized as an additional temporal degree of freedom, orthogonal to the conventional notion of time. This extra dimension allows for a richer description of dynamical processes. It may have implications for understanding various phenomena in physics, such as the nature of causality and the behavior of particles at high energies. In Bars' theory, time isn't linear; instead, it forms a 2D plane in curvature interwoven throughout the dimensions.

Previously, two prominent scientists have explored similar ideas related to multiple time dimensions, although their proposals may not be identical to Bars'. They are,

David Bohm: Theoretical physicist, proposed a theory of quantum mechanics that includes a concept called "implicate order," where, time is viewed as multidimensional and unfolds in an interconnected manner, suggesting a more intricate relationship between time and space. His distinguished statement in 1973 is that "*space is not empty, and is the ground for the existence of everything, including ourselves.*"[2]

John Archibald Wheeler: He introduced the concept of "*spacetime foam*," suggesting that at the most minor scales, spacetime may have a fluctuating, foam-like structure with additional temporal degrees of freedom beyond the conventional notion of time. His famous saying in 1955 is that "*spacetime is a theoretical phenomenon arising from quantum fluctuations at extremely small scales.*"[3]

Recently, in the past decade, a physicist David Deutsch, who known for his work on quantum computing and the theory of parallel universes, subsequently, has explored the idea in 2013 that time may have *multiple branching paths or dimensions*, leading to different possible futures.[4]

Back to Itzhak Bars. As for recognition within the academic community, Bars' proposal has generated interest and discussion among physicists, particularly those working in theoretical physics and related fields. While it hasn't been universally accepted as a mainstream concept; it has stimulated further research and debate, showcasing its impact on the field.

Currently, several novel studies have emerged making valuable contributions to their respective fields and yielding many supportive outcomes;[5-6] these contributions have been compiled in a monograph.[7] This theory incorporates the fundamental concepts of higher-dimensional space time proposed by Kaluza, Itzhak Bars, and other scientists. By merging Einstein's theory of relativity with quantum mechanics, it established a relatively comprehensive and self-contained theoretical framework. This groundbreaking work is attributed to B. Feng and is called"*B. Feng's new physics theory*."In the context of five-dimensional space, researchers have theoretically derived a concise set of elegant mathematical formulas. These formulas yield results consistent with actual measurements, including fundamental quantities such as basic charge, electron mass, proton mass, electron radius, proton radius, and the fine-structure constant. Surprisingly it does not require any physical constants to calculate the fine structure constant, but merely some high-dimensional geometric parameters; then, when calculating the primary charge, there is no need for it to use the fine structure constant, but only three essential physical constants as vacuum dielectric constant, vacuum speed of light and Planck constant. The critical point is that, when calculating the mass and radius of a particle, the concept of the"*radius of light-based manifold"* is proposed and utilized as an additional parameter. The radius of the manifold (R_0) has been established as the fourth fundamental physical constant in nature.

B. Feng's new physics theory has attracted the attention of some physicists; yet it remains unacknowledged on a widespread scale and has not gained an extensive recognition. Neverthless, this article asserts the need for further improvement and fill in gaps, guided by its sound reasoning and a harmonious and consistently well-constructed conclusion. The original intent behind writing this article aligns with the goal stated in title.

II. EXPLORING THE ORIGIN OF FOUR-DIMENSIONAL SPACETIME

The discovery and proposal of an extra space dimension originated with Einstein's special relativity. From a physical perspective, time is integrated into the properties of space, rendering the theory of special relativity plausible, its accuracy has been validated through experiments and practical applications. Initially, Einstein merged time with space, introducing the concept of four-dimensional spacetime denoted by coordinates (x, y, z, t). However despiting its mathematical elegance, this representation did not reflect a genuine physical spacetime due to the disparity in scale dimensions between time (t) and space. Einstein later refined this perspective, incorporating Minkowski's spacetime framework, adjusting the coordinates to (x, y, z, ict) within his theory of general relativity. Thus, the concept of an actual physical four-dimensional spacetime emerged, albeit with time represented in an imaginary form. Despite these advancements, Einstein still maintained a mathematical interpretation of spacetime, akin to his approach to quantum theory; at the same time, he acknowledged the findings of quantum mechanics, he resisted accepting the wave-particle duality and non-local characteristics of physical matter, hindering his pursuit of a unified field theory.

Returning to the original premise, if (x, y, z, ict) signifies genuine physical space, velocity is projected into time through imaginary numbers. By extension, one may inquire whether acceleration could be spatialized in time likewise. With general relativity's validation, there is merit in exploring the existence of a five-dimensional space in inferential physics (x, y, z, ict, iat^2), indicating Einstein's reminder of time's dual dimensions. Based on this notion, B. Feng's theory of new physics posits a five-dimensional space.

The concept of five-dimensional space was initially proposed by Kaluza and endorsed for publication by Einstein, while Einstein perpetuated his belief in time's mono-dimension property. However, Kaluza's interpretation remained confined to a mathematical framework, lacking a physical connotation. Nonetheless, Einstein's foundational contributions paved the way for the establishing of the five-dimensional physics space.

By the way, in contrast, the eleven-dimensional space pertains to string theory, where the additional eight dimensions lack distinct physical significance and are postulated to curl within a minuscule spatial range, lacking a theoretical basis for this curvature. In my assessment, compared to a five-dimensional space, the additional six dimensions serve as a mathematical correction, rectifying the initial misconception and aligning with reality. Pursuiting of perfect symmetry necessitated concessions they are, ultimately resorting to the insertion of Higgs particles or fields via spontaneous symmetry breaking in mathematical Lagrangians to acquired mass of elementary particles. Thus, the additional six dimensions might be compensating for their "quarks" error, I guess.

III. EXPLORE THE COORDINATE (X, Y, Z, ICT, IAT^2)

The coordinate system (x, y, z, ict, iat^2) shows us the universe space of a five-dimensional and complex, and the extra dimensions are two imaginary dimensions related to time.

In the fourth dimension, ict, the information is clear, where c is velocity and also the extreme velocity carried by light. However,

In the fifth dimension, iat^2, where the information has not been cleared, symbol a is known as acceleration; however, what does it to be in value?

Well, you see, generally we have,

$$a = \frac{v^2}{R},$$

Let's substitute the value into its corresponding limit. Then, c replaces v. Here, we only replace R with the radius of light base manifold, R_0, which appears to be reasonable. The radius of light base manifold R_0 in B. Feng's theory system[6] is,

$R_0 = 5.521469059 \times 10^{-15}$ m, then we have,

$$a = \frac{c^2}{R_0} = \frac{(2.99792457982 \times 10^8)^2}{5.521469059 \times 10^{-15}} = 1.627746473 \times 10^{31}\ \mathrm{m/s^2}$$

In this way, the problem has been solved. The character "a" here has been specially defined as the *curvature acceleration constant of light* in physics, a new concept introduced in this paper.

IV. DISCUSSION

Light travels in speed of constant c. However, when it travels in a circle, its acceleration is in a constant a; and a becomes the greatest acceleration in the universe, nothing can exceed it. When light travels in a circle, a basic particle is born; reverse looking, the fundamental particles are indeed a circled light with different energy. In B. Feng's theory framework, only electrons and protons moving in opposite circular directions can stably exist in nature, as determined by solving the relevant equations therein.

In coordinate (x, y, z, ict, iat^2), the imaginary dimensions act as actual degree of freedom. They cannot be recognized as nonexistent, nor do they exist in the same way as the real dimensions. It participates in controlling or describing the laws of motion of things. When it encounters square cases, it will return to a real, but negative value, which cannot be ignored. The imaginary numbers are not just mathematics, but physical reality. May the imaginary dimensions result in spatial contraction and convergence, equivalent to relativistic effects according to the analysis in the text. Looking into the future, a possible theoretical application is that the complex solution process of the results of general relativity can be obtained through simple operations in the five dimensional space under the proposed coordinates.

Furthermore, it can be said that the constant curvature speed of light (acceleration) and conservation of angular momentum result in the charge properties of particles and their masses, as well as their corresponding positive and negative charges, causing space to bend. Its coexistence leads to the neutralization of charge in neutrons and atoms, greatly canceling out the spatial property of charge. The remaining two dipole interactions in mathematics are reflected in the form of intermolecular forces and an invariant weak force coefficient. At this point, quantity is quality, and the accumulation of mass creates a macroscopic space warp.

V. CONCLUSION

The five-dimensional space corresponds to coordinates of (x, y, z, ict, iat^2), where c is the speed of light, and a represents the acceleration of light in a curved state, with a value of $1.627746473 \times 10^{31}$ m/s^2. The essence of the two time dimensions is special relativity and general relativity.

Postscript

To clarify, the main points and concepts of this article are brief, clear, and prominent for easy grasp. However, It's normal to have some doubts when reading roughly, to gain a deeper understanding, it is necessary to have a thorough familiarity and mastery of references 5-7 in advance, which would require a lot of effort.

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In Silico Identification of Natural Inhibitors Targeting Helicobacter Pylori Carboxyspermidine Dehydrogenase: A Computational Study

Alex J Mbise, P.V.Kanaka Rao, F.M.Stanley & M. S Gurisha

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ABSTRACT

Gastritis, peptic ulcers, and gastric cancer are the most common disorders and the leading cause of death worldwide. Helicobacter pylori is a bacterium that has been related to stomach inflammation, Peptic Ulcer, as well as gastric cancer. The current study sought to identify natural inhibitors of the Crystal Structure of Carboxyspermidine Dehydrogenase in a complex with Nicotinamide adenine dinucleotide phosphate (PDB ID: 8H52) with good resolution of 3.10*A*° and R-value free of 0.047. Bioactive compounds appear to be a potential treatment strategy for inhibiting H. Pylori. 1102 Bioactive compounds from blueberry, gooseberry, plum, cantaloupe, celery, lyngniangbru, tea plant, spinach, ginger, turmeric, radish, fenugreek seeds, carrot, and indigo were selected. Before molecular docking, initial selection of the BACs was based on the physiochemical, lipophilicity, water solubility, pharmacokinetics, druglikeness and pharmaceutical chemistry performed by SwissADME. Binding energy calculations and interaction analysis were applied to identify safe and efficient results. 17 Bioactive compounds were found with binding affinities between -7.8 Kcal/mol and -9.9 Kcal/mol. Among 17; curcumin pyrazole, scoparol, tryptanthrin and 4'-O-methylcatechin were found to bind strong in the protein pocket with docking scores of -9.9 Kcal/mol, -9.6 Kcal/mol, 9.5 Kcal/mol, and -9.5 Kcal/mol respectively compared to the control drug Omeprazole (-8.8 Kcal/mol).

Keywords: BACs, H. pylori, binding affinities, molecular docking, and MD simulations, traditional medicinal herbs, garboxyspermidine dehydrogenase, peptic ulcers, gastric disorders, therapeutic agents.

Classification: DDC Code: 615.323

Language: English

Great Britain Journals Press

LJP Copyright ID: 925684
Print ISSN: 2631-8490
Online ISSN: 2631-8504

London Journal of Research in Science: Natural and Formal

Volume 24 | Issue 7 | Compilation 1.0

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Keywords: BACs, H. pylori, binding affinities, molecular docking, and MD simulations, traditional medicinal herbs, garboxyspermidine dehydrogenase, peptic ulcers, gastric disorders, therapeutic agents.

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I. INTRODUCTION

The prime reservoir of bacteria in humans is in the digestive tract and Helicobacter pylori (H. pylori) is one of the threats leading to ulcers. H. pylori has the capacity to endure in the hostile environment of the stomach (Fagoonee & Pellicano, 2019). Moreover, H. pylori has become one of the most prevalent infections in humans and a major causative factor in a number of stomach conditions, such as gastritis, peptic ulcers, and gastric carcinoma (Haley & Gaddy, 2015). People diagnosed with H. pylori are expected to have a more than twice higher risk of developing gastric cancer relative to non-infected individuals (Queiroz et al., 2012).

1.1 Level of H. pylori

Proportionally, the major affected population with H. pylori has been falling in the Western world with high levels of industrialization around the turn of the twenty-first century, whereas it has stagnated at high levels in developing and recently industrialized nations. H. pylori occurs more frequently in Asia, Latin America, and Africa than in North America and Oceania, where it has been discovered in only 24% of the population (Sjomina et al., 2018) (FitzGerald & Smith, 2021) (Elbehiry et al., 2023). 50.8% of people with H. pylori infection reside in developing countries compared to 34.7% in industrialized countries (Elbehiry et al., 2023). The future global occurrence of disorders related to H. pylori, such as peptic ulcer and gastric cancer, will be significantly impacted by the increasing industrialization (Hooi et al., 2017).

1.2 The virulence of H. pylori

This bacteria (H. pylori) is a gram-negative bacterium with a helical structure that colonizes the human gastrointestinal tract, especially leading to infection of the stomach epithelium (Charitos et al., 2021). Four essential steps are necessary for H. pylori bacteria to achieve effective colonization, persistent infection, and disease pathogenesis once they have entered the stomach of the host: (a) survival in the stomach's acid; (b) motility toward epithelial cells via flagella; (c) adhesion/receptor contact for attachment to host cells; and (d) release of toxins that cause tissue damage (Kao et al., 2016). Infection normally causes silent stomach inflammation, but chronic exposure to more pathogenic strains causes serious pathological changes such as gastric and duodenal ulcers, as well as tumor progression that ends in gastric malignancies and carcinoma (Peek & Blaser, 2002). Gastric and duodenal ulcer wounds are at least 5 mm broad but can be much larger and deeper ulcers involving the capillaries of the muscularis propria and even the serosa layer can induce bleeding and perforation, although ulcers in the pyloric canal can produce pyloric smooth muscle spasm, resulting in pyloric obstruction (Gurusamy & Pallari, 2016).

An enzyme known as urease is produced by H. pylori. Due to its weakening effect on the gastric lining, this enzyme neutralizes and acidity of stomach acids and help H. pylori survival before the mucous layer .A thick coat of mucous coating the stomach wall shields it against its own gastric acid (Penta et al., 2005). Mucins, which are high molar mass and extensively glycosylated glycoproteins, form the mucous membrane and protect stomach epithelial cells. The primary mucins produced in the stomach are MUC 1 (membrane-bound) and MUC5AC and MUC6 (secreted), MUC5AC, constituting the majority of the adherent unstirred mucus layer, is released by surface foveolar cells. In contrast, MUC6 is released by neck and gland cells, and both are highly expressed in normal stomach lining (Boltin & Niv, 2013). H. pylori enzymes, protease and lipase, break down gastric mucus and disrupt the phospholipid-rich layer on the surface of apical epithelial cells, permitting gastric epithelium cells damage from the backward flow of gastric acid (Smoot, 1997). The mucosal layer's primary elements are associated with H.pylori and aid in the bacterium's adhesion to the gastric epithelium (Van den Brink et al., 2000). The role of this pathogen in stomach disorders remains uncertain and controversial. H. pylori induces passive inflammation in the gastric epithelium and disrupts signal transduction pathways, which facilitates pathogenesis. Additionally, it acquires antimicrobial resistance through genetic changes and biofilm formation (Baj et al., 2020) (Elbehiry et al., 2023).

8H52 is the crystal structure of Helicobacter pylori carboxyspermidine dehydrogenase (CASDH) in combination with Nicotinamide adenine dinucleotide Phosphate (NADP). This protein contains spermidine, a positive polyamine that is important in a variety of biological activities. CASDH aids H. pylori's survival and virulence by enabling the metabolism of polyamines, which are essential for the bacterium's growth, stress response, and ability to colonize the acidic stomach environment. (Ko et al., 2022). To biosynthesize spermidine, H. pylori uses the enzymes CASDH and carboxyspermidine

decarboxylase (CASDC), the presence of spermidine is necessary for bacterial growth (Zhang & Au, 2017).

1.3 Herbs bioactive compounds (BACs) and drug designing

The usage of phytochemicals, often known as nutritional supplements, is growing faster all over the world for treating a variety of health issues (Organization, 2004). Numerous substances originating from natural sources have shown pharmacological properties against H. pylori, which makes them extremely promising candidates for future medication. These medicines derived from plants are largely used and are a better option due to safety in use, availability, and have few side effects compared to the synthetic alternatives (Iwu et al., 1999).

Drug designing is an important area of research where computational biophysics, biochemistry, and data science have recently gained popularity and the use of computational methods can assist researched results from sizable databases and synthesized new tiny molecules (Preman et al., 2022). Computer-aided drug design (CADD) has gained general recognition among scientists as part of a comprehensive drug-designing strategy (Sabe et al., 2021). Therefore, this work focused on uncovering new possible leads from herbs that could be used to inhibit spermidine production in battling H. pylori using computational methods, which is a major cause of gastritis, peptic ulcers, and gastric cancer.

II. METHODOLOGY

2.1 Protein Preparation

The crystal structure CASDH from H. pylori in combination with NADP (PDB ID: 8H52) was retrieved from Protein Data Bank (https://www.rcsb.org/). NADP alters the structure ordering of carboxyspermidine dehydrogenase by optimizing its configuration for efficient catalysis in polyamine metabolism, thereby enhancing the protein's functional activities crucial for cellular processes. (Ko et al., 2022). Protein was prepared in to receptor by the addition of charges, polar hydrogen, and deletion of the heavy atoms, including co-crystallized ligands, water molecules, heteroatoms, Actosite, and co-factors. And the addition of polar Hydrogen took place performed in BIOVIA discovery and UCSF Chimera with charmm force field parameter to perform energy minimization of the receptor.

Figure 1: Helicobacter pylori carboxyspermidine dehydrogenase crystal structure in combination with NADP (PDB ID: 8H52)

2.2 Ligand Preparation and Virtual screening

The Zinc Data Base was used to obtain all-natural chemical structures (ligands) in SDF format. Before molecular docking, ligands were filtered by druglikeness for the preliminary assessment of physiochemical, pharmacokinetic, and ADMET properties performed in SwissADME. The ligands preparation and virtual screening were done in PyRx 0.9x and UCSF chimera software with an Autodock vina to find the BACs fit to the target and acquire a variety of binding conformations andc binding affinities (BA) by approximates the Gibbs free energy change upon binding. Table 1 represents the alternative medicines uses or other biological activities.

Table 1: Complementary medicine uses, herbal sources and selected BACs

Major BACs chosen for anti-peptic ulcers	Source of BACs	Complementary medicine uses
Hydroxybenzoic acid, Hydroxycinnamic acid, Cyanidin, Delphinidin, Malvidin, Peonidin, Petunidin, Pelargonidin and Procyanidin B1, Procyanidin B2, Procyanidin B3, Procyanidin A1, Procyanidin A2 and Proanthocyanidins (Tannis)	*Ribes uva-crispa and Vaccinium sect. Cyanococcus*	Enabling digestion, lower fever, detoxify blood, lower cough, significant for eyes, enhance hair growth (Annapurna, 2012)
Isoflavonoids, Dihydroflavanols, Dihydrochalcone, Cinamic acid, Feruloylquinic acid, Comaroylquinic acid, Shikimic acid, Ellagic acid, Propionic acid, Abscisic acid, β-carotene and α-carotene.	*Prunus Domestica*	Anti-cancer, Anti-bacteria, Anti-fungal (Hussain et al., 2021)
β-carotene, α-carotene, Hydroxybenzoic acid, Hydroxycinnamic acid, dehydroascorbic acid (DAA), Chlorophyll, lycopene, lutein, Ellagic acid, Gallic acid, Kaempferol, xanthophyll and flavonoids	*Cucumis melo var. cantalupensis*	Anti-oxidant, Anti-microbial, maintain radical stability, anti-carcinogenic (Vella et al., 2019)
Cyanidin, Chlorogenic acid, apigenin, apiin, Rutin, niacin, riboflavin, pantothenic acid, choline, phylloquinone, dehydroascorbic acid (DAA), Vitamin E succinate, oleic acid, β-linoleic acid, α-linoleic acid, (3,7-dihydroxyflavonoid), Cirtusin A, Abietin, Peucedanin, Citropten, Osthenol, Xanthophyll, diadinoxanthin, violaxanthin, artemisin, ganoderic acid V, ganoderic acid R, α-ionone, diosmetin, tomatine, corticrocin, and safflomin A	*Apium graveolens*	Anti-oxidants, Anti-microbial, hypolipidemic, hypoglycemic, and anti-platelet aggre(Sowbhagya, 2014)
Epicatechin, Quercetin, Kaempferol, Galic acid, Ellagic acid, Caffeic acid (Hydroxycinnamic acid)	*Potentilla Fulgens*	Antimicrobial, anticancer, antioxidant, anti-inflammatory, and antiulcerogenic, as well as anti-hyperglycemic, anti-hyperlipidemic(Nath & Joshi, 2013)
Catechin, Theaflavin, flavonol glycosides, L-theanine, Caffeine, theobromine.	*Camellia sinensis*	Therapy of cardiovascular conditions, cancer, digestive issues, obesity, and diabetes. Also show strong anti-oxidants, and

		anti-inflammatory attributes (Samanta, 2022)
Hydroxybenzoic acid, Hydroxycinnamic acid, Flavonoids and Carotenoids	*Spinacia oleracea*	Anti-tumor, Antioxidant, bile acid binding, and Anti - inflammatory actions (Singh et al., 2018)
Gingerols, Shogaols, Paradols, Quercetin, Zingerone, Gingerenone-A, 6-dehydrogingerdione, β-bisabolene, α-circumene, Zingiberene, α-farnesene, β-sesquiphellandrene.	*Zingiber officinale*	Gastrointestinal protection, cholesterol lowering, anti-obesity, cardioprotective, anti-diabetic, anti-inflammatory, and anti-cancer activities and digestive stimulant (Srinivasan, 2017)
Demethoxycurcumin, bisdemethoxycurcumin, Ar-turmerone, α-phellandrene, Terpionele, α-zingiberene, β-sesquiphellandrene, Ar-turmerol, farnesol, β-bisabolol, Germacrone, Caffeic acid, Catechin, Chlorogenic, Cinnamic acid, Myricetin, Rutin, Quercetin, Sinapic acid, curcumin pyrazole, and Vanilic acid	*Curcuma*	Antioxidant qualities, anti-inflammatory properties, anti-cancer properties, neuroprotective properties, antibacterial and antiviral effects, asthma and diabetes prevention properties (Sahoo et al., 2021)
Ascorbic acid, α-tocopherol, Glucoraphanin, 4-hydroxyglucobrassicin, Neoglucobrassicin, Sulforaphene, Sulforaphane, Indole-3-carbinol	*Raphanus sativus*	Prevention of cancer by apoptosis, Inhibit growth of H.Pylori due to antioxidants presence, therefore lower the risk of Gastric cancer (Lim et al., 2015)
vitexin-7-O-glucoside, vicenin-2, vicenin-2, orientin, luteolin, naringenin, quercetin, diosgenin, yamogenin, yuccagenin, tigogenin, and smilagenin	*Trigonella foenum-graecum*	Gastroprotective, anti-hypercholesterolemic Preventing liver demage, Stabilize blood glucose level, cytotoxic (Olaiya & Soetan, 2014)
β-carotene, Tocopherol, Xanthophyll, Lutein, Chlorogenic acid, Falcarinol, Falcarindiol, Falcarindiol-3-acetate, Glutamic acid, Caffeic acid, Thiamin, Riboflavin, Niacin.	*Daucus carota*	Antitumor, cytotoxic, anti-inflammatory, cardiovascular diseases (Ahmad et al., 2019)
Alkaloid (Tryptanthrin), Flavanoids, terpinoids, Indigotine, Induruben and ratenoids.	*Indigofera tinctoria*	Anti-viral, Anti-bacterial, Anti-inflammatory, Gastroprotective also prevent liver demage (Motamarri et al., 2012)

2.3 Molecular docking

The AutoDock Vina tool was used to dock the selected BACs with the crystal structure of Carboxyspermidine dehydrogenase from Helicobacter pylori in combination with NADP, with Vina search center (X: -16.2076, Y: -29.6123 and Z: -24.0957) and Dimension (Angstrom) (X: 71.9734 Y: 47.2377 Z: 74.8061) using PyRx, and the best responses were subjected to site specific docking using UCSF chimera with coordinates center (X: -37, Y: 4, and Z: -18) and coordinate size (X: 10, Y: 22, and Z: 15). Center coordinates target binding site by center the box on the known or predicted binding site of the target protein, while dimensions ensuring entire binding pocket is covered, including possible

sub sites which allow ligands to explore all potential binding conformation with the binding site (Zhao et al., 2020) . Hydrogen bonds interaction, hydrophobic interaction, solvation effects and binding affinities scores estimated by autodock vina provide the optimal conformation with lowest docking potential and best poses. The potential scores with best poses were picked for visualization and interaction analysis using Maestro (reddy Peasari et al., 2018) and UCSF Chimera (Pettersen et al., 2004).

2.4 Physiochemical, Pharmacokinetics, and Drug Likeness Aspects of BACs

Typical computational pharmacokinetics parameters and drug-likeness were developed for the assessment of physicochemical, pharmacological, and drug-like features during the drug development process. Ghose, Veber, Egan, and Muegge rules are characteristics of drug likeness that define Lipinski (Lipinski, 2004). Any bioactive compound potential for treatment has to obey Lipinki's rule of five and the data from the ADMET investigations were filtered and confirmed for Lipinski's rule of five that are stated as follows: hydrogen-bonding donors < 5 (the overall amount of nitrogen-hydrogen and oxygen-hydrogen bonds), hydrogen bond acceptors < 10 (all nitrogen or oxygen atoms), a molecular weight < 500 daltons, and a coefficient of octanol-water partitioning $\log P < 5$ (Lipinski, 2004). The first two rules for Hydrogen bond donor and acceptor imply adequate intestinal availability, and the latter two rules imply excellent oral absorption thus this decides whether a molecule is drug-like or not (Schneider, 2013) (Lipinski, 2004). All BACs were ADME/T screened using the internet web SwissADME to determine the drug-likeness agents (Bakchi et al., 2022).

2.5 MD modeling of protein-ligand interactions

Molecular Dynamics Simulation was conducted to understand in deep how 8H52 interacts with potential phytochemicals when it binds to a target protein, molecular dynamics (MD) simulation aids in the visualization of protein flexibility (Hansson et al., 2002). Analyzing the underlying motions of protein-ligand complexes can reveal several new unexplored bioactivities and intricate dynamic processes (Anwer et al., 2015). GROMACS was utilized to investigate the stability of the complexes, energy minimization, and equilibration (Gapsys et al., 2022). The GROMACS was also utilized in the simulation of Receptor-ZINC519621, Receptor-ZINC33299, Receptor-ZINC14642912, and Receptor-ZINC19816066 at 300K, with CHARMM27 force fields then hybrid ligand structure and force field properties of chosen ligands were determined using Swiss Param

In a "cubicbox" with a basic diameter of 1 nm with all the default settings, Receptor-ZINC519621, Receptor-ZINC33299, Receptor-ZINC14642912, and Receptor-ZINC19816066 were wet. The heat of all systems was raised from 0 to 300 K during the length of the equilibration time (1000 ps), while preserving a steady volume and periodic boundary conditions, and the system was then reduced using 1000 "sharpest decline" steps. The resulting trajectories were utilized to examine the system stability as well as to evaluate each complex's behavior. Root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), Hydrogen bonding (H-bond), and Total energy calculations were used to examine the variations of the macromolecule and macromolecule-ligand complex system (Salaria et al., 2022).

NVT ensemble and NPT ensemble were the two phases of the equilibration process. While all other atoms were allowed to move freely in both NVT and NPT, the C backbone atoms of the original structures were constrained. The MD was then run at 300 K with a 10 ns time frame. The obtained trajectories were examined using GROMACS analysis modules. UCF Chimera and Maestro were used to produce MD movies and interaction diagrams respectively.

III. RESULTS AND ISCUSSION

This study tested 1102 BACs derived from traditional herbs with the goal of targeting spermidine, which is biosynthesized by carboxyspermidine dehydrogenase (CASDH) in H. pylori. Initially, 323 BACs found to have druglikeness after filtering physiochemical, lipophilicity, water solubility, pharmacokinetics and medicinal chemistry. Four BACs were found to have significance scores from molecular docking for the inhibition of 8H52 protein. These were curcumin pyrazole (ZINC19816066), scoparol (ZINC519621), tryptanthrin (ZINC33299) and 4'-O-methylcatechin (ZINC14642912). Curcumin pyrazole was from *curcuma*, scoparol from *trigonella foenum-graecum*, tryptanthrin from *indigofera tinctoria*, and 4'-O-methylcatechin from *camellia sinensis* and *curcuma*. Spermidine is significant for bacteria growth and cell survival. Therefore H.pylori binds on the surface and facilitates adherence to the gastric epithelial cells. These bioactive substances were observed to be crucial for the suppression of spermidine to stop the protein's development. The physicochemical, pharmacokinetic, drug-likeness, and ADMET aspects of curcumin pyrazole, scoparol, tryptanthrin, and 4'-O-methylcatechin are presented in Table 2.

Table 2: ADME evaluation of curcumin pyrazole, scoparol, tryptanthrin and catechin

Property	Attribute	Value				Unit
		Curcumin pyrazole ZINC19816066	Scoparol ZINC519621	Tryptanthrin ZINC33299	Catechin ZINC14642912	
Physiochemical	Molecular weight Number of heavy atoms Number of aromatic heavy atom Number of rotatable bonds Number of H-bond acceptors Number of H-bond donors Molar Refractivity	364 27 17 6 5 3 106.36	300.26 22 16 2 6 3 80.48	248.24 19 16 0 3 0 70.77	290.27 21 12 1 6 5 74.33	g/mol
Lipophilicity	*Log* $P_{o/w}$	3.12	2.18	2.08	0.85	
Water solubility	*Log S* Solubility Class	-4.73 6.83e-03; 1.88e-05 Moderately soluble	-4.06 2.61e-02; 8.69e-05 Moderately soluble	-2.77 4.22e-01; 1.70e-03 Soluble	-2.14 2.09e+00; 7.19e-03 Soluble	mg/ml; mol/l
Pharmacokinetics	GI absorption BBB permeant P-gp substrate CYP1A2	High No No No Yes No	High No No Yes No Yes	High Yes No Yes No No	High No Yes No No No	

	CYP2C19 CYP2C9 CYP2D6 CYP3A4 *Log* K_p	No -5.64	Yes -5.93	Yes -6.36	No -7.82	cm/s
Druglikeness	Lipinski Ghose Veber Egan Muegge Bioavailability score	Yes; 0 violation Yes Yes Yes Yes 0.55	Yes: 0 violation Yes Yes Yes Yes 0.55	Yes: 0 violation Yes Yes Yes Yes 0.55	Yes: 0 violation Yes Yes Yes Yes 0.55	
Pharmaceutical Chemistry	PAINS Brenk Lead likeness Synthetic accessibility	0 alert 0 alert MW>350 3.14	0 Alert 0 Alert Yes 3.06	0 Alert 0 Alert MW< 250 2.42	1 Alert 1 Alert Yes 3.50	

These four BACs were found to have the highest binding scores as compared to the synthetic medicine omeprazole, with a binding affinity of -8.8 Kcal/mol. Curcumin pyrazole from curcuma has the highest docking score of -9.9 Kcal/mol, scoparol from trigonella foenum-graecum exhibits favorable interaction with a docking result of -9.6 Kcal/mol, followed by tryptanthrin from indigofera tinctoria and 4'-O-methylcatechin from camellia sinensis and curcuma which has -9.5 Kcal/mol.

Curcuma possesses antioxidant, anti-inflammatory, anti-cancer, neuroprotective, antibacterial, and antiviral properties, as well as asthma and diabetes-preventative characteristics (Sahoo et al., 2021), curcumin pyrazole formed π–π stacking bonding with PHE183. Furthermore, curcumin pyrazole formed three hydrogen bonds (H-bonds) with the receptor's residues. The H-bonds was formed with ASH143, LEU85, and SER34. The ASH143 and SER34 are the hydrogen bond acceptors (HBA), and LEU85 is the hydrogen bond donor (HBD). H-bonds are important for the stability of the complex structure and also for drug absorption and distribution (Coimbra et al., 2021). Atoms exposed to solvent for curcumin pyrazole from the 2D interaction diagram are C19, C20, C21, C2, O1, C1, C7, C9, C11, C13, C14 and C17 as depicted in Figure 2 (a and b).

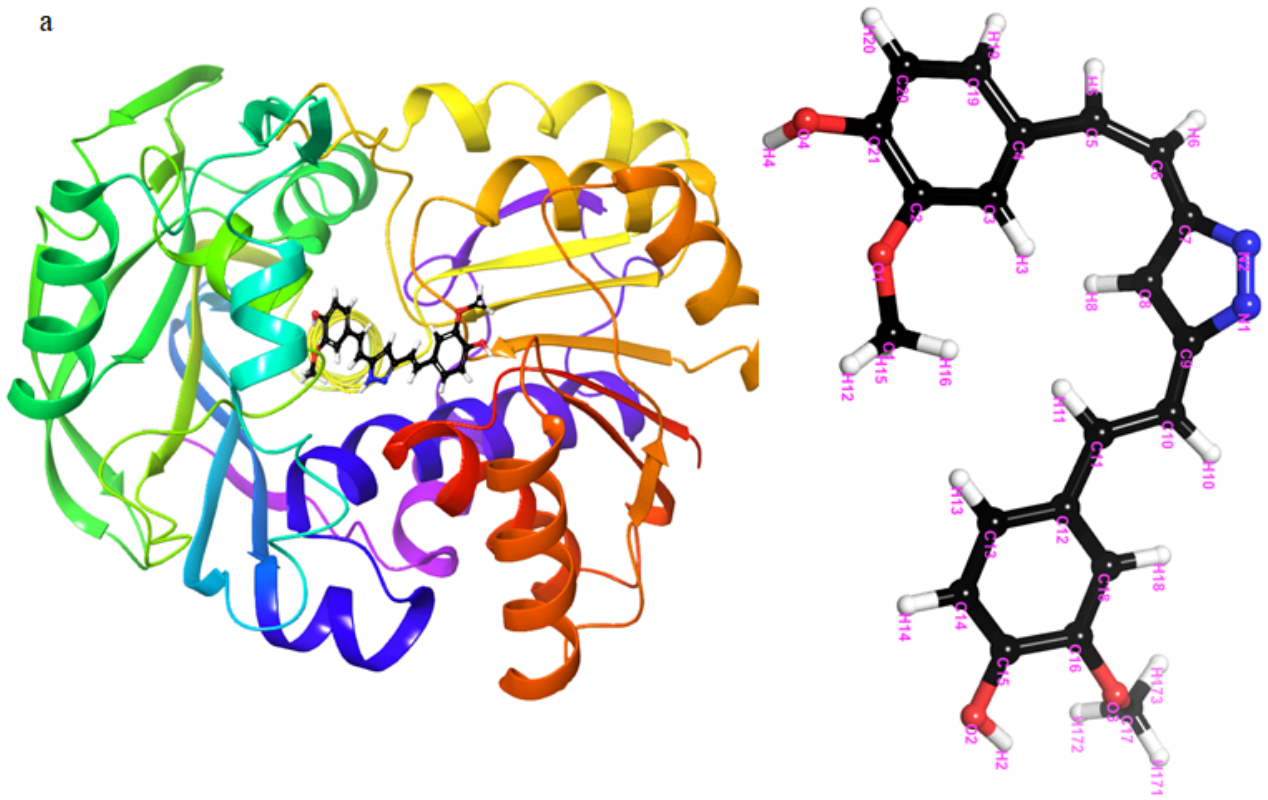

Figure 2 a: 3D visualization of receptor-curcumin pyrazole and curcumin pyrazole structure.

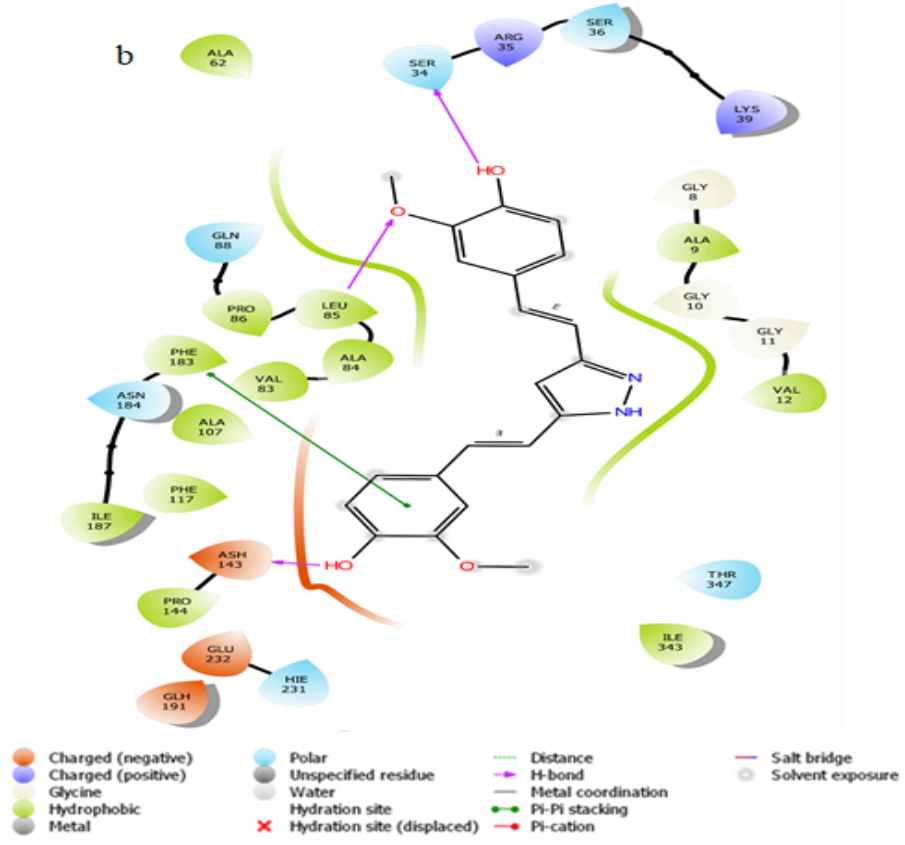

Figure 2 b: 2D interaction diagram of curcumin pyrazole inside binding pocket of 8H52

Scoparol during docking produces two different pose structures which are visualized in 2D interaction. Figure 3b, initially, the 2D interaction diagram of scoparol shows scoparol formed two π–π stacking

with residue PHE183, and four H-bonds with ASH143, GLH191, GLU232, and VAL83. In these configurations ASH143, GLU232, and VAL83 were HBAs while GLH191 was HBD. The final structure in Figure 3c, scoparol formed two π–π stacking with residue PHE183, and three H-bonds with GLH191, GLU232, and VAL83. In this interaction diagram GLU232 and VAL83 are HBAs while GLH191 is the HBD. In the first pose structure, solvent exposure of scoparol atoms inside the receptor is observed in Figure 3b in the ring with C12, C11, C8, and O6. For the second pose structure, in Figure 3b, atoms C12, C11, O5, and O6 are exposed to solvent as depicted in scoparol atoms in Figure 3a.

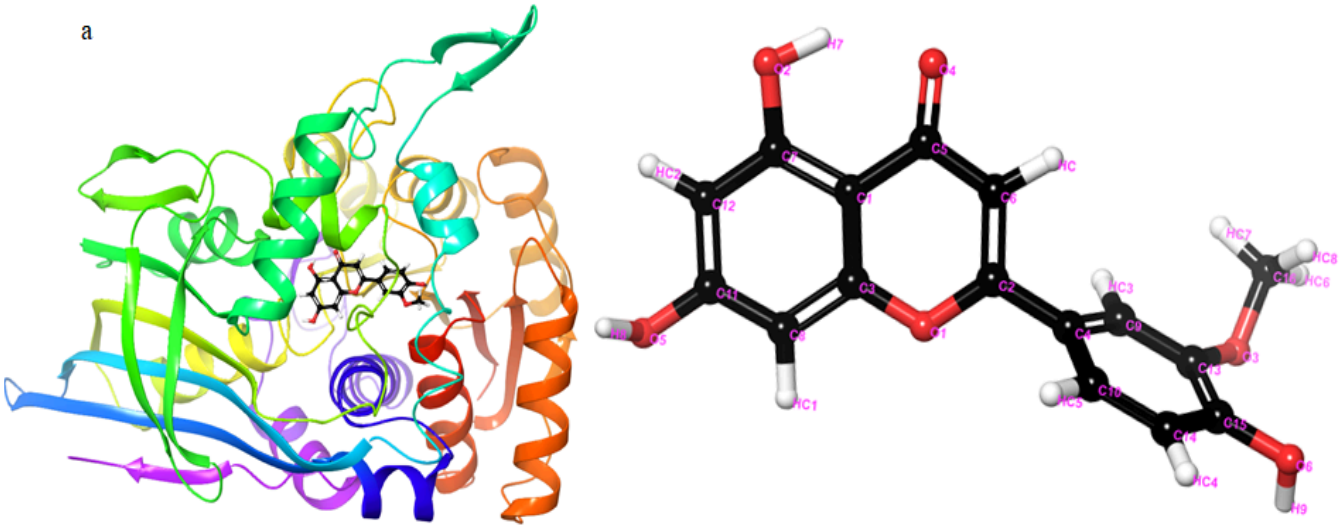

Figure 3a: 3D visualization of receptor-scoparol and scoparol structure.

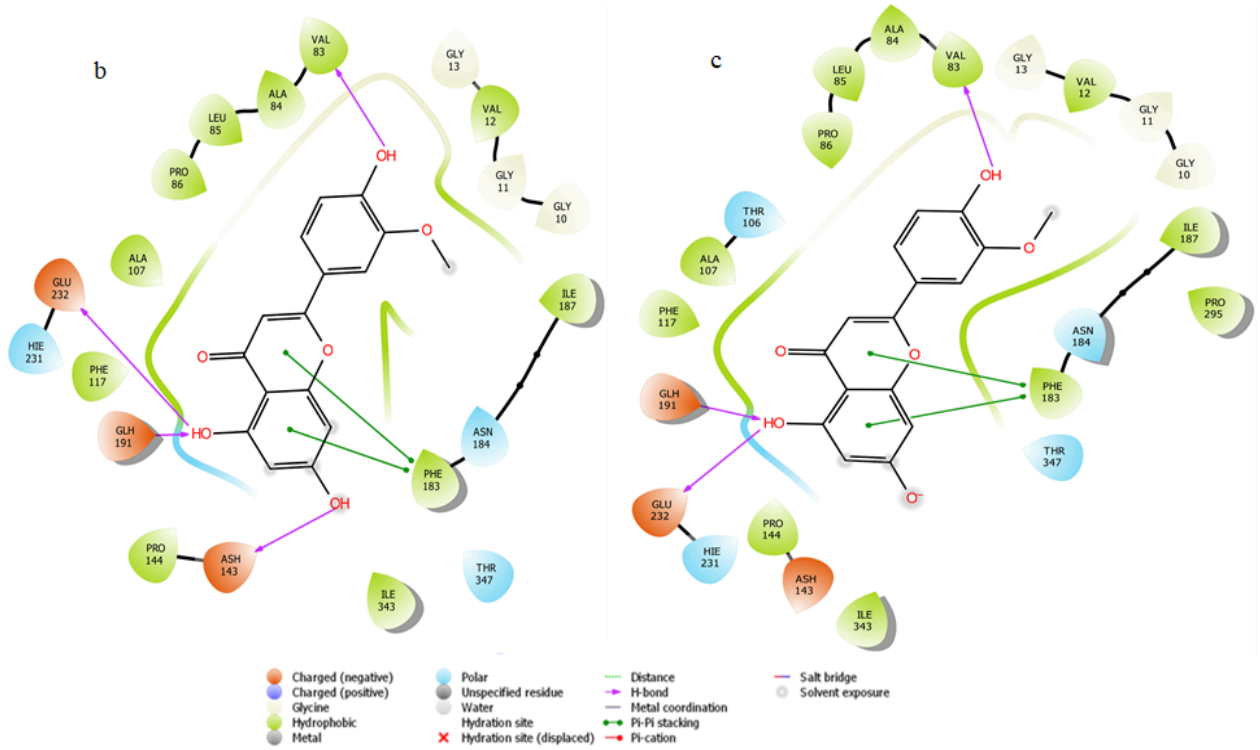

Figure 3 (b and c): 2D interaction diagram of two different poses of scoparol inside the binding pocket of 8H52

It has been found that *indigofera tinctoria* contains antiviral, antibacterial, anti-inflammatory, and gastroprotective properties that also inhibit liver damage (Motamarri et al., 2012). Tryptanthrin formed two π–π stacking bonds with the PHE183. Moreover, there is one hydrogen bond with GLH191, in which GLH191 is the HBD. It is also observed that C11, C12, C13, C15, and C14 are exposed to solvents compared to other atoms as shown in Figure 4 (a and b).

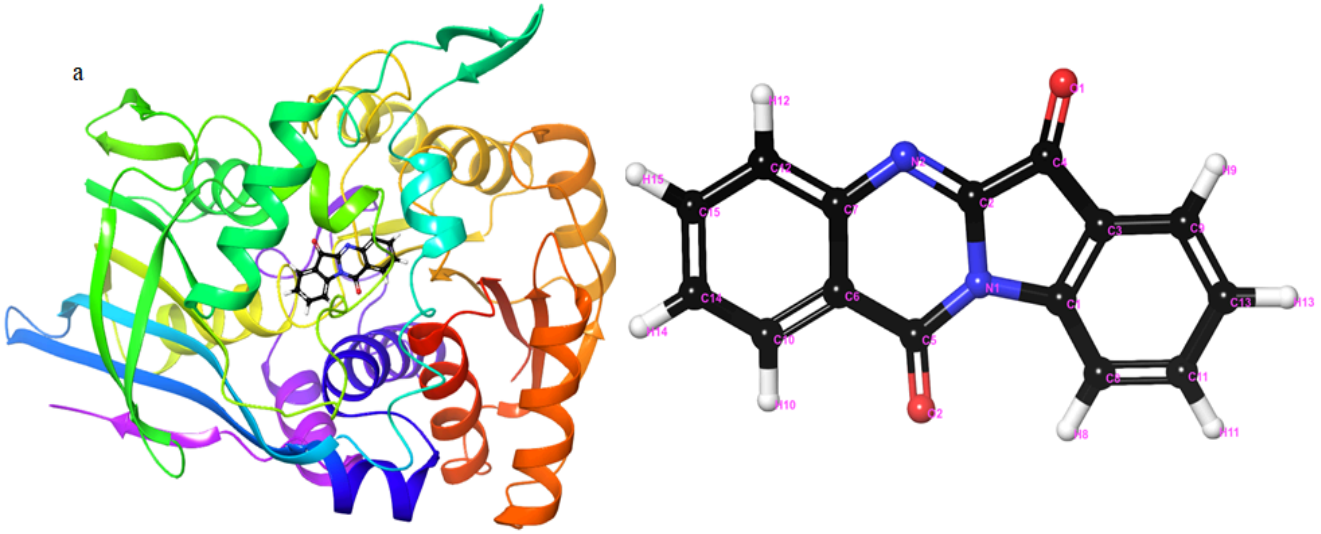

Figure 4a: 3D visualization of receptor-tryptanthrin and tryptanthrin structure

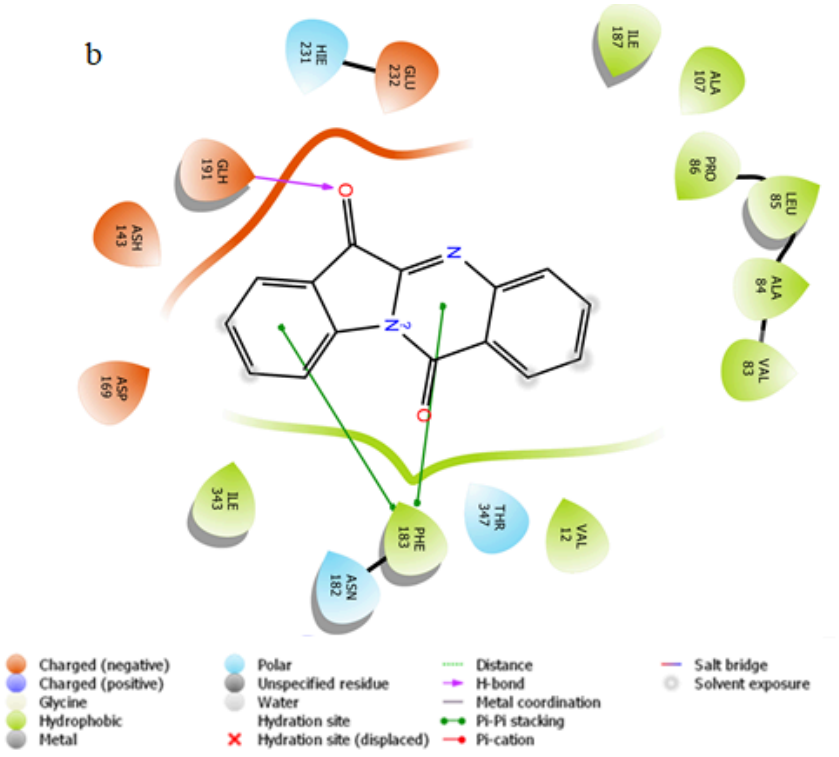

Figure 4b: 2D interaction diagram of tryptanthrin inside the binding pocket of 8H52

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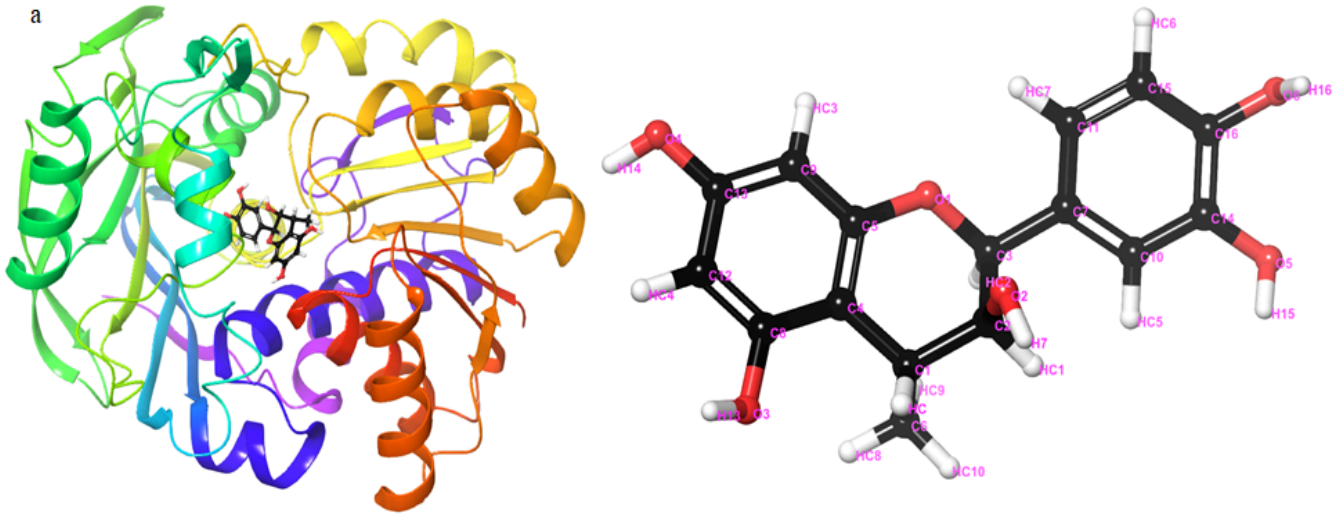


Figure 5 a: 3D visualization of receptor-4'-O-methylcatechin and 4'-O-methylcatechin structure.

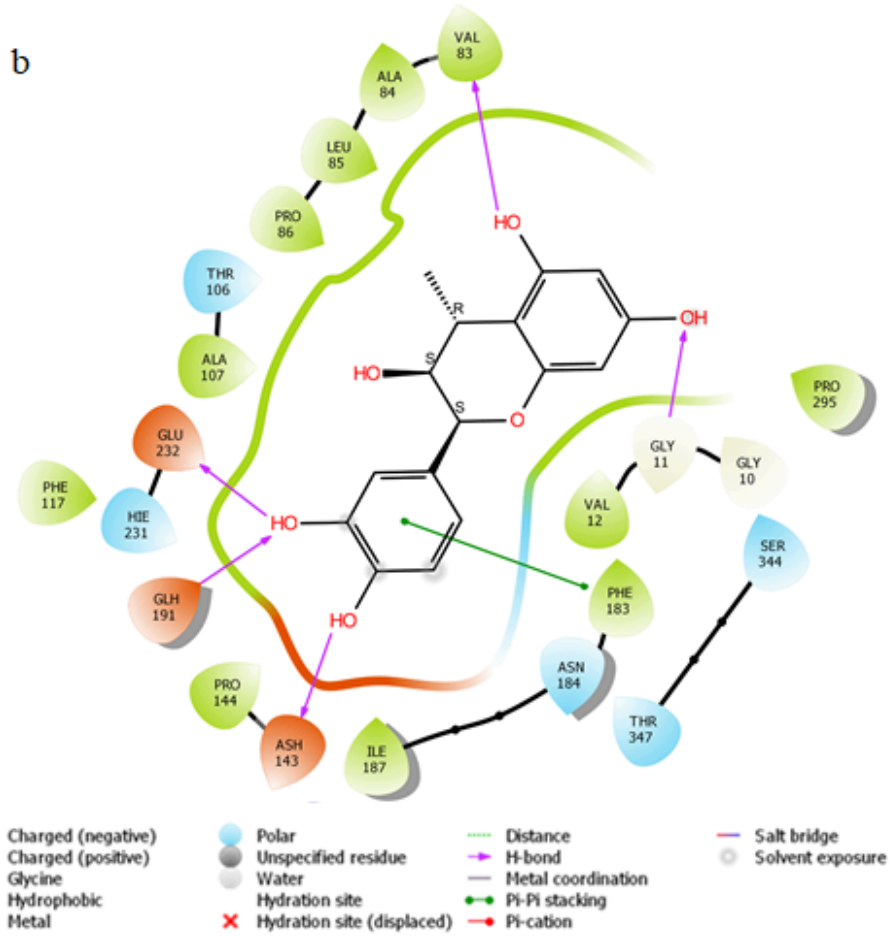


Figure 5 b: 2D interaction diagram of 4'-O-methylcatechin inside binding pocket of 8H52

Antioxidants, anti-inflammatory, gastrointestinal protection, and antitumor activities have also been reported from Camellia sinensis and Curcuma (Sahoo et al., 2021; Samanta, 2022). 4'-O-methylcatechin formed π–π stacking bonding with PHE183, in this there are five hydrogen bonds formed with the residues. Three are HBAs, ASH143, VAL83, and GLU232; while the GLY11 and GLH191 are HBDs. This contributes to the overall binding affinity of the 4'-O-methylcatechin inside the

protein structure. It is shown also that C15, C16, and C14 are exposed to solvent compare to other 4'-O-methylcatechin atoms as shown in Figure 5 (a and b).

H.Pylori has been becoming resistant to a number of synthetic drugs that are used as a therapy (Qureshi & Graham, 2000). One of the commonly used therapeutic drugs which is widely used for inhibition of H.Pylori is Omeprazole. From the docking result of Omeprazole against the target (8H52), the binding affinity was observed to be 8.8Kcal/mol. It was observed that, omeprazole had no bonds formed with the residues. As seen from Figure 6, C12, C14, C13, O1, C4, S1, C2, C3, C6, C8, C11, and C16 are exposed to solvent.

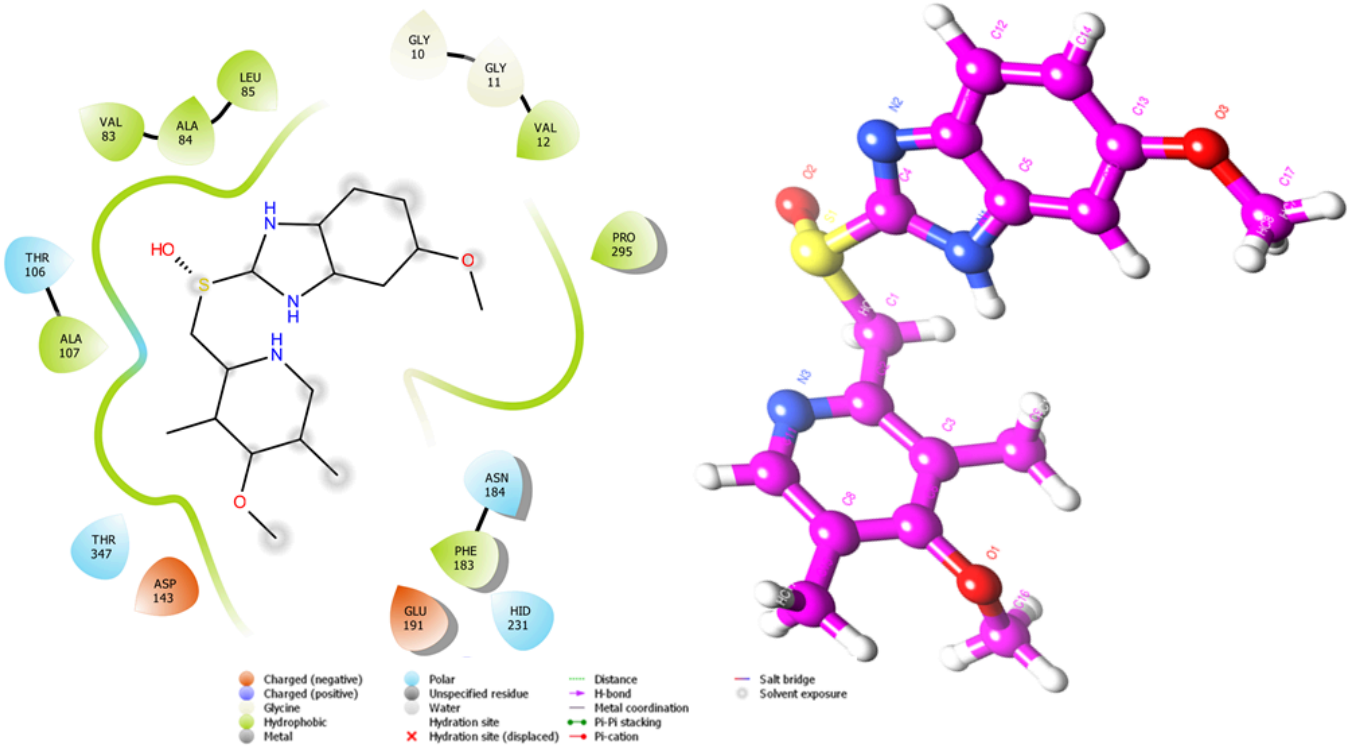


Figure 6: 2D interaction diagram of omeprazole inside binding pocket of 8H52

Inhibiting Spermidine, which is essential for bacterial biofilm development and cell growth, is as important as for bacterial ablation because it prevents bacterial adherence to stomach epithelial cells. Thus, the receptor-ligand interaction is a promising technique for H.pylori suppression in the prevention of peptic ulcers and gastric cancer. It has been observed that curcumin pyrazole, scoparol, tryptanthrin, and 4'-O-methylcatechin interact well with 8H52, and the interesting is the formation of H-bonds that maintain the stability of the complexes. RMSD analysis was employed to assess the stability of the protein-ligand complex throughout a defined time period of 10 ns. This was an essential metric in determining structural stability. Findings from molecular dynamic simulation indicated that the mean stabilities of the studied protein-ligand complexes have been found to be 0.42 nm for 8H52-curcumin pyrazole, 0.39nm for 8H52-scoparol, 0.395nm for 8H52-tryptanthrin, 0.18nm for 8H52- 4'-O-methylcatechin, while it was 0.56 nm for 8H52-Omeprazole. Analysis from RMSD indicated that the maximum deviation exhibited by OM (omeprazole) and CP (curcuminpyrazole) was 0.63 nm and the minimum deviation was shown by CA (4'-O-methylcatechin) with the value of 0.18 nm. This shows that 4'-O-methylcatechin has good stability compared to the four ligands as depicted in the line and box plot (Figure 7) (Castro-Alvarez et al., 2017). Furthermore, the total energy interaction

profile for the five ligands is less ranged from −480000 KJ/mol to −478300 KJ/mol. This indicating that the system is stable during the simulation (Figure 8) (Peach et al., 2017).

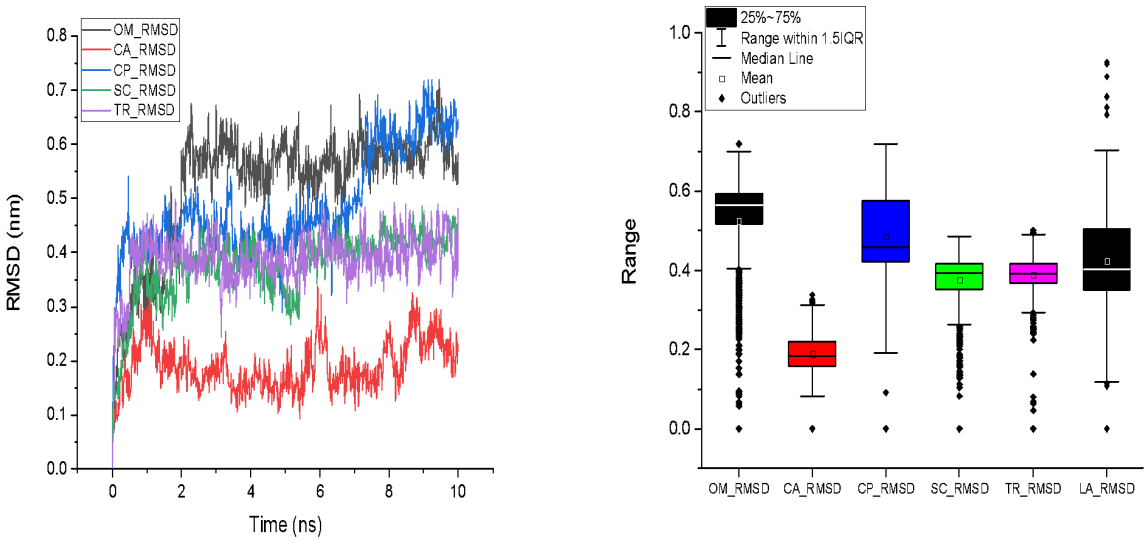


Figure 7: RMSD plot of BACs and control drug in complexation with 8H52

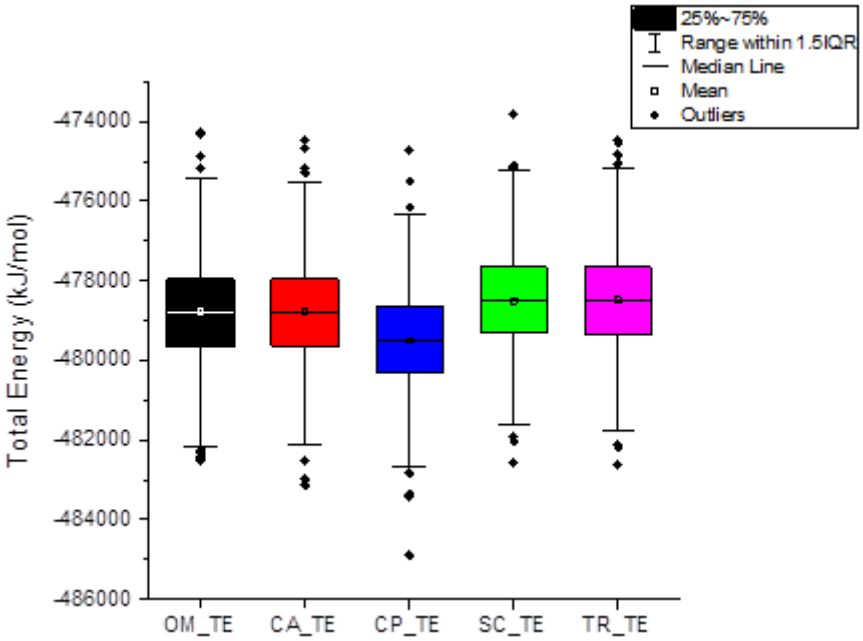
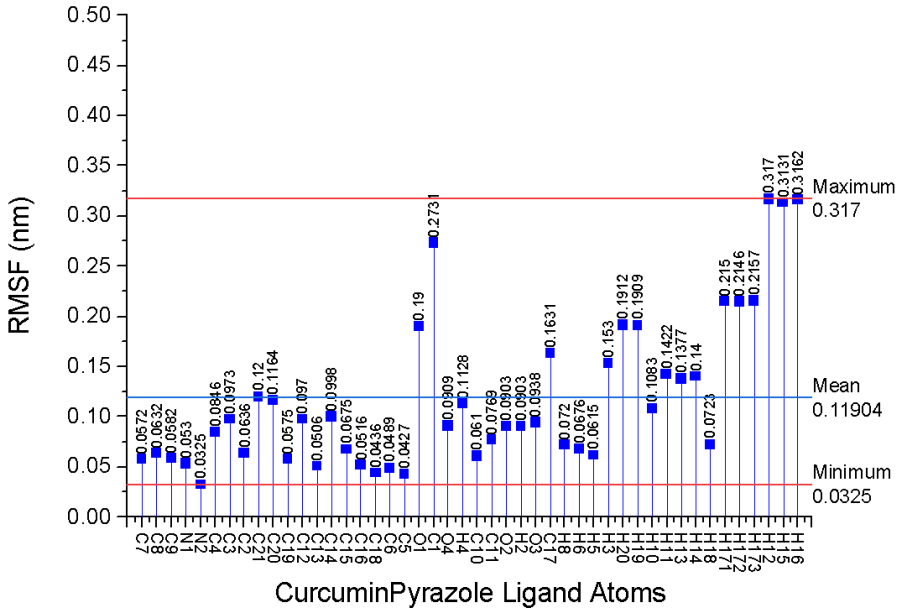
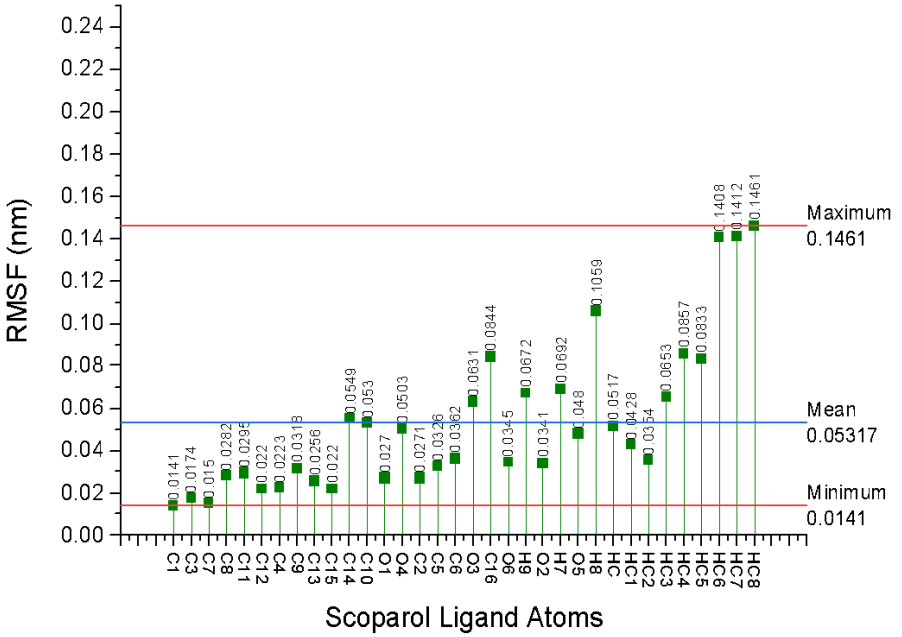
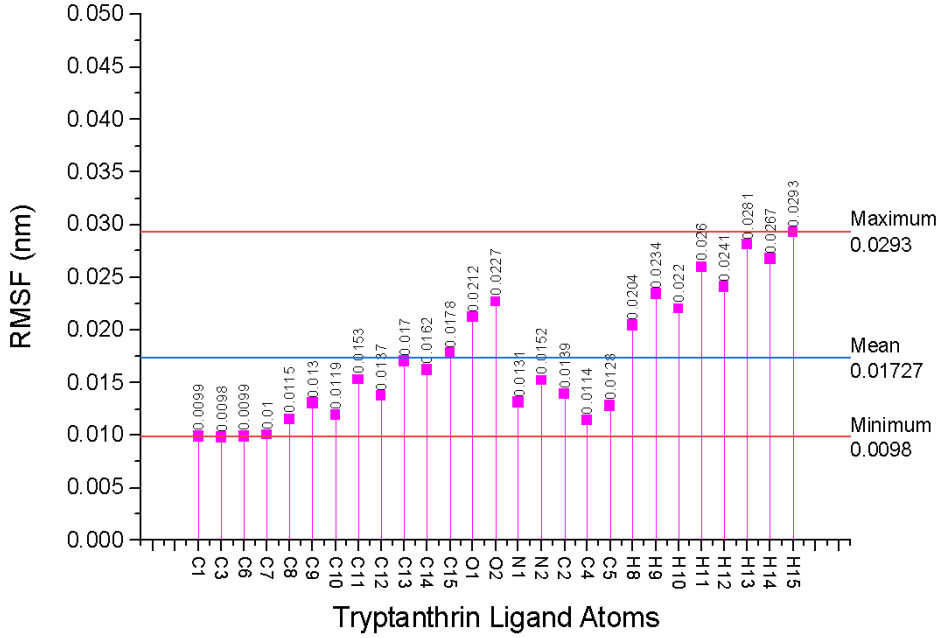


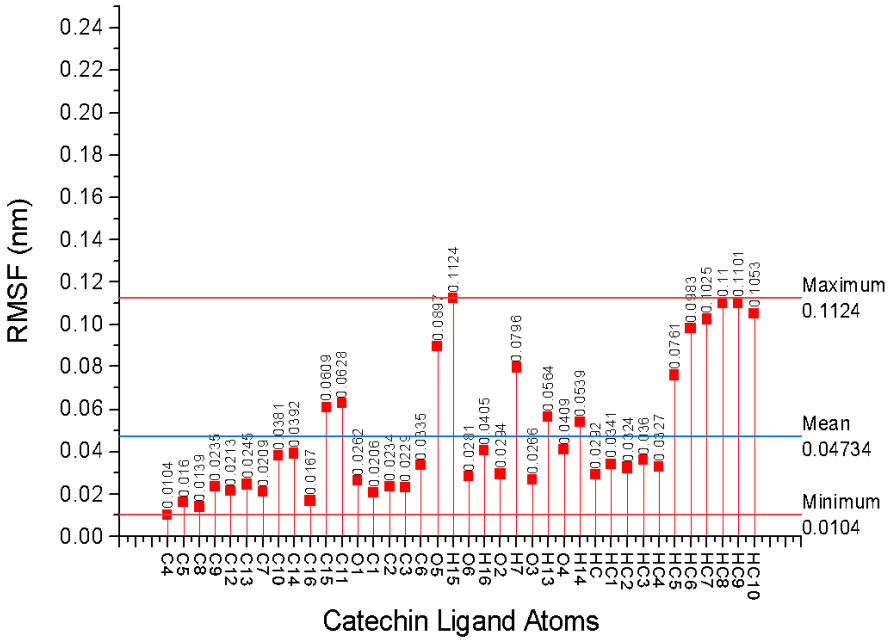
Figure 8: Total energy interactions profiles

In a protein's three-dimensional structure, RMSF is an average over the number of atoms measurement of how far an individual atom, or group of atoms, has moved away from the reference structure. The mean flactuations of the ligand's atoms were 0.11904 nm for curcumin pyrazole, 0.05317 nm for scoparol, 0.01727 nm for tryptanthrin, 0.04734 nm for 4'-O-methylcatechin, and 0.11255 nm for omeprazole. As it is seen from these results tryptanthrin had minimium RMSF indicating that their atoms does not move far away from the reference structure. The maximum fluctuations of ligand's atoms are influenced by the environmental exposure. The minimium, mean and maximum fluctuations of the ligand's atoms are represented in Figure 9.









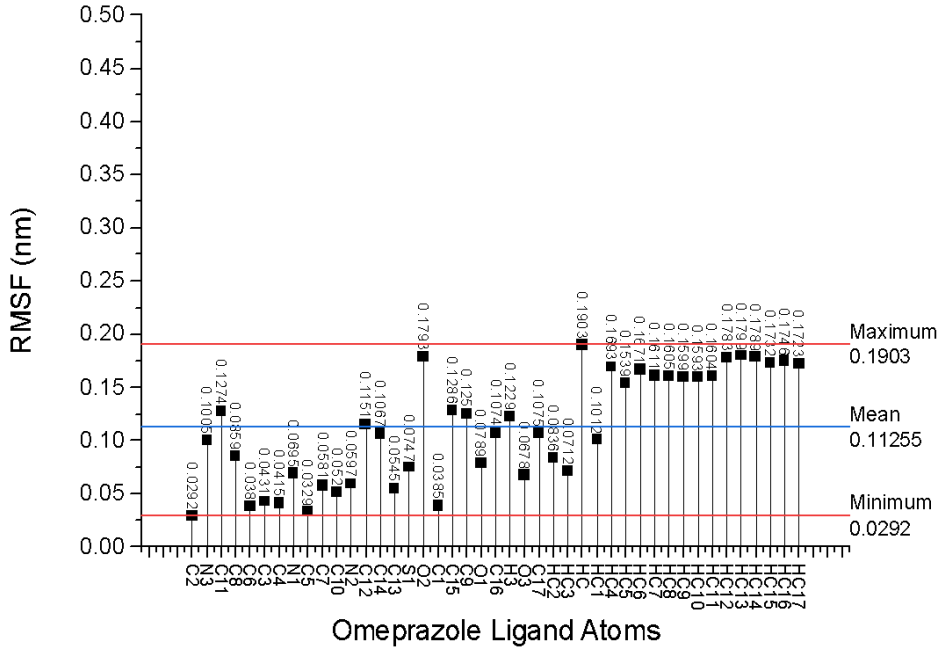


Figure 9: RMSF plots for curcumin pyrazole, scoparol, tryptanthrin 4'-O-methylcatechin, and Omeprazole.

The analysis of radius of gyration was used to determine the compactness of atoms in a structure under study. Thus, the radius of gyration tells about the distribution fo atoms in the protein structure. The average values of radius of gyration for the five ligands are presented in Figure 10. As it is seen from Figure 10, tryptanthrin and 4'-O-methylcatechin had the minimium value of radius of gyration. This indicating that tryptanthrin (0.29 nm) and 4'-O-methylcatechin (0.375 nm) had minimum distribution of atoms along all axes, thus are stable inside the binding pocket (Chen et al., 2016). The analysis reveals that curcumin pyrazole binds in the active pocket of 8H52 with stable 2 – 3 H-bonds bonds formed in the time of 10 ns which also supports the docking findings. Scoparol initially had 4 -5 unstable H-bonds formed with the target, at the end of 10 ns, 1 - 2 H - bonds remained stable, as a result, the decrement ends up with 2 strong H – bonds. For tryptanthrin, during molecular dynamics simulation, there were no stable hydrogen bonds formed in the run of 10 ns. This indicates that tryptanthrin is not stable in the binding pocket of 8H52. 4'-O-methylcatechin binds in the active pocket of 8H52 initially with 4 – 5 hydrogen bonds with fluctuations. It was also observed that a minimal stable of 2 - 3 H - bonds formed around 2 ns to 8 ns, from 8 ns till the end, 2 - 3 H - bonds remained stable for the 4'-O-methylcatechin - 8H52 complex. It was discovered that omeprazole binds in the active pocket of 8H52 with a total of 2 – 3 H - bonds with fluctuations initially. From 5 ns till the end, there were 1 – 2 stable H – bonds formed and makes a maximum of 2 H – bonds formed for the omeprazole – 8H52 complex (**Figure 11**), Therefore, 4'-O-methylcatechin formed 3 stable H-bonds indicating the stability in the binding pocket (Fatriansyah et al., 2022).

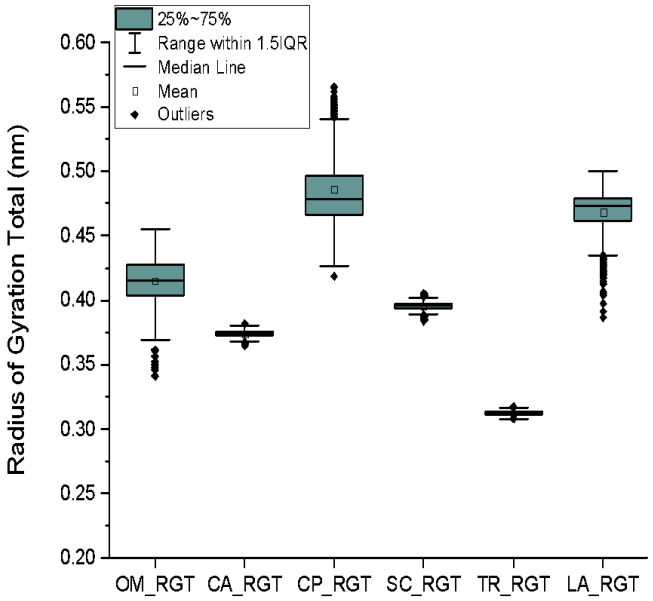
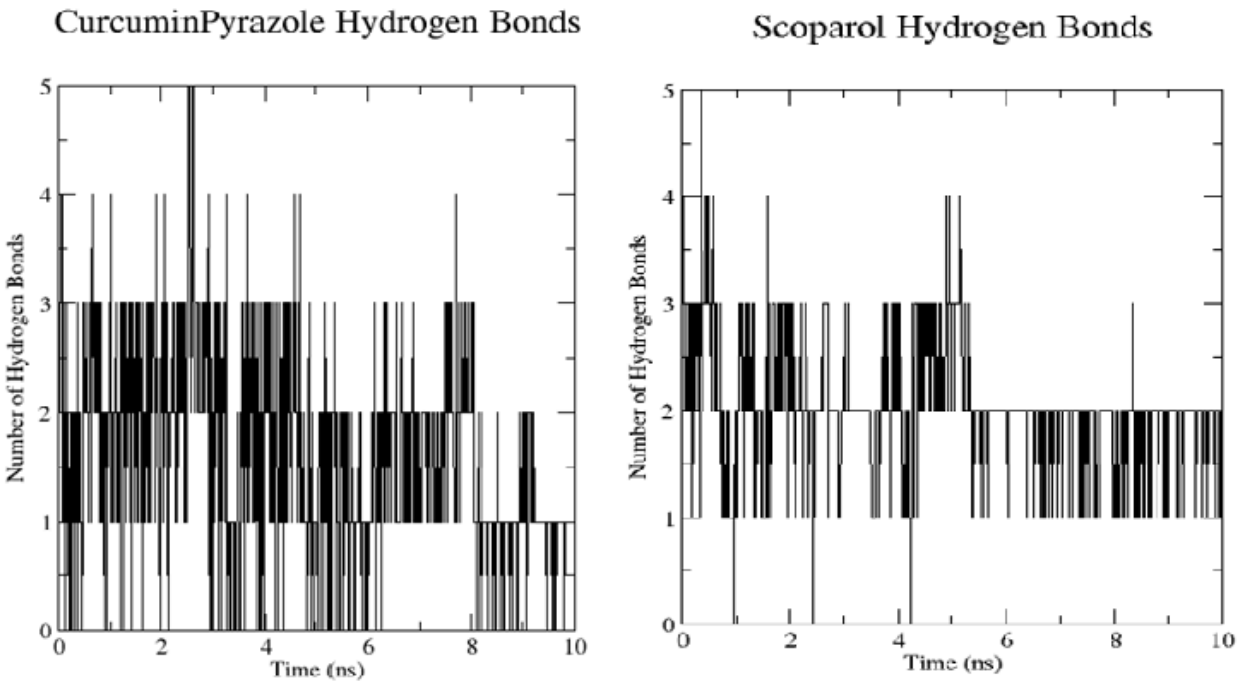


Figure 10: The average radius of gyration for the five hits



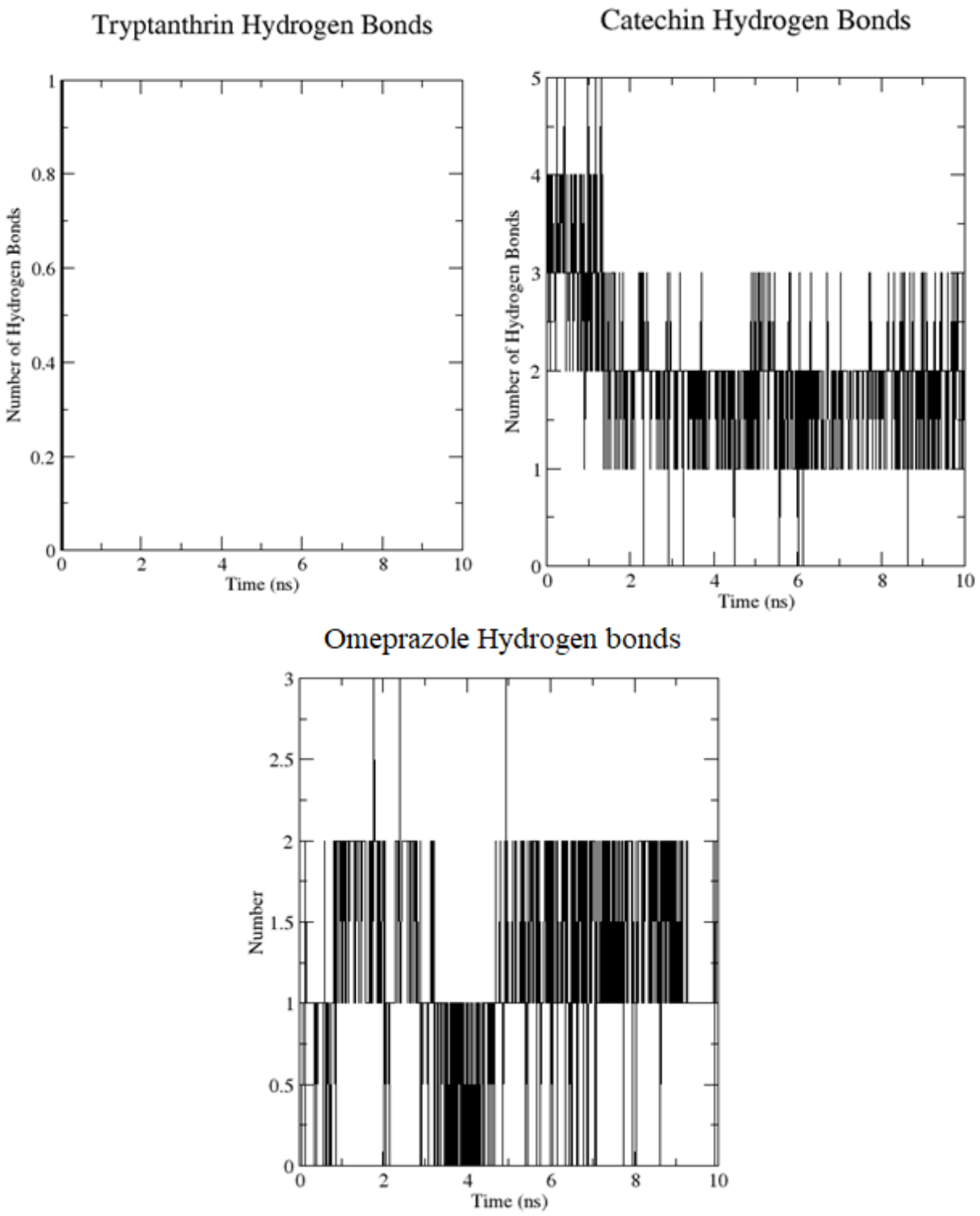


Figure 11: BACs and control drug hydrogen bonds

IV. CONCLUSION

In this study 1102 BACs from traditional medicinal herbs were investigated as a potential inhibitor for the treatment of peptic ulcers. Among those, four compounds curcumin pyrazole, scoparol, tryptanthrin, and 4'-O-methylcatechin were the ligands that outperformed Omeprazole were found to be promising for peptic ulcers treatment. Molecular docking results displayed docking scores of -9.9 Kcal/mol, -9.6 Kcal/mol, -9.5 Kcal/mol, -9.5 Kcal/mol, and -8.8 Kcal/mol for curcumin pyrazole, scoparol, 4'-O-methylcatechin, tryptanthrin, and omeprazole respectively. Therefore, these structures

have been identified to possess significant inhibitory activities against H-pylori. Further analysis was then performed using molecular dynamic studies to understand the flexibility and physical movement of the BACs and the control drug in complex with 8H52 as the target protein. Molecular dynamic results showed that all of the BACs had good findings. 4'-O-methycatechin had the best results compared to the control drugs in terms of binding affinity (-9.6 Kcal/mol), RMSD (0.18 nm), RMSF (0.04734 nm), H – bonds formed (2 to 3 stable H- bonds), and radius of gyration (0.375 nm). This study thus concludes that four BACs that were studied have inhibitory activities against 8H52, therefore these BACs are proposed to be possible candidates for medicines against 8H52 to inhibit bacterial growth and cell development to promote health and well-being for peptic ulcer disorders. MMPBSA, and other parameters such as temperatures, volume, bond energies, and lamb energies can be extended for further research to widen validation of results through in vitro and in vivo studies.

Funding: The authors express deep gratitude to University of Dodoma (UDOM) and Tanzania Atomic Energy Commission (TAEC) for supporting this work.

Conflict of interest: The authors disclose no conflict of interest.

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The Importance of Retrosynthesis in Organic Synthesis

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ABSTRACT

The process of designing- an- effective synthesis plan for a target molecule remains a signifi1cant challenge in organic synthesis. Synthesis planning involves determining the steps to synthesize a desired molecule. Retrosynthesis, developed by Elias James Corey and recognized with a Nobel Prize in 1990, is a systematic approach that involves working backwards from- the target- molecule to identify the - starting materials-. Retrosynthetic analysis is a-- valuable technique but requires a comprehensive understanding of chemical substances, compound classes, reactions, and reaction conditions. This understanding enables chemists to effectively plan and analyze the synthesis of the target molecule. Through analyzing the target molecule and identifying possible disconnections, chemists can think creatively and devise innovative solutions for complex synthetic problems. This article serves as an introduction to retrosynthesis, highlighting its importance and fundamental theoretical concepts (strategies) that can be combined to plan the synthesis of organic compounds.

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Classification: LCC Code: QD305

Language: English

Great Britain Journals Press

LJP Copyright ID: 925685
Print ISSN: 2631-8490
Online ISSN: 2631-8504

London Journal of Research in Science: Natural and Formal

Volume 24 | Issue 7 | Compilation 1.0

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The process of designing- an- effective synthesis plan for a target molecule remains a signifi1cant challenge in organic synthesis. Synthesis planning involves determining the steps to synthesize a desired molecule. Retrosynthesis, developed by Elias James Corey and recognized with a Nobel Prize in 1990, is a systematic approach that involves working backwards from- the target- molecule to identify the - starting materials-. Retrosynthetic analysis is a-- valuable technique but requires a comprehensive understanding of chemical substances, compound classes, reactions, and reaction conditions. This understanding enables chemists to effectively plan and analyze the synthesis of the target molecule. Through analyzing the target molecule and identifying possible disconnections, chemists can think creatively and devise innovative solutions for complex synthetic problems. This article serves as an introduction to retrosynthesis, highlighting its importance and fundamental theoretical concepts (strategies) that can be combined to plan the synthesis of organic compounds.

Keywords: disconnections strategies, organic synthesis, retrosynthesis, synthetic plan, target molecule. [1]

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I. INTRODUCTION

The main objective of organic synthesis is to efficiently construct a target compound using available starting materials and reagents, which involves designing a synthetic plan [1].

When planning the synthesis of a target molecule, various factors such as simplicity, availability of starting materials, product yield, economics, and safety must be taken into account [2].

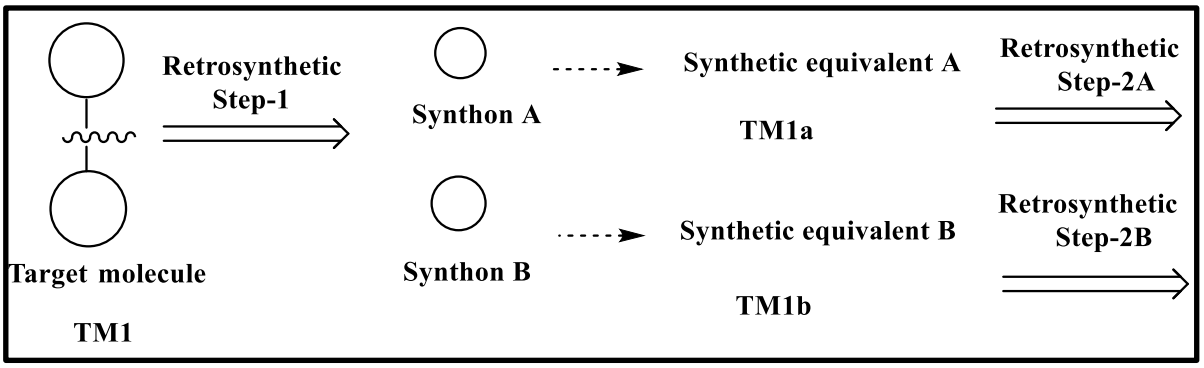
Syntheses can be broadly categorized into two types: linear and convergent. Linear synthesis involves a series of sequential transformations, resulting in lower overall yield due to the longest route to the target molecule [2]. Convergent synthesis involves synthesizing key fragments independently and then combining them to make the target molecule, leading to a higher overall yield and greater efficiency [2].

The process of designing a synthesis is similar to solving a puzzle, with multiple pathways available to reach the desired end. Some pathways are productive while others are not [1]. The retrosynthetic approach, or disconnection approach, is commonly used to design the synthesis plan for a target molecule [3,4], and has introduced a new way of thinking about synthetic problems, and inspiring several synthetic organic chemists [5].

II. PRINCIPLES OF RETROSYNTHETIC ANALYSIS

To make the target molecule, use of a series of one-step reactions [6] and determining which reactions to use follows a technique called retrosynthetic analysis [1].

The principle of retrosynthesis analysis involves working backwards from a target molecule to identify precursor molecules and their corresponding synthetic strategies [7]. This involves breaking bonds in the target molecule to obtain simpler precursors and determining the synthetic strategies required to produce them [1,8]. This requires a thorough knowledge of chemical reactions and their mechanisms, as well as practical experience [2]. For- every structure- derived from- a target, it in turn becomes a template for further- analysis- [1]. The process involve the use of synthons, which are not real hypothetical molecules or fragments generated from bond disconnections during retrosynthetic analysis, simplifies the synthetic strategy and enables chemists to plan the synthesis of complex molecules more efficiently [9,10] and The synthetic- plan- resulting- from retrosynthetic- analysis- functions as a blueprint- for the synthesis of the desired- molecule [2]. The symbols used in retrosynthetic analysis include a wavy line to represent disconnection and a retrosynthetic arrow to show the backward movement from the target molecule to simpler molecules. The strategic plan should be clear, while tactical issues deal with the actual execution of the plan [1,2].



Scheme 1: General scheme of retrosynthetic analysis.

2.1 Goals of Retrosynthetic Analysis

This approach has proven successful in synthesizing a wide range of intricate natural products and pharmaceuticals [11].

- The aim of disconnection is to simplify the target molecule by identifying possible disconnections, breaking it down into readily obtainable starting materials [12].
- It is crucial to carefully select the building blocks to ensure they can be assembled efficiently in a convergent manner to form the desired molecule [13].
- Chemists are encouraged to think creatively and come up with innovative solutions to overcome complex synthetic challenges (13).
- The objective is for organic chemists to devise a chemically feasible synthetic pathway That- is- economically- efficient and environmentally- viable, and- minimizes the- number of- reaction steps required [14,15].

2.2 Retrosynthetic Techniques (The Strategies)

The probable substrate and product are related through two key processes: the- conversion of one- functional- group- to another- (known as functional group interconversion), and reactions that involve the formation or breaking of C-C bonds and lead to changes in the carbon skeleton [6,16].

Retrosynthesis involves a variety of techniques for breaking down target molecules into simpler precursor molecule such as retrosynthetic disconnections, is often used in combination with other retrosynthetic techniques, such as functional group interconversion and retrosynthetic analysis of protecting groups, to arrive at a feasible synthetic route [2].

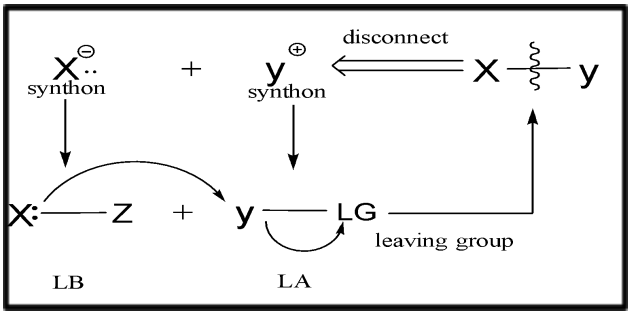
In addition, computer-aided retrosynthetic analysis is a new and powerful approach that can greatly accelerate the development of new drugs and materials by rapidly evaluating thousands of possible synthetic routes [17].

Retrosynthetic disconnections is an essential part of the retrosynthesis approach, allowing the chemist to break down a target molecule into simpler fragments [2]. The process determines the bonds that need to be formed to create the final product. By doing this, chemists can identify the important structural elements and functional groups needed in the precursor molecules, and create a synthetic route that constructs these molecules from simple starting materials [18].

In organic chemistry, a chemical bond can be broken in two ways: Homolytic cleavage and heterolytic cleavage. The specific bond cleavage that occurs is dependent on the reaction conditions and the molecules engaged. Heterolytic cleavage creates ions with positive and negative charges and this type of cleavage is frequent in reactions of polar molecules, driven by differences in electronegativity. Homolytic cleavage generates two radicals, and it usually happens in reactions involving free radicals, initiated by the supply of energy [19].

A-Polar- disconnections- are- intuitive- and- form the foundation- of a considerable- portion- of retrosynthetic- logic- [16] and a valuable technique which involves the breaking of polar bonds, a bond between carbon and a heteroatom, such as oxygen, nitrogen, or sulfur to generate two fragments. The resulting fragments can then be further manipulated and functionalized before being reconnected to form the desired target molecule [2].

The concept of bond polarity is important in the disconnection process [13], and the introduction of the "synthon" has provided insight into the origin of reaction products [20]. In polar disconnection, there are two categories of synthons that are utilized: electron donor synthons (d) and electron acceptor synthons (a). The former refers to nucleophilic fragments that possess a negatively polarized (electronegative) carbon atom, while the latter refers to electrophilic fragments that have a positively polarized (electropositive) carbon atom [10,16].



Scheme 2: Polar disconnection, LB (Lewis base) and LA (Lewis acid)

A key aspect of successful retrosynthetic analysis which requires experience and practice is recognizing which synthons are stable can be used directly and which ones require conversion into synthetic equivalents [20], is a real molecule or reagent capable of being designated as a synthon and employed in a synthetic procedure and functional group interconversion (FGI) [2].

Table 1: Common donor and acceptor synthons and their synthetic equivalent [9,13].

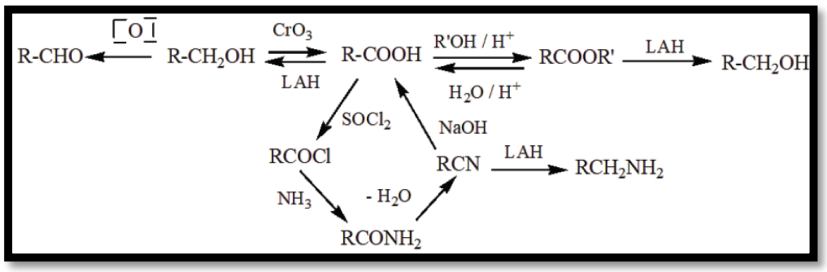
d-Synthons	Synthetic equivalent	a-Synthons	Synthetic equivalent
R^- (alkyl anion)	RMgX, RLi,R_2Cd, RCuLi	R^+(alkyl cation)	RX, $ROSO_2R$
Ar^- (aryl anion)	Ar MgX, Ar Li, Ar_2Cd, Ar CuLi	Ar+(aryl cation)	Ar X, Ar OSO_2R

$^{-}CH_2CHO$	CH_3CHO	$^{+}CHOHR$(acylium ion)	RCHO
$RC\equiv C^{-}$ (acetylide)	$RC\equiv C^{-}Ag+$	$^{+}CH_2CH_2CHO$	$CH_2{=}CH_2CHO$
MeS^{-}	MeSH	$^{+}CH_2OH$(oxocarbenium ion)	HCOH
RO^{-}	RONa	$R{-}^{+}C{=}O$ (acylium ion)	RCOCl, RCOOR, RCOOOR
^{-}CN(cyanide)	KCN	$RC\equiv C^{+}$	$RC\equiv CBr$
		$HC^{+}{=}O$	$HCOOR$, $CH(OR)_3$
		CR_2OH	$R_2C{=}O$
		$RC(OH)CH_2^{+}$	R-epoxide

2.3 Manipulation of the Functional Groups

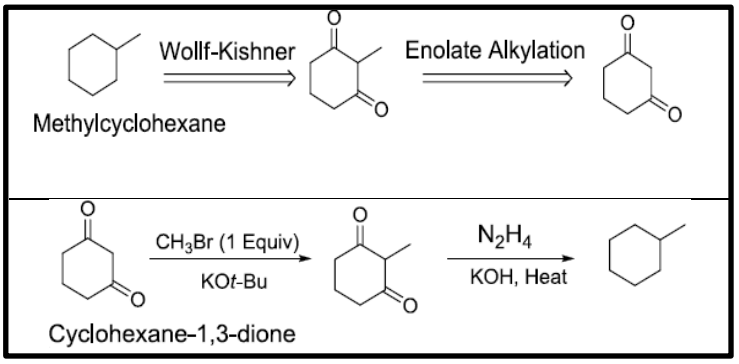
In synthetic organic chemistry, before the disconnection of a target molecule, manipulation of functional groups may be necessary when disconnection fails to facilitate the generation of synthetic equivalents, also can simplify reactions and reduce molecular complexity[13]. Functional group interconversion (FGI), Functional group addition (FGA) and functional group removal (FGR) are methods of manipulating chemical groups that can simplify syntheses [9].

1-Functional group interconversion: is technique that involves transforming one functional group into another if the carbon skeleton remains unchanged through substitution, addition, elimination, oxidation, or reduction [13] and FGI simplifies disconnection to arrive at a feasible synthetic route for the target molecule [21]. For example, alcohols can be converted into various other functional groups, making them a versatile starting material for many functionalized aliphatic compounds [13].



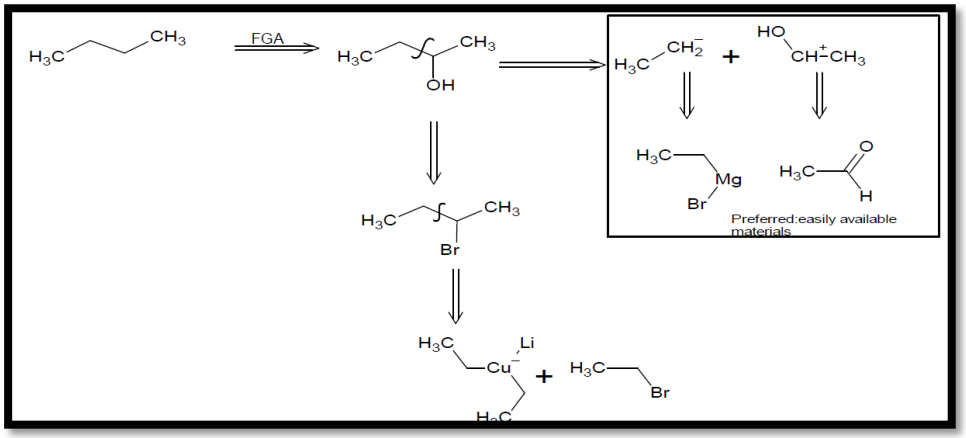
Scheme 3: Functional group interconversion of alcohols

2-Functional Group Addition (FGA): Can be beneficial in directing reactivity towards particular sites of a molecule and streamlining a synthesis. Adding functional groups like double bonds or carbonyl groups can be useful in guiding the introduction of substituents. An example of this is introducing a carbonyl group into a substituted cyclohexane target molecule, which could potentially facilitate the introduction of a substituent via enolate alkylation [2,13].



Scheme 4: An example of functional group addition (FGA) in directing reactivity to specific sites

Before disconnection of a target molecule (TM), FGA may be done to facilitate synthetic equivalents are got [9].



Scheme 5: An example for Functional Group Addition (FGA) to facilitate synthetic equivalents

3-Functional Group Removal (FGR): involves extracting a specific functional group to obtain the precursor required for the target molecule. [13,22].

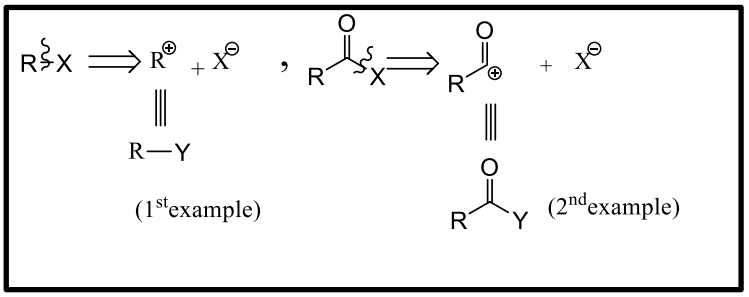
Table 2: Reactions for function group removal

Function group	Reaction for function group removal
R-C≡C-, RC=C-	H_2/Pd
R-OH	TsCl(P-toluene sulfonyl chloride), MsCl (methane sulfonyl chloride) -$LiAlH_4$ (Lithium aluminum hydride), BH_3(Trihydridoborate)
R-C=O	a) Treatment with NaBH4 (sodium borohydride) followed by hydroxide group (OH) addition. b) Reduction using Kizhner reagent (NH2NH2). c) Reduction utilizing Clemmensen conditions (Zn/Hg; HCl).
R-SH	Raney nickel catalyst
R-NH_2	Diazotization with nitrous acid (HNO2).

Certain inherent characteristics of a molecule can provide guidance during analysis.:
Disconnection of molecules according to the functional groups present in the target molecule [16].

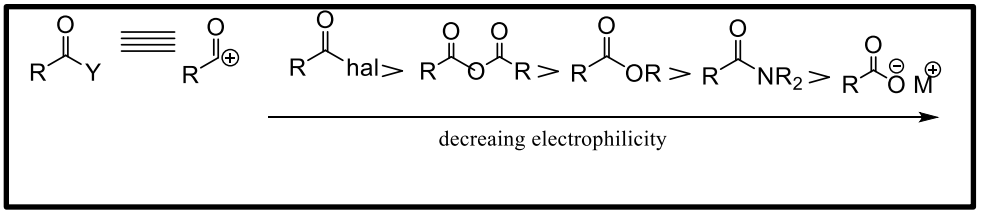
1-One-group disconnections, target molecule with one function group
A- C–X bond disconnection

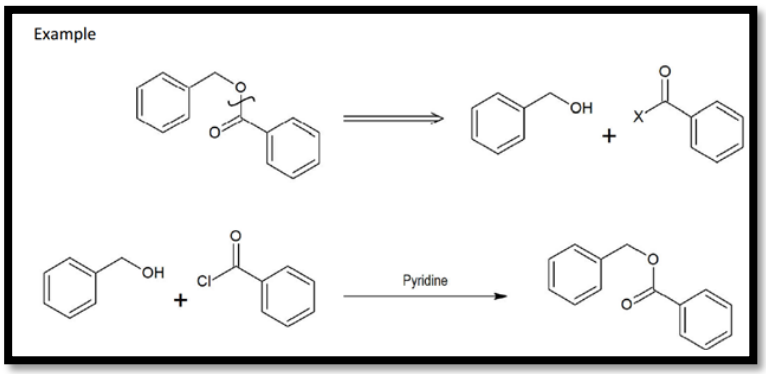
In the C-X bond disconnection, the reactions are typically ionic and involve heteroatoms. The resulting synthon is usually cationic and the corresponding synthetic equivalent will have a good leaving group (Y) attached [9].



Scheme 6: General scheme for C–X bond disconnection

The importance of the second example is huge as it involves reactions that result in acylation [9].





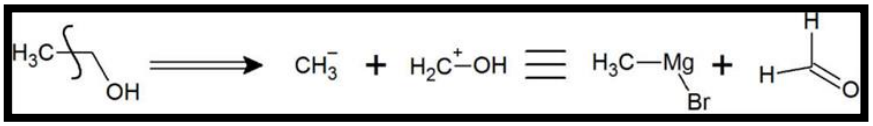
Scheme 7: C–X Bond disconnection of ester

B- C-C Disconnection, Disconnection next to a functional group.

Alcohols

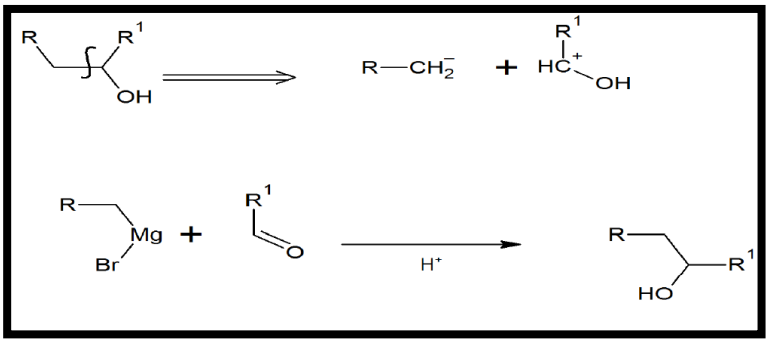
Alcohols are a prominent illustration of disconnection adjacent to the hydroxyl functional group, specifically involving the carbanion synthon and α-hydroxyl cation synthon. The synthetic equivalent of carbanion resembles an organometallic compound [9].

- If the alcohol is primary go for HCHO + RMgBr.



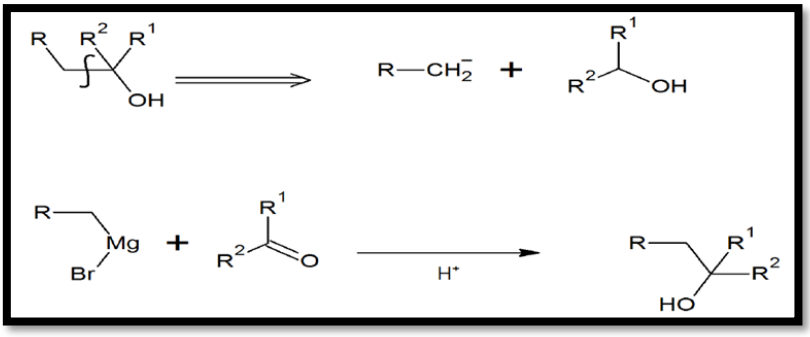
Scheme 8: C–C Bond disconnection of primary alcohol

- If the alcohol is secondary go for RCHO + R'MgBr



Scheme 9: C–C Bond disconnection of secondary alcohol

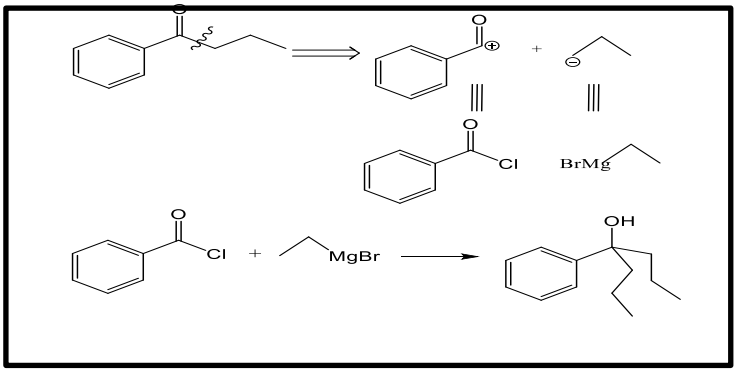
- For tertiary alcohol, disconnection adjacent to a branching carbon in a chain



Scheme 10: C–C Bond disconnection of tertiary alcohol

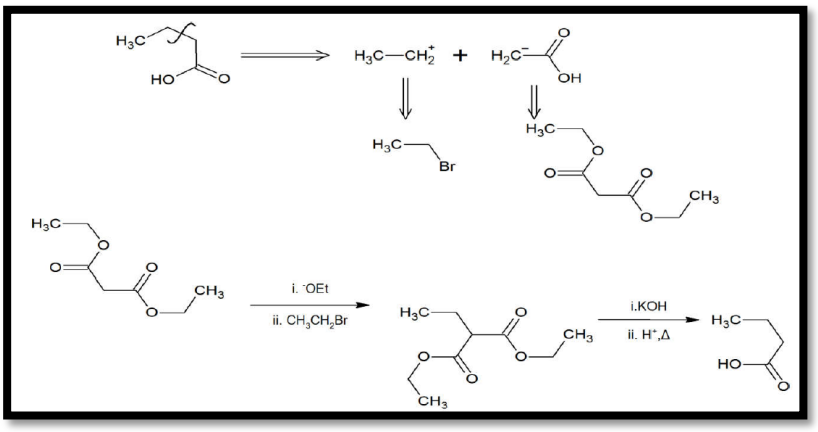
2.4 Carbonyl compounds

- Carbonyl compound disconnected at carbonyl group back to acyl cation and carbanionic synthons [9].



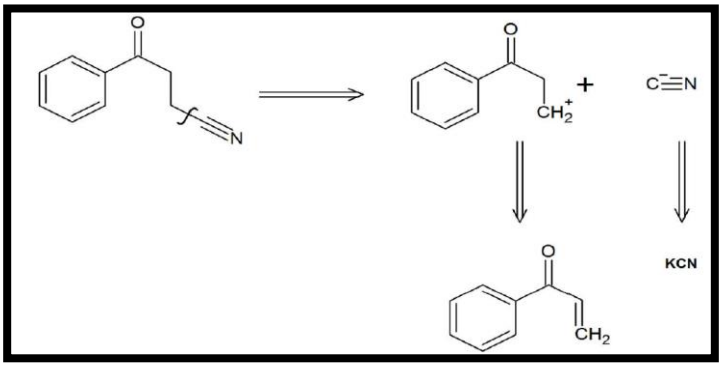
Scheme 11: C–C Bond disconnection of carbonyl compound

- Disconnection between the alpha(α) and beta (β) carbon atoms adjacent to the carbonyl group [16].



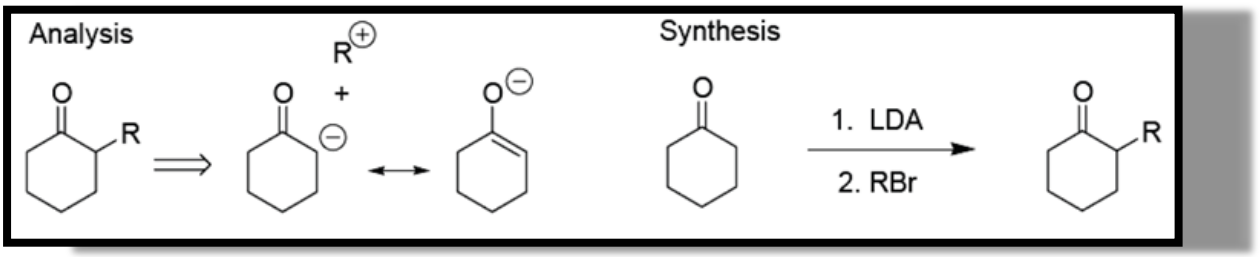
Scheme 12: C–C Bond disconnection between the alpha(α) and beta (β) carbon atoms adjacent to the carbonyl group

- Disconnection between the β and γ carbons of carbonyl group [16].



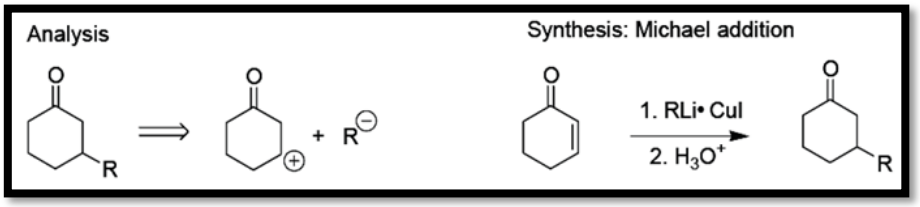
Scheme 13: C–C Bond disconnection between the β and γ carbons of carbonyl group.

- Disconnection of carbonyl compounds brunched at α-carbons [16].



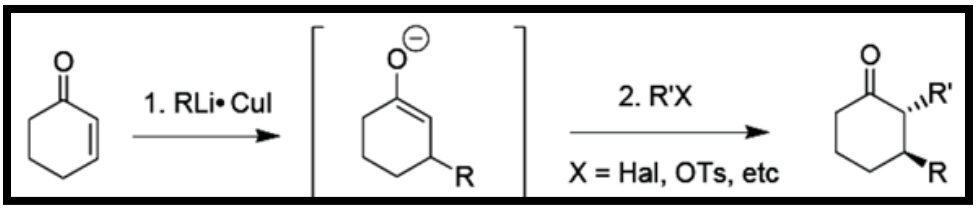
Scheme 14: C–C Bond disconnection of carbonyl compound brunched at α-carbons (LDA=Lithium diisopropylamide)

- Disconnection of carbonyl compounds brunched at β-carbons [16].



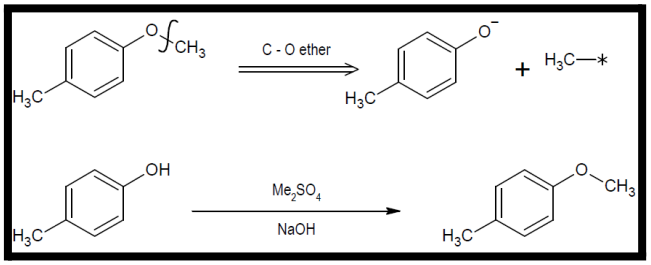
Scheme 15: C–C Bond disconnection of carbonyl compound brunched at β -carbons

- The amalgamation of the preceding two synthetic methods enables the incorporation of two additional functional groups [16].

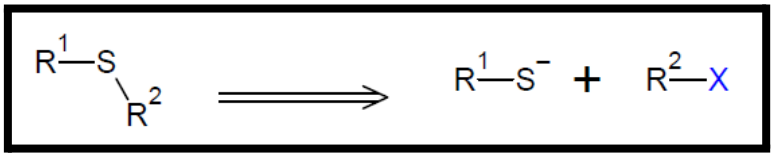


Scheme 16: Synthetic approach t for the incorporation of a two new groups.

C- Disconnection at the heteroatom is performed in compounds comprising two segments connected by a heteroatom. For example disconnection of ethers and sulphides [16]:

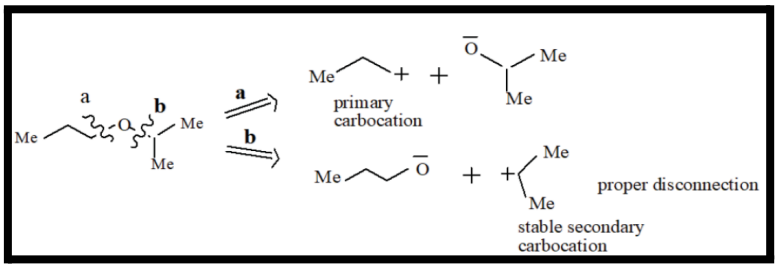


Scheme 17: An example of ethers disconnection



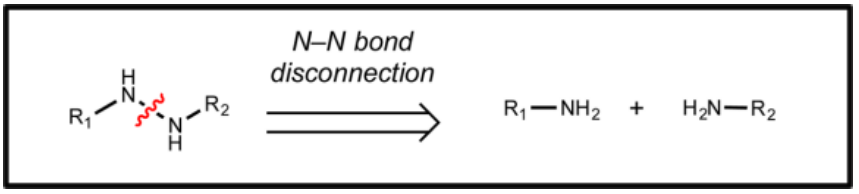
Scheme 18: General scheme for sulphides disconnection

The disconnection occurring at the heteroatom within linear compounds is likewise influenced by the stability of the synthons [13].



Scheme 19: Disconnection of ethers

D- Heteroatom-Heteroatom Disconnections: In this approach, the target molecule is Disconnected at a bond between two heteroatoms, such as oxygen-oxygen, nitrogen-nitrogen, or sulfur-sulfur. The resulting fragments can be functionalized and reconnected to form the target molecule [23].



Scheme 20: Heteroatom-heteroatom disconnections

2- Two-group disconnection

When analyzing the synthesis of difunctional group compounds, the strategy chosen for disconnection depends on the functional group and their positions within the molecule. If the chemical groups are in proximity to one another, it is preferable to use the convergent disconnection strategy, as they can be derived from a common intermediate. However, if the functional groups are far apart and cannot be derived from a common intermediate, the linear disconnection strategy is preferred [15].

In two group disconnections, the molecule is disconnected somewhere else because of presence of a functional group and the relationship between two function group depend on how distance they are and polarization that they impart on the backbone [9].

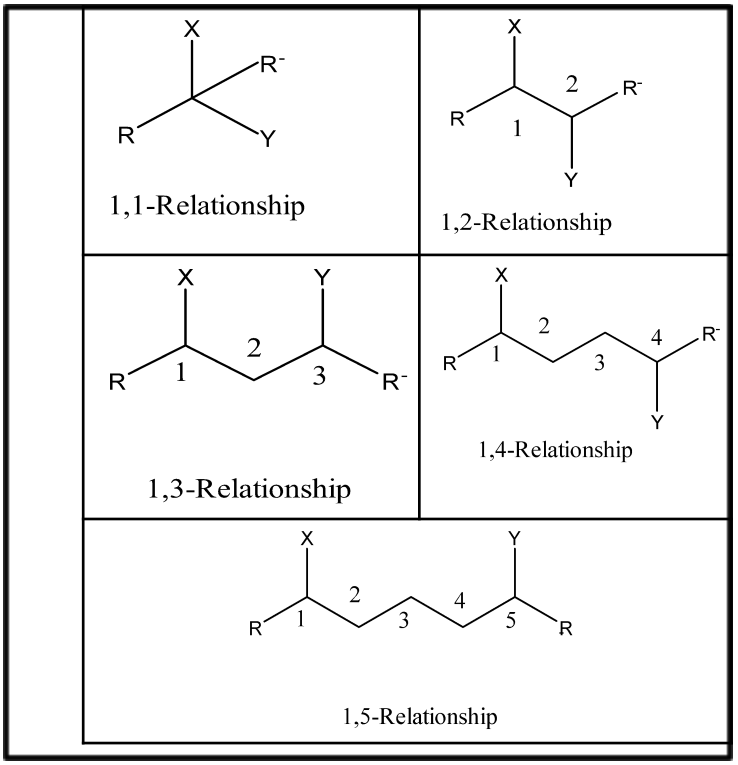
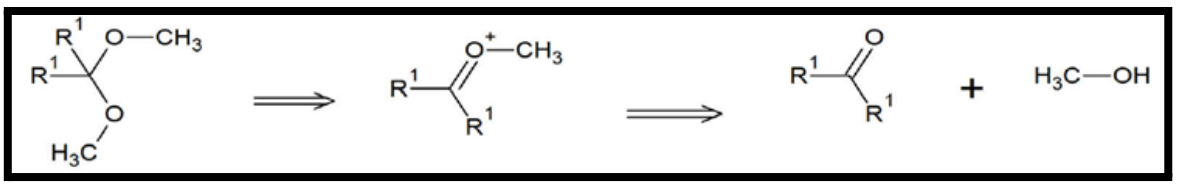


Figure 1: The relationship between two function group

A- In a 1,1-Relationship:

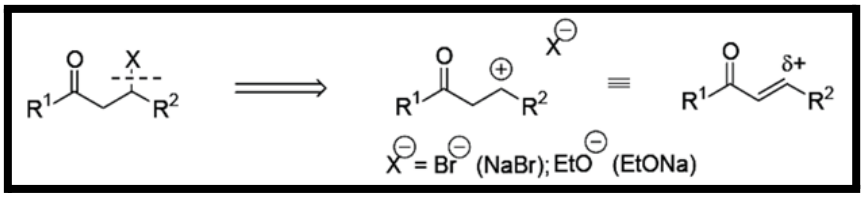
In organic chemistry, when discussing acetals, the disconnection of one carbon-oxygen (C-O) bond results in the automatic disconnection of the other C-O bond, known as a 1,1-disconnection [9].



Scheme 21: 1,1-Disconnection of acetals

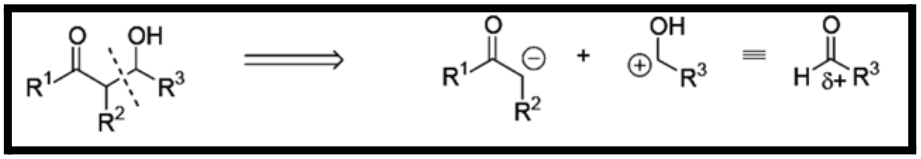
B- In a 1,3-Relationship

In organic chemistry, disconnection of a carbonyl compound with a nucleophile at the third carbon generates an electrophilic synthon, which can be obtained from an α, β-unsaturated carbonyl compound. Typically, this type of synthesis involves a Michael-type reaction [9].

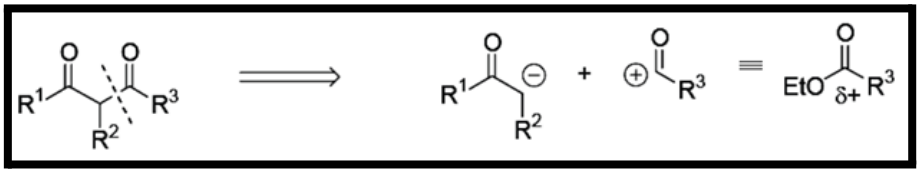


Scheme 22: Disconnection of 1,3- carbonyl compound

But carbonyl- and/or hydroxgroups are found in a 1,3, this provides a clue to employ one of the traditional carbonyl reactions for synthesis, namely the Aldol reaction or Claisen condensation. [16].



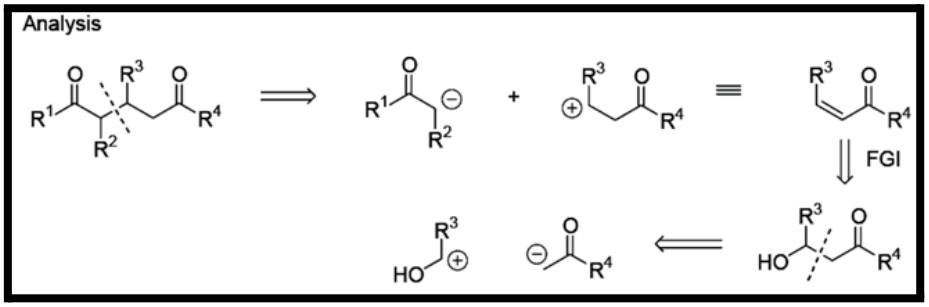
Scheme 23: Disconnection of 1,3- carbonyl- and hydroxgroups



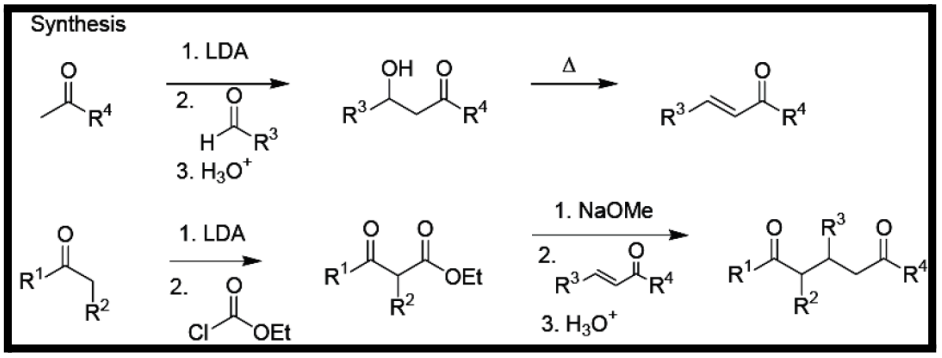
Scheme 24: Disconnection of 1,3- dicarbonyl compound

C- In a 1,5-Relationship

If Carbonyl- and/or hydroxgroups are found in 1,5 patterns, this provides a suggestion to utilize one of the traditional carbonyl reactions for synthesis. 1,5-Michael additions result in 1,5 dioxygenation patterns. [16].



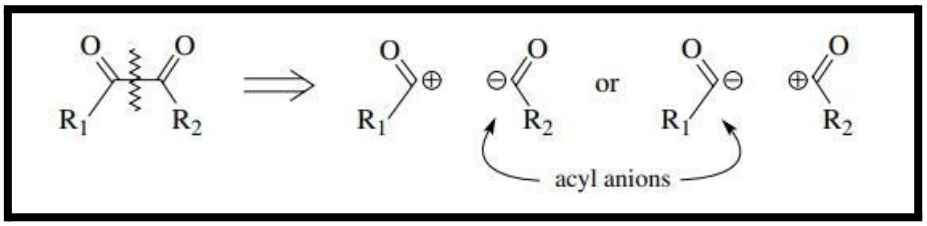
Scheme 25: Disconnection of 1,5- dicarbonyl compound



Scheme 26: Synthesis of 1,5- dicarbonyl compound

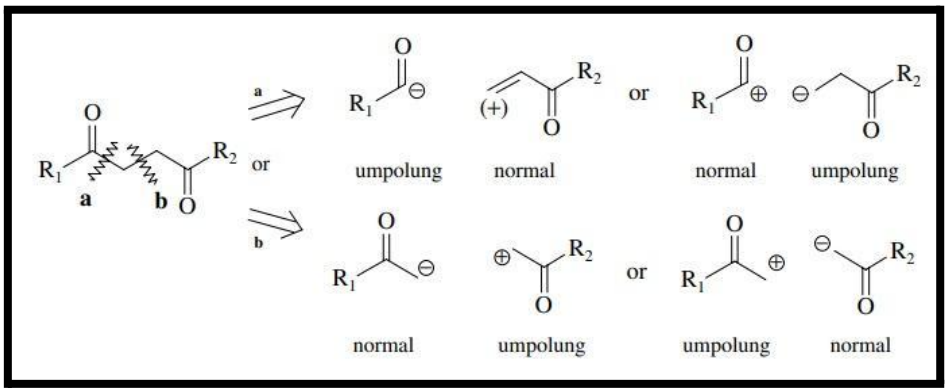
D- In a 1,2 and 1,4-dicarbonyl Relationship present a challenge in terms of disconnecting them by valid retrosynthetic steps.

For instance, the disconnection of the bond between the carbonyl groups in a 1,2-diketone presents complexity, requiring one carbonyl group to display typical electrophilic behavior while the other carbonyl carbon must exhibit nucleophilic character, such as an acyl anion or equivalent, contrary to the typical polarity of a carbonyl group. [7].



Scheme 27: Disconnection of 1,2-dicarbonyl compound

To disconnect a 1,4-diketone, an acyl anion equivalent can be employed to react with a standard β-carbonyl electrophile, or a standard α-carbonyl nucleophile can react with an atypical α-carbonyl electrophile [7].



Scheme 28: Disconnection of 1,4- carbonyl compound

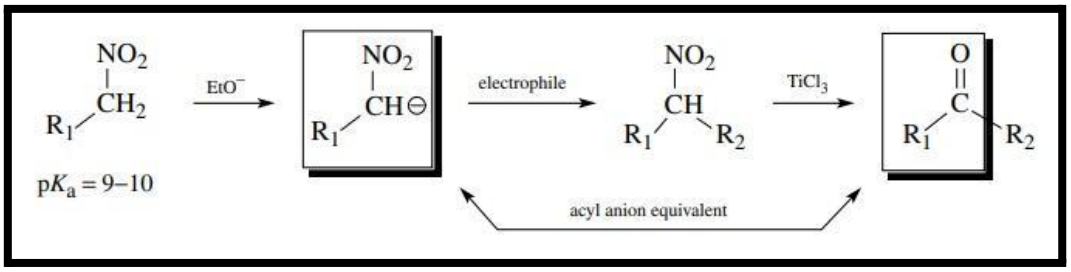
2.5 Umpolung of reactivity

This indicates the necessity for synthetic counterparts or synthons demonstrating reversed polarity (umpolung). The advancement of reagents featuring umpolung reactivity has proven to be a significant enhancement in contemporary synthetic techniques [24].

Umpolung of reactivity is a concept in organic chemistry that involves reversing the polarity of a functional group through chemical modification. The term was introduced by D. Seebach and E.J. Corey and has been extended to the reversal of any commonly accepted reactivity pattern. This alteration facilitates subsequent reactions of the functional group that would otherwise be unattainable. It is crucial to comprehend and devise techniques for inducing umpolung in organic reactions, as polarity assessment during retrosynthetic analysis aids chemists in identifying instances where umpolung strategies are necessary to synthesize a target molecule [21].

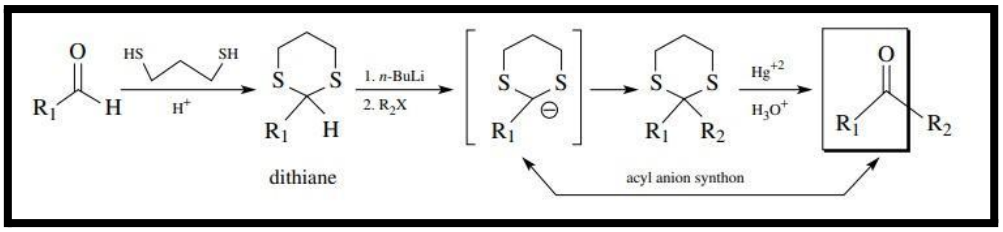
1-Carbonyl umpolung: Acyl anion equivalents represent the prevailing umpolung synthons, with three strategies employed for their generation, all adhering to a comparable methodology. These strategies incorporate functional groups capable of preserving a negative charge on an adjacent carbon and can subsequently be converted back into a carbonyl group [25].

A-Nitroalkanes can function as nucleophiles and as equivalents of acyl anions, and the nitro group can undergo cleavage to produce the carbonyl group. [25].



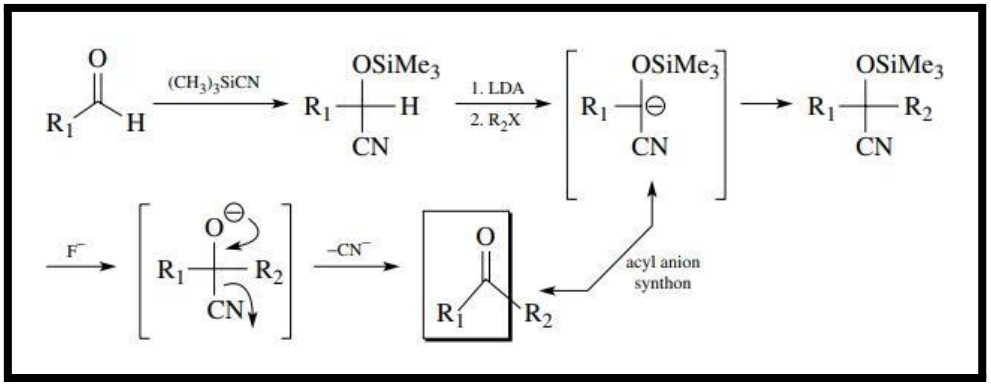
Scheme 29: Carbonyl umpolung by nitroalkanes

B-1,3-dithianes (thioacetals), can be used as a synthon for the acyl anion. Alkyl lithium bases can deprotonate 1,3-dithianes (thioacetals), resulting in strong nucleophilic anions. The carbonyl group can be regenerated by hydrolyzing the dithiane group [21].



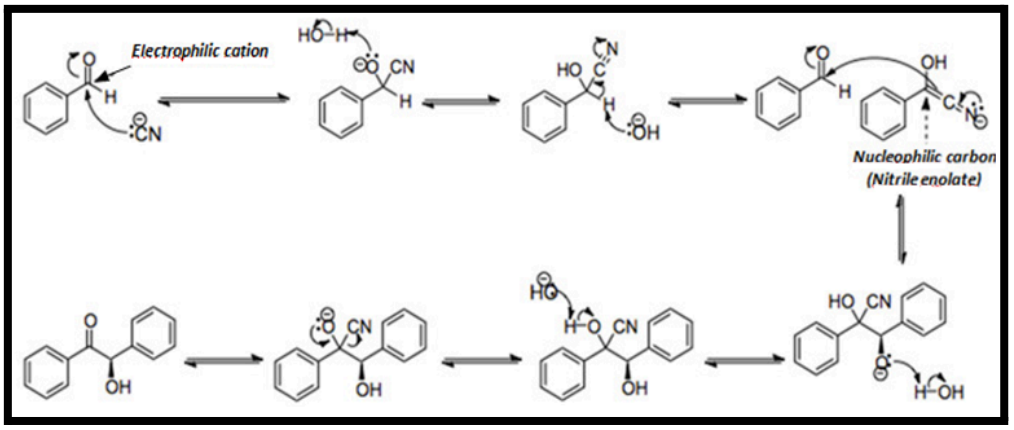
Scheme 30: Carbonyl umpolung by 1,3-Dithianes (A thioacetals).

C-Cyanide Umpolung: The cyanide ion is a unique umpolung reagent that undergoes polarity inversion in many reactions. Cyanohydrin derivatives, derived from carbonyl compounds via addition of hydrogen cyanide or trimethylsilyl cyanide, have found extensive utility as acyl anion synthons. The cyano group acidifies the α position of these derivatives, enabling alkylation of the anion and subsequent unveiling of the hydroxy group through cyanide elimination [25].



Scheme 31: Carbonyl umpolung by Trimethylsilyl cyanide [26].

For instance, Cyanide serves as a pivotal catalyst in the benzoin condensation reaction, wherein a bond is forged between two carbons that conventionally act as electrophiles [21].

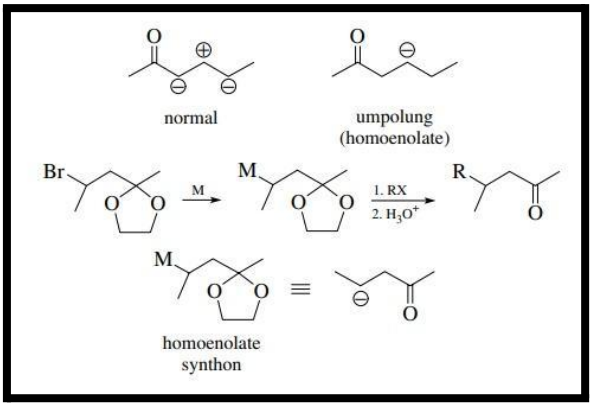


Scheme 32: Carbonyl umpolung by hydrogen cyanide.

2- β-Carbonyl umpolung

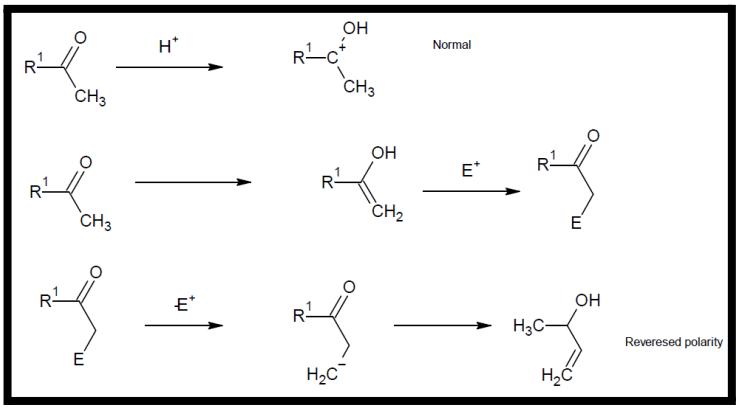
A- The use of homoenolates is a common strategy in organic synthesis to transform the β position of a carbonyl compound from an electrophilic to a nucleophilic center, a β-bromo acetal is employed, which can undergo metallation to yield a β-carbanion equivalent. Subsequent hydrolysis of the resulting acetal group yields the ketone, thereby serving as a synthon for a β-carbonyl anion, which functions as an umpolung reagent.

These strategies enable reactions that would otherwise be difficult or impossible to achieve, making them an important tool in organic synthesis [22].



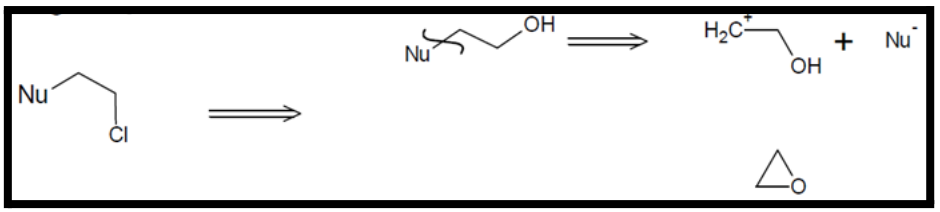
Scheme 33: β-Carbonyl umpolung by β-bromo acetal.

B-Enolization: by enolizing a ketonic moiety with an electrophile at 2nd carbon we can make a terminal carbon at 2nd position as negative [9].

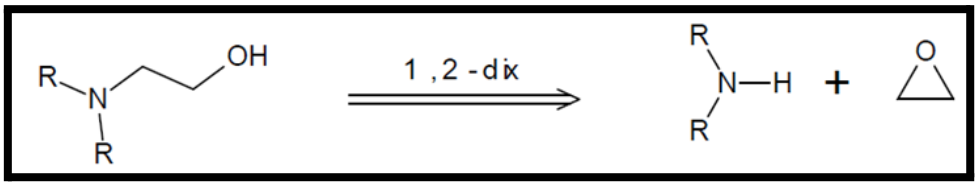


Scheme 34: β-Carbonyl umpolung by enolization

3- Epoxidation: In a 1,2 –Relationship, molecules containing heteroatom adjacent to C atoms are considered as derivatives of alcohols. Disconnection of such molecules need umpolung of reactivity to an epoxide [16].



Scheme 35: 1,2-Disconnection need umpolung of reactivity by an epoxide.



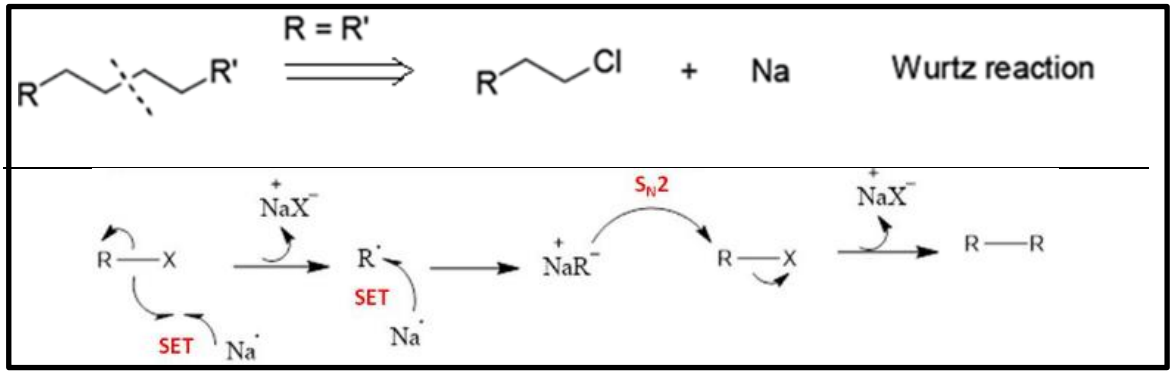
Scheme 36: 1,2-Disconnection need umpolung of reactivity by an epoxide.

The epoxide is a highly reactive and versatile three-membered cyclic ether with a significant ring strain. Its oxygen atom is electrophilic while the carbon atoms are nucleophilic. Substituting the ring carbon atoms with substituents that either donate or withdraw electrons. enhances the epoxide's reactivity [27]. Epoxides are frequently used as synthons for the preparation of other compounds, such as alcohols, amines, and carboxylic acids, through nucleophilic ring-opening reactions with Grignard reagents, organolithium compounds, or amines. Additionally, epoxides are valuable precursors for the synthesis of β-hydroxy carbonyl compounds, which are intermediates in organic synthesis that can be further transformed into a variety of functionalized compounds [19].

B-Radical Disconnection

While polar disconnections are integral to retrosynthetic analysis, the utilization of radical disconnections also plays a significant role in this analytical approach. can provide a more direct and efficient route to synthesizing organic compounds, minimizing the need for chemistry involving the use of protective groups and interconversions of functional groups. [28]. In this approach, the target molecule is disconnected at a carbon-carbon bond, typically at a point of unsaturation, using a radical reaction [29] and in the absence of functional groups, alkyl and aryl groups should be preserved as building blocks and not disconnected. The resulting fragments can be functionalized and reconnected to form the target molecule[10].

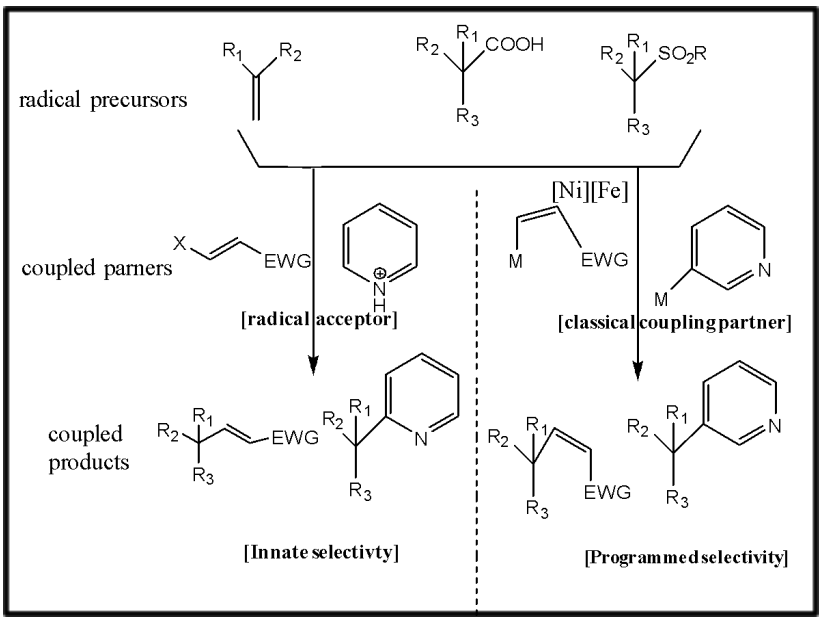
The Wurtz reaction exemplifies a reaction that facilitates the formation of carbon-carbon bonds that used to connect two alkyl or aryl halides and involves the use of metallic reducing agents to generate alkyl radicals. Although the Wurtz reaction can synthesize a variety of organic compounds, it is limited to coupling identical alkyl or aryl halides.



Scheme 37: Radical disconnection at a carbon-carbon bond (the Wurtz reaction)

Methods for cross-coupling involving one-electron radicals have recently gained attention for their chemoselective profiles and ability to simplify synthesis. Two broad classifications of Radical Cascade Reactions (RCC) can be delineated: innate and programmed [28].

Innate RCC involves the addition of a radical to a radical acceptor, with the regio- and stereochemical result being determined by the innate bias of the acceptor [30]. Programmed RCC, on the other hand, involves the interception of a radical by a mediator (e.g., a metal catalyst) facilitates bond formation with a functionalized counterpart [31]. One notable aspect of Radical Cascade Reactions (RCC) is their utilization of both starting materials (such as olefins and carboxylic acids) and intentionally designed functional groups (e.g., sulfones) as platforms for precise bond creation [28].

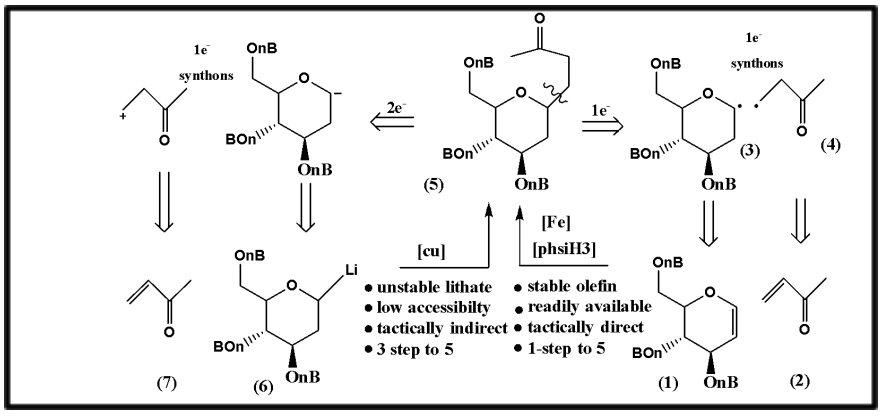


Scheme 38: Innate and programmed radical cross coupling.

III. APPLICATION OF RADICAL CROSS-COUPLING

1- Hydrogen atom transfer radical cross-coupling

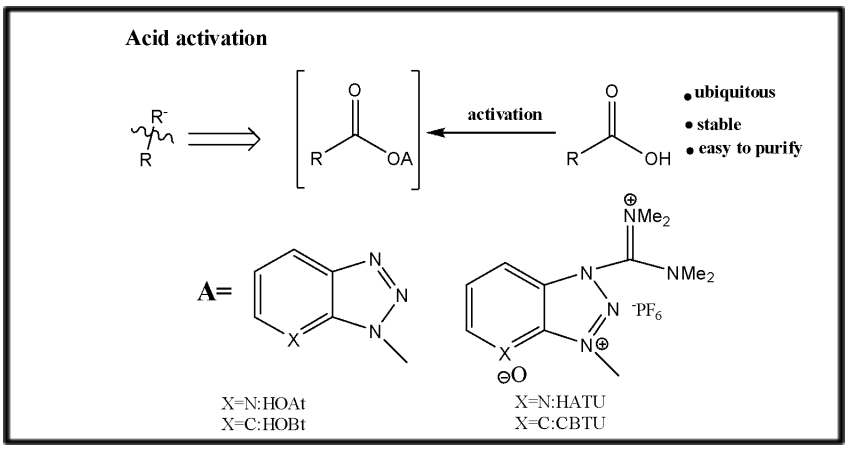
Hydrogen atom transfer (HAT) has emerged as a potent strategy for strategically constructing C–X and C–C bonds using olefinic substrates [32].



Scheme 39: Different strategic methods for glycan

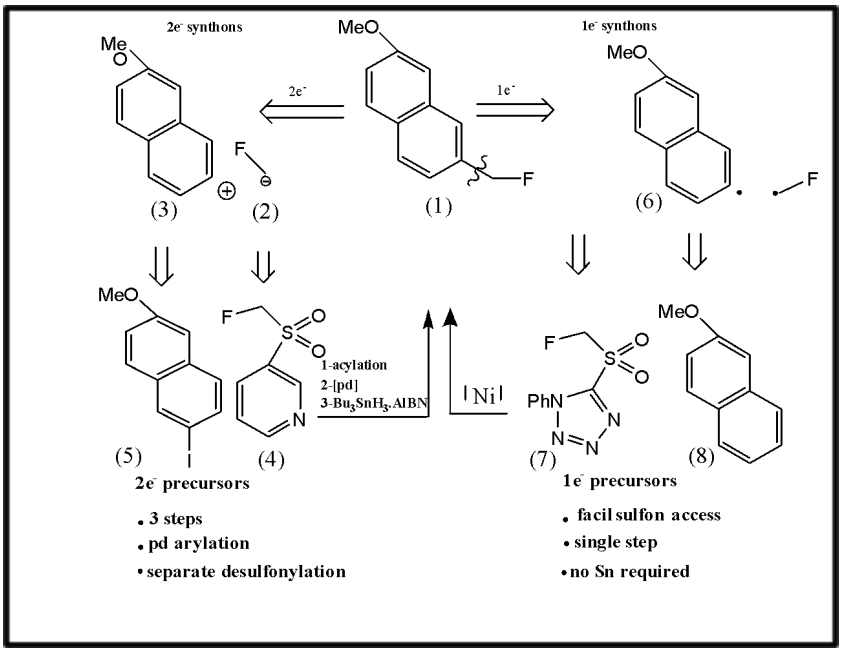
Scheme (39) include different strategic methods for preparation glycan, The conventional two-electron approach for synthesizing glycoside derivatives necessitated the laborious preparation of a litigated precursor 6 from olefin (1) before its coupling with Michael acceptor (7), whereas the one-electron strategy involved the direct radical combination of synthons (3) and (4). In practice, olefin (1) was employed as a one-electron precursor in an intrinsic radical coupling reaction with (2) under Fe catalysis, employing PhSiH3 as a stoichiometric hydride source [33].

2-Redox- active ester radical cross-coupling (RCC), carboxylic acids can undergo conversion into redox-vactive esters (RAEs), serving as reactive partners in the RCC process. This method involves specific active esters like HOAt, HOBt, NHPI, and TCNHPI, which possess the capability to accept an electron, initiating a series of reactions that ultimately release CO2 from the original alkyl group. These esters can be employed in radical decarboxylative transformations, generating carbon-centered radicals essential for the formation of new C–C/C–X bonds. Combining these RAEs with premetalated nucleophiles and a transition metal catalyst enables their involvement in programmed, decarboxylative RCC reactions, offering inherent advantages in terms of chemo- and regioselectivity. This advancement facilitates the direct synthesis of unnatural amino acid derivatives and the straightforward preparation of simple arenes [34–37].



Scheme 40: RAE formation

3- Desulfonylative radical cross- coupling: The sulfone functional group offers versatility in various nucleophilic substitution reactions, particularly fluorination. A subsequent reductive radical desulfonation typically follows. Recognizing N-phenyl sulfonyl tetrazoles as suitable counterparts for RCC represents a robust trategy for efficiently introducing fluorine atoms into valuable synthetic intermediates [39].



Scheme 41: Different strategic methods for naphthalene synthesis.

Scheme (41), the synthesis of naphthalene (1) was documented employing a two-electron approach catalyzed through copper (Cu), with retrosynthetic analysis utilizing synthons (2) and (3). Nevertheless, this approach presented a limitation, as it necessitated the generation of a highly reactive nucleophile from (4), which involved two supplementary steps to obtain compound (1). In contrast, an alternative tactic was implemented utilizing sulfone (7), capitalizing on radical synthon (6). This radical synthon was subsequently coupled with arylzinc8 under the influence of a nickel (Ni) catalyst. This direct methodology obviates the requirement for toxic tin (Sn) reagents and prefunctionalization, facilitating a direct and controllable integration of the fluoromethyl group.

IV. COMPUTER-AIDED RETROSYNTHETIC ANALYSIS OR SYNTHETIC PLANNING

Computer-aided retrosynthetic analysis is a new technique that uses computational algorithms to generate feasible synthetic routes for a target molecule. This approach can greatly accelerate the development of new drugs and materials by rapidly evaluating thousands of possible synthetic routes [17]. The development of computer-aided synthesis planning (CASP) was aimed at improving the efficiency of chemical synthesis by integrating chemical knowledge, resulting in significant time and resource savings for synthetic chemists [40]. This approach has the potential to revolutionize the way synthetic chemists plan and design synthetic routes for target molecules, ultimately leading to the discovery of new reaction pathways [41].The first CASP system, called Logic and Heuristics Applied to Synthetic Analysis (LHASA), was created by Corey in 1972. Since then, standardized tools such as SMILES[41], CML[42], SMARTS[43], ECFP [44], and InChI [45] Advanced techniques have been devised to convert chemical compounds or reactions into data that can be read by machines.

4.1 General structure of CASP system

One key principle of retrosynthesis analysis is breaking down the target molecule into simpler building blocks and proposes a synthetic route to assemble them.

The CASP system is made up of four modules (Figure 2) [46]: The initial module comprises the reaction template database, housing established reactions along with their bond-breaking regulations. This database can be populated either manually or automatically extracted from both commercial and publicly available databases[47]. During bond disconnection processing, the program retrieves relevant reaction templates and adheres to their associated guidelines. The efficacy of the resultant synthetic pathway hinges upon the breadth of the reaction template database, with a more expansive database increasing the likelihood of optimal retrosynthetic analysis. The second component is the retrosynthetic module, which aligns input molecule structures with known reactions from the template database and returns the most compatible outcome. The program iterates to break down generated precursors until commercially available precursors are identified or the user-defined maximum step limit is reached. The third module, the tree guide and evaluation module, assesses candidate precursors and synthetic routes, directing the retrosynthesis toward locally and globally optimal directions. The fourth and final component is the database of commercially available compounds, serving as the terminus of the retrosynthetic analysis system and preventing the algorithm from further dissecting commercially available precursors [48–51].

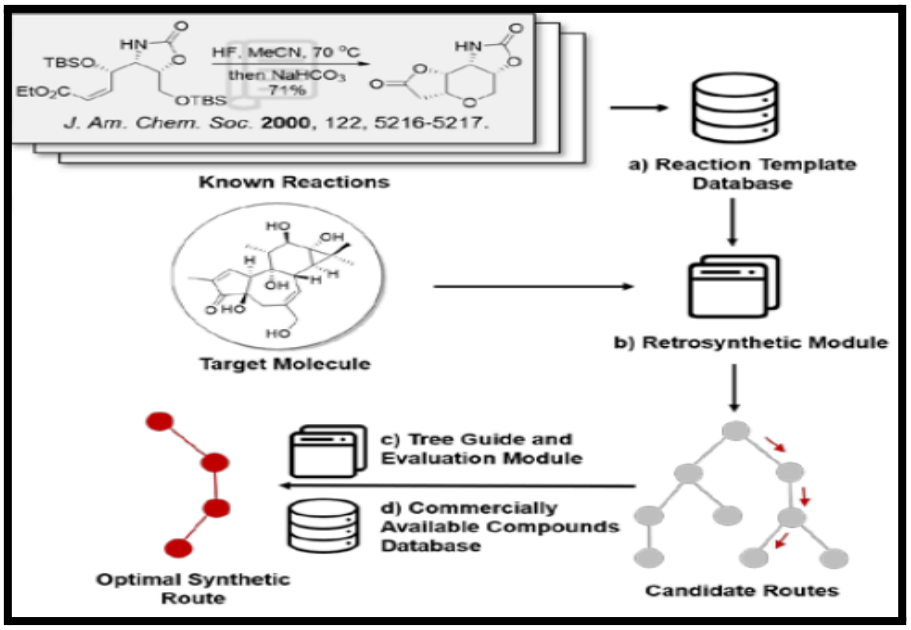


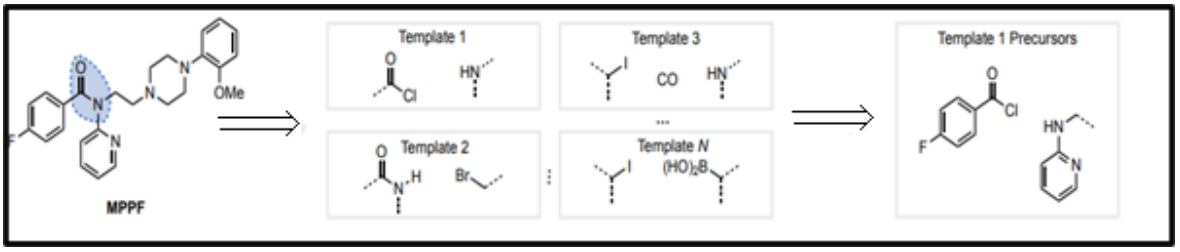
Figure 2: The typical elements of a CASP Program

4.2 Computational techniques

Computer aided synthetic planning involves several computational techniques**.** Automated retrosynthesis programs commonly utilize data-driven approaches, which can be categorized into two main types: template- based and template-free [52]. Template-based approaches involve extracting large reaction templates from reaction data [53–55] and applying them to products to find a match using subgraph isomorphism. Conversely, template- free approaches do not depend on pre-established templates and are subdivided into: (i) graph- based methods and (ii) sequence -based methods. Graph-based techniques utilize computational repositories to recognize structural attributes within the target molecule, such as aromatic rings, acyclic rings, alkyl groups, and more. This method employs a

dataset to identify all compounds containing a specific substructure that matches the target molecule, along with a vast array of organic reactions accessible for application.[56–58].

Sequence-based methodologies, conversely, reframe the challenge of devising reaction pathways as akin to language translation, employing a string representation of molecules. This representation transforms the three- dimensional structure of a chemical into a sequence of symbols that can be readily interpreted by computer software [48,59,60]. Cutting- edge predictors for both forward and reverse reactions are constructed based on the Transformer architecture and utilize SMILES as the string representation. These approaches have achieved considerable success in making broad predictions and have laid the groundwork for the advancement of retrosynthesis predictors [61].



Scheme 42: A retrosynthetic analysis of a complex molecule using a template-based approach.

There are many different CASP programs available, ranging from older ones like, LHASA [62] and SECS to newer ones like Chematica [63], IBM RXN [64], and 3N- MCTS [46]. The evolution of CASP programs has empowered computers to strategize the synthesis of intricate molecules incrementally. Additionally, the incorporation of artificial intelligence (AI) into retrosynthetic analysis has yielded substantial advancements in this domain. [65,66].

The development of CASP programs can be divided into three categories:

1-Hand coded rules with logical algorithms, which were used by early CASP programs due to hardware limitations. Although manual encoding requires deep chemical expertise, it remains an important method for database collection. Early programs encountered various problems such as incapability for stereoselective design, ignorance of reaction context (the factors that can influence the outcome of a reaction, such as temperature, pressure, solvent, concentration, and reaction time), and limited scope of chemical rules. However, there are limitations in keeping up with the daily updates of thousands of new chemical reactions reported, as well as the potential for inadvertent mistakes during manual encoding. These programs have offered valuable insights and served as inspiration for the creation of more pragmatic software solutions, such as Chematica. [47].

2-Automated extraction of reaction templates have emerged as a cost-effective and efficient approach for database maintenance. This technique reduces the labor costs associated with manual input and enables the rapid incorporation of vast chemical knowledge at an unmatched pace. Some commercial software has emerged in recent years that adopt automatic extraction of reaction rules, such as ICSYNTH and Scifinder [67]. Nevertheless, auto-extraction still faces challenges, including limitations in reconciling the extension degree from reactive centers with computational speed and the mechanical incorporation of activating groups, potentially overlooking the influence of distant functional groups. The identification of activating functional groups and the integration of compatibility information in a more intelligent manner remain unresolved issues for future research [68].

3-Machine learning algorithms are complex and require iterative operations to simulate human learning behaviors. In recent years, machine learning has become a popular direction in computer

science, especially for tasks that are difficult for conventional algorithms [69]. Within CASP programs, machine learning algorithms employ chemically labeled reactions to train models capable of forecasting potential retrosynthetic pathways for novel target molecules. Over the past decade, machine learning has become a prevalent tool in CASP programs, enhancing their capabilities and broadening their scope. Techniques such as ANN and seq2seq models excel at extracting extensive sets of reaction templates, enriched with chemical context, thereby enhancing the reliability and precision of retrosynthesis. However, challenges remain in the development of machine learning in CASP programs, such as the high computational cost of training reinforcement learning models and the complicated nature of the simulations generated by ANN and seq2 seq models. Despite these challenges, it is clear that the synthetic community will continue to drive advancements in machine learning models for CASP programs [70].

4.3 Evaluation process

The evaluation process has posed a considerable hurdle for CASP programs until recent times [55]. To tackle this challenge, a dual scoring methodology is implemented, which encompasses assessing both the executed reaction steps and the intricacy of the substrates. This strategy introduces the Chemicals Scoring Function (CSF) and Reaction Scoring Function (RSF) concepts, which evaluate the "synthetic positions" (sets of substrates) and "synthetic moves" (reactions) respectively. The CSF prioritizes the simplest substrates, while the RSF prioritizes the shortest syntheses without encountering reactivity conflicts or necessitating protection chemistries [41]. The aggregate difficulty or "cost" of synthesis is quantified by summing these functions, with the aim of minimizing this sum in sought-after syntheses. Typically, a comprehensive scoring function encompasses considerations such as the cost of building blocks, yield at each step, avoidance of toxic compounds and functional group incompatibility, and pathway length. Nonetheless, the formulation of an ideal pathway scoring function remains an unresolved challenge. Artificial intelligence models, like the Monte Carlo Tree Search (MCTS) algorithm, are often utilized to approach the global optimum by conducting numerous simulations [41].

Chemists have access to various computer-based retrosynthesis software, each with unique capabilities and interfaces. Some examples include:

1. SciFinder: A chemical database with over 150 million substances and 68 million sequences of chemical reactions. It has a retrosynthesis planning tool that suggests synthetic routes for target molecules based on its reaction database.
2. Reaxys: A web-based platform with a database of over 240 million organic and organometallic reactions. It has a retrosynthesis tool that allows users to search for synthetic routes to target molecules.
3. Chematica: A software program that uses algorithms and machine learning techniques to propose synthetic routes for target molecules. It searches a database of over 40 million organic reactions and optimizes the synthetic route based on various factors.
4. USP-DIPPR: A software program that provides data and tools for drug synthesis and formulation. It includes a retrosynthesis tool that suggests synthetic routes based on a database of over 400,000 organic and inorganic compounds.
5. Synthia: A software program that uses machine earning algorithms to predict the outcomes of chemical reactions and suggest synthetic routes for target molecules, including small molecule and peptide synthesis.

4.4 Limitation and challenge

Overall computer-aided synthetic planning (CASP) is a promising area of research that aims to assist chemists in designing and optimizing synthetic routes for target molecules. However, there are still several challenges and limitations associated with CASP. One of the main challenges is the availability and quality of data, which is limited and of varying quality. Another challenge is the complexity of chemical reactions, which can involve multiple steps and various reaction pathways, making it difficult to predict the most efficient synthetic route. Additionally, CASP currently relies heavily on expert input and rule-based algorithms, which may not capture the full complexity of chemical reactions. Finally, there is also a need for user-friendly interfaces and tools to enable chemists to use CASP effectively. Addressing these challenges and limitations is necessary for the effective implementation of CASP in the future [53,71,72].

V. CONCLUSION

Retrosynthesis is a strategic approach in organic chemistry that involves breaking down complex target molecules into simpler building blocks through retrosynthetic analysis. The goal is to design an efficient and practical synthetic route by considering factors such as reactivity and availability of starting materials. Retrosynthetic analysis relies on fundamental organic chemistry principles and requires a deep understanding of chemical reactions. After completing the analysis, chemists proceed with forward synthesis to execute the planned synthetic steps in the opposite direction. This involves selecting suitable reaction conditions, purification methods, and characterization techniques to successfully synthesize the target molecule.

Future remarks

retrosynthesis is a foundational concept in organic chemistry that continues to evolve and play a crucial role in the development of synthetic routes for complex molecules.

Advancements in computational chemistry and artificial intelligence are expected to enhance the efficiency and accuracy of retrosynthetic analysis, aiding chemists in generating pathways, predicting reactions, and optimizing synthetic routes.

The integration of retrosynthesis with emerging fields like flow chemistry and automation holds the potential for more streamlined and automated synthesis processes, enabling faster and more cost-effective production of complex molecules.

The future of retrosynthesis involves the integration of advanced computational tools and technologies to expedite the discovery and synthesis of new molecules, with wide-ranging applications across pharmaceuticals, materials science, and fine chemicals.

ACKNOWLEDGMENT

We extend our heartfelt gratitude to the individuals associated with the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Baghdad, for their invaluable support and assistance during the progression of this research endeavor.

Conflicts of Interest

The authors affirm that there are no conflicts of interest pertaining to the publication of this manuscript.

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