IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Benzothiazole Derivatives As Promising Leads In Drug Discovery

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Abstract:-

Among the numerous natural substances and pharmaceutical agents that include heterocyclic compounds, benzothiazole (BTA) and its derivatives are particularly noteworthy. BTA analogs offer substantial structural variety, which has proven advantageous in the search for innovative therapeutic agents, and BTA itself showcases numerous pharmacological characteristics. Given that each BTA derivative possesses its distinctive pharmacological effects, it is evident that this category of chemicals is fascinating. Medicinal chemistry centered on BTAs is currently a trending topic, with a wealth of new studies and developments occurring in the area. Notably, there is an abundance of BTA-based compounds that have gained extensive clinical application as highly effective treatments for various ailments.

Keywords :- Benzothiazole, Drug Design, Drug Discovery,Molecular Docking

Introduction:-

Drug discovery:-

Heterocyclic compounds are widespread in various aspects of life sciences. These compounds serve multiple important roles in nature, medicine, and technology. Heterocyclic hybrids possess great potential as leading structures for the creation of innovative drug candidates in

the realm of contemporary drug discovery. The quest for new drugs and pharmaceuticals stands as a critical and formidable challenge for both academic researchers and the pharmaceutical sector [1,2]. Benzothiazoles have proven to be a notably intriguing biophore in research, as they are utilized as synthons for the creation of bioactive structures [3]. They are found in compounds under investigation for novel products that exhibit valuable biological activities like antitumor [4,5], antimicrobial [6-8], anti-inflammatory [9], anti-tubercular [10,11], anti-HIV [12], anti-malarial [13], anti-convulsant [14], anthelmintic [15,16], antioxidant [17], and analgesic properties. The adaptable synthetic applicability of bioactive heterocyclic scaffolds aids organic synthesis and pharmaceutical chemists in strategizing new approaches to the discovery of newer benzothiazoles. Benzothiazoles are classes of organic compounds characterized by the fundamental structure (C7H5NS). They belong to the group of bicyclic heterocyclic compounds featuring a benzene nucleus fused with a five membered ring containing nitrogen and sulfur atoms. The 2-substituted benzothiazole has emerged as a pivotal structure in diverse therapeutic applications. The analysis of structure-activity relationships interestingly shows that alterations in the substituent group at the C-2 position typically lead to variations in bioactivity.

QSAR:-

The identification of numerous antibacterial substances was primarily a result of chance, with the notable exceptions of trimethoprim, monobactams,

fosfomycin, and carbapenems, which were found by screening fermentation products and compound libraries for their ability to inhibit bacterial proliferation [18]. The innovative strategy of rational antibacterial drug development emerged in the 1990s as a response to the increasing problem of antibacterial resistance. This strategy involved pinpointing molecular targets within bacterial cells, employing high-throughput screening to discover active compounds, and subsequently synthesizing new series of compounds informed by data from structure-activity relationship (SAR) investigations. Utilizing rational drug-design techniques, various novel compounds from diverse scaffolds have been identified that target specific molecular sites in bacterial cells. Nevertheless, none of these compounds has been commercialized up to now [19,20].

Benzothiazole functions as a prevalent scaffold in numerous therapeutically beneficial compounds [21]. Benzothiazole-derived compounds are heterocyclic systems that consist of a benzene ring fused with a thiazole ring (Fig. 1). The presence of nitrogen and sulfur atoms in the thiazole portion has been shown to influence the activities of benzothiazoles [22]. The benzothiazole scaffold is amenable to substitution at various positions on the rings, and it is relatively straightforward synthetically to create new derivatives that may demonstrate enhanced biological activities. The most typical substitutions of the benzothiazole scaffold occur at position 2 [23,24]. General pharmacological activities of benzothiazole-based compounds have been outlined in several reviews [25-28]. Furthermore, the anticancer attributes of benzothiazole-based compounds [29] and their potential to interact with the central nervous system have also been discussed [30]. In this review, we concentrate on the

antibacterial and antibiofilm capabilities of benzothiazole-based compounds, particularly regarding their specific interactions with bacterial cell targets. We evaluate the significance of the benzothiazole scaffold in the pursuit of new antibacterial agents and the prospective future of benzothiazole-derived antibacterials.

QSAR introduction:-

The QSAR approach seeks to identify and quantify the physicochemical characteristics of a drug to ascertain whether any of these properties affect the drug's biological efficacy, utilizing a mathematical equation.

PHYSICOCHEMICAL PROPERTIES:-

•Hydrophobicity of the compound

Hydrophobicity of substituents

•Electronic characteristics of substituents

•Steric attributes of substituents

A variety of compounds is created to alter one physicochemical property and to evaluate its impact on bioactivity.

 A chart is subsequently created to plot the biological activity on the y-axis against the physicochemical feature on the x-axis.

 It is essential to draw the most accurate line through the data points on the chart. This is accomplished through a procedure called linear regression analysis using the least squares method.

 When a line is drawn through a grouping of data points, they tend to scatter on either side of the line. The optimal line will be the one nearest to the data points.

 To assess the proximity of the data points, vertical lines are drawn from each point.

Hydrophobicity:-

The hydrophobic nature of a drug is vital for its ease of crossing the cell membrane and may also influence receptor interactions.

The hydrophobicity of a drug is experimentally evaluated by assessing the drug's relative distribution in an octanol-water mixture. This relative distribution is termed the partition coefficient.

Partition Coefficient P = concentration of drug in octanol

concentration of drug in water

ELECTRONIC EFFECT (Hammet's electronic parameter):-

The electronic effects of different substituents will undoubtedly influence drug ionization and polarity. They affect the ease with which a drug can traverse the cell membrane or the strength of its interaction with a binding site. The Hammet substituent constant (σ) measures the electron-withdrawing or electron-donating capability of substituents on an aromatic ring.

STERIC FACTORS (Tafts steric parameter):-

The mass, dimensions, and configuration of a drug will affect its ability to approach and engage with its binding site. Large substituents may function as a barrier, obstructing the optimal interaction between the drug and its binding site. However, bulky substituents may assist in properly orienting the drug and enhancing its activity.

To assess the potential of the synthesized compounds as drug candidates, the calculated drug likeness, adherence to various criteria, and ADMET properties were determined using Molsoft software and the SwissADME program. A molecule is more likely to exhibit poor oral bioavailability during drug discovery if it possesses more than five hydrogen bond donors, ten hydrogen bond acceptors, a molecular weight exceeding 500 g/mol, and a calculated Log P greater than 5.

The structure–activity relationships indicated that compounds featuring a benzothiazole substituted with either the pyrazolone ring (16a–c) or the pyridone ring (12a–c) are the most promising drug candidates due to the absence of violations, a low TPSA and Log P, along with a favorable drug-likeness score. Additionally, compounds containing the benzylidine moiety of benzothiazole sulfonylhydrazide (14a–c) could be classified as good drug candidates, despite having one violation, as they also exhibit a low TPSA, Log P, and a solid drug-likeness score. Moreover, both the blood-brain barrier (BBB) permeability, gastrointestinal (GI) absorption, and bioavailability of the synthesized compounds were investigated using the SwissADME program; none of the synthesized compounds were found to be BBB permeant. Conversely, some of the evaluated compounds, such as 6a–d, 14a–c, and 19a–e, exhibited low GI absorption, suggesting good absorbance within the human intestines, while others, like 12a–c and 14a–c, demonstrated high GI absorption. Furthermore, all tested compounds received a bioavailability score of 0.55, with the exception of 6b, indicating favorable pharmacokinetic properties.

Computer-aided drug design :-

The primary objective in drug development is to anticipate whether a specific molecule will interact with a target and, if so, to what extent.

➢ Molecular mechanics or molecular dynamics are commonly employed to gauge the intensity of the intermolecular interaction between the small molecule and its biological target.

➢ These techniques are also utilized to forecast the conformation of the small molecule and to simulate the conformational alterations in the target that might take place upon the binding of the small molecule.

➢ Methods in molecular mechanics can also yield semi-quantitative estimates of the binding affinity. Additionally, knowledge-based scoring functions may be applied to generate binding affinity assessments.

➢ These approaches utilize linear regression, machine learning, or other statistical methods to formulate predictive binding affinity equations by correlating experimental affinities with computationally derived interaction energies between the small molecule and the target.

- ➢ Ideally, the computational technique should be capable of forecasting affinity prior to the synthesis of a compound, thus theoretically
- ➢ only a single compound needs to be created, resulting in significant savings in both time and expenses.
- ➢ The truth is that current computational techniques are not flawless and provide, at most, only qualitatively reliable approximations of
- ➢ affinity.
- ➢ Computer-assisted drug design can be utilized at any of the following phases of drug discovery:
- ➢ 1. hit identification through virtual screening (structure- or ligand-based design)
- ➢ 2. hit-to-lead refinement of affinity and selectivity (structure-based design, QSAR, etc.)
- ➢ 3. lead enhancement of additional pharmaceutical properties while preserving affinity
- ➢ There are two primary categories of drug design.
- ➢ ligand-based drug design
- ➢ structure-based drug design.
- ➢ Ligand-based drug design
- ➢ Ligand-based drug design (or indirect drug design) is founded on the understanding of other molecules that interact with the biological target in question.
- ➢ These different molecules can be employed to develop a pharmacophore model that outlines the essential structural features a
- ➢ molecule must have to bind with the target. In simpler terms, a model of the biological target may be constructed based on
- ➢ the understanding of what attaches to it, and this model can subsequently be utilized to design new molecular entities that engage with the target.
- ➢ Alternatively, a quantitative structure-activity relationship (QSAR), where a connection between calculated properties of compounds

- and their experimentally observed biological activity is established, can be formulated. These QSAR correlations may then be employed to anticipate the
- effectiveness of new analogs. Structure-based drug design
- (or direct drug design) is based on the knowledge of the three-dimensional configuration of the biological target obtained through techniques like
- X-ray crystallography or NMR spectroscopy. By utilizing the structure of the biological target, candidate drugs predicted to bind with
- strong affinity and specificity to the target may be devised using interactive graphics and the insights of a medicinal chemist.
- Alternatively, various automated computational methods may be employed to propose new drug candidates..

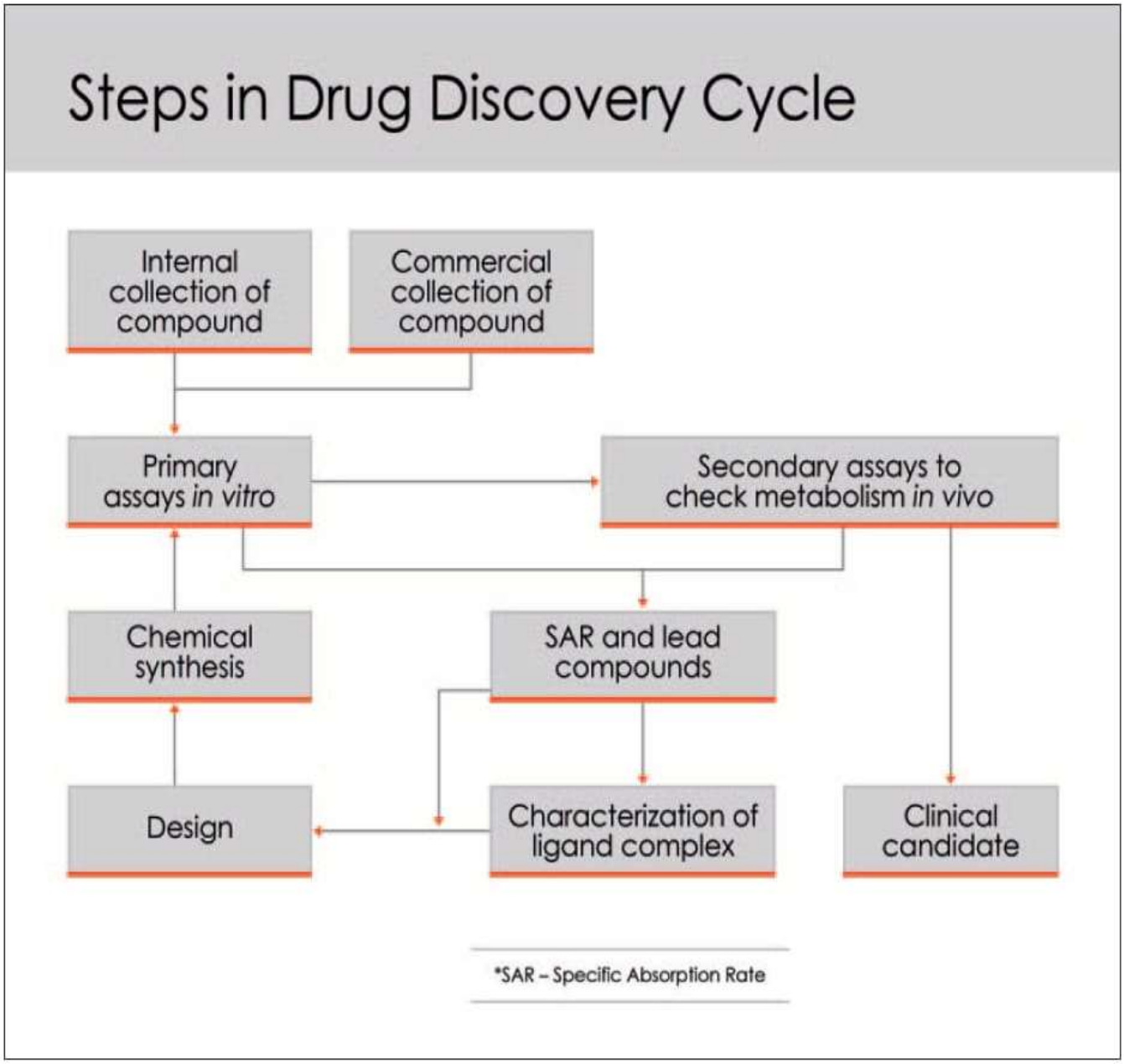


Fig.1:- Steps in Drug Discovery Cycle

Pharmacophore introduction:-

"A pharmacophore represents the collection of spatial and electronic characteristics essential for facilitating the ideal supramolecular interactions with a certain biological target structure and for initiating (or inhibiting) its biological response." A pharmacophore does not depict an actual molecule or a genuine arrangement of functional groups, but rather an entirely abstract notion that describes the shared molecular interaction abilities of a set of compounds regarding their target structure. In the realm of drug design, the word 'pharmacophore' pertains to a group of features that is characteristic of a series of active compounds. A pharmacophore is specified in terms of atoms or centers that can engage with the

Receptor through various interaction centers as outline:

- Hydrogen bond donors
- Hydrogen bond acceptors
- Positive charge centers
- Aromatic ring centers
- Hydrophobic centers

An atom is considered an acceptor if it is capable of attracting a hydrogen (such as nitrogen, oxygen, or sulfur but not amide nitrogen, aniline nitrogen, sulfonic sulfur, or nitrogen from the nitro group), and a donor if it can provide a hydrogen. Pharmacophore modeling is a successful yet highly varied subdiscipline of computer-aided drug design. The idea of the pharmacophore has been extensively utilized in the rational design of new pharmaceuticals.

Molecular Docking:-

Docking is a method based on structural principles that aims to find the optimal alignment between two molecules. Molecular docking is a well-established computational approach that estimates the interaction energy between two molecules. Docking studies are utilized to assess the interaction of two molecules and to identify the ideal orientation of the ligand that would create a complex with the lowest energy overall. The small molecule, referred to as the ligand, typically fits within the cavity of the protein as predicted by the search algorithm. These protein cavities become active upon contact with external compounds and are thus known as active sites. The outcomes are evaluated through a statistical scoring function that transforms the interaction energy into numerical values termed as the docking score; the interaction energy is also computed. Anticipating the mode of protein-ligand interaction can help in identifying the active site of the protein molecule and assist further in protein annotation. Additionally, molecular docking plays a significant role in drug discovery and design.

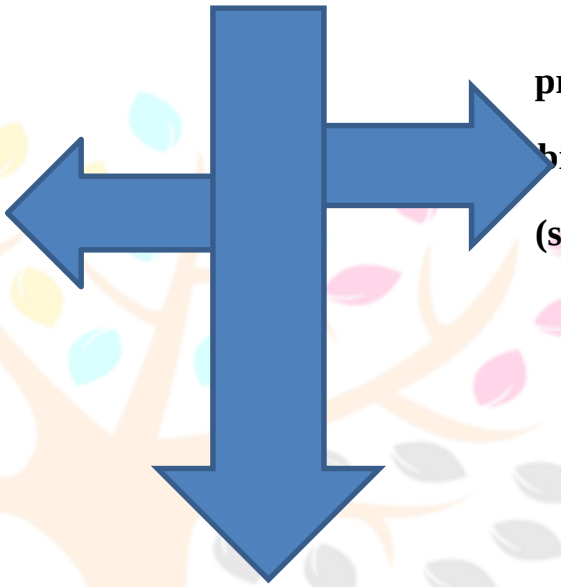
• In the domain of molecular modeling, docking serves as a technique that forecasts the preferred orientation of one molecule relative to another when they are bound together to create a stable complex.

Diagram of ligand receptor complex:

IMPORTANCE

Molecular docking

Identification of the Ligands correct binding geometry (pose) in the binding site (binding mode)



prediction of the binding affinity (scoring function)

Rational desining of drugs

TYPES OF DOCKING The following are primarily used types of docking:

• Lock and Key or Rigid Docking – In rigid docking, both the internal geometry of the receptor and the ligand remain fixed throughout the docking process.

• Induced fit or Flexible Docking - In this approach, the ligand is maintained in a flexible state, and the energy for various conformations of the ligand fitting into the protein is computed. Although this method requires more time, it can assess numerous potential conformations, making it more dependable.

A typical docking work flow

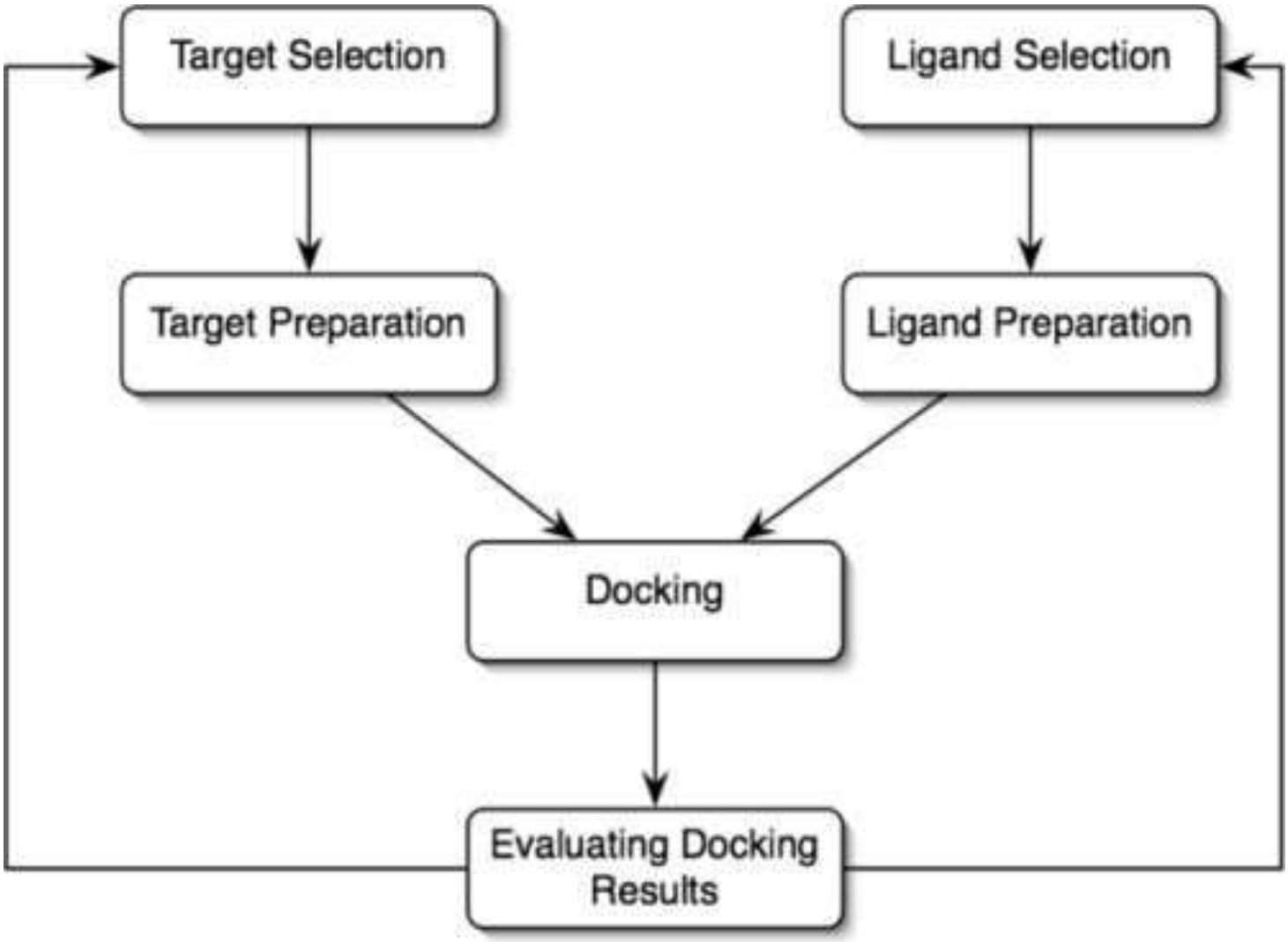


Fig.2:- A Typical Docking Work Flow

Docking Study :-

In vitro assessments of the most effective synthesized compounds demonstrated that the benzothiazole compounds containing a pyrazolone ring, 16a–c, have the capability to inhibit the DHPS enzyme. Consequently, docking studies were performed utilizing a crystal structure of DHPS (PDB ID: 3TYE) sourced from the Protein Data Bank to gain a clearer understanding of how these compounds interact with the binding sites of the DHPS enzyme. The DHPS enzyme features two binding sites: one that accommodates dihydropterin pyrophosphate (DHPP) and another that associates with p- aminobenzoic acid (PABA). The significant amino acid residues that identify the pterin substrate through hydrogen bonding include Asn120, Asp184, Lys220, along with a water molecule, while the residues that engage with the PABA binding site via arene-H interactions are Lys220, Phe189, and Ser221 via hydrogen bonds from the amino group. Docking the cocrystallized ligand (XTZ) into the active site after extraction from the specific receptor was employed to confirm the docking study. The docking of cocrystallized ligand XTZ produced a root mean square deviation

value of −6.9784 kcal/mol. The docking findings indicated that XTZ established four hydrogen bond acceptors with Ser221, Asp184, and Lys220, three hydrogen bond donors with Asp184 and Asn120, and one arene-H interaction with Lys220. Conversely, it illustrates the different types of interactions between the ligand XTZ and the DHPS pockets.

The highest ranked conformations of the most effective compounds 16a–c within the active site of DHPS were outlined. Interestingly, the docking assessment of the compounds analyzed showed that all three compounds fit within the PABA pocket. Compound 16a displayed three arene-H interactions: two between the pyrazolone and the benzene ring of benzothiazole with Lys220, and one involving the thiazole ring and Arg234, in addition to one hydrogen bond donor with a bond length of 2.22 Å between Gly188 and the NH group in the pyrazolone ring, along with similar interactions in compounds 16b and 16c in the active site of DHPS, as well as an additional arene-H interaction between the NH group in the pyrazolone ring and Phe189. Based on these observations, all three compounds are associated not merely by one but two arene-H interactions with Lys220 within the PABA pocket. This indicates that these novel compounds could serve as substitutes for sulfonamide medications to address bacterial resistance.[31]

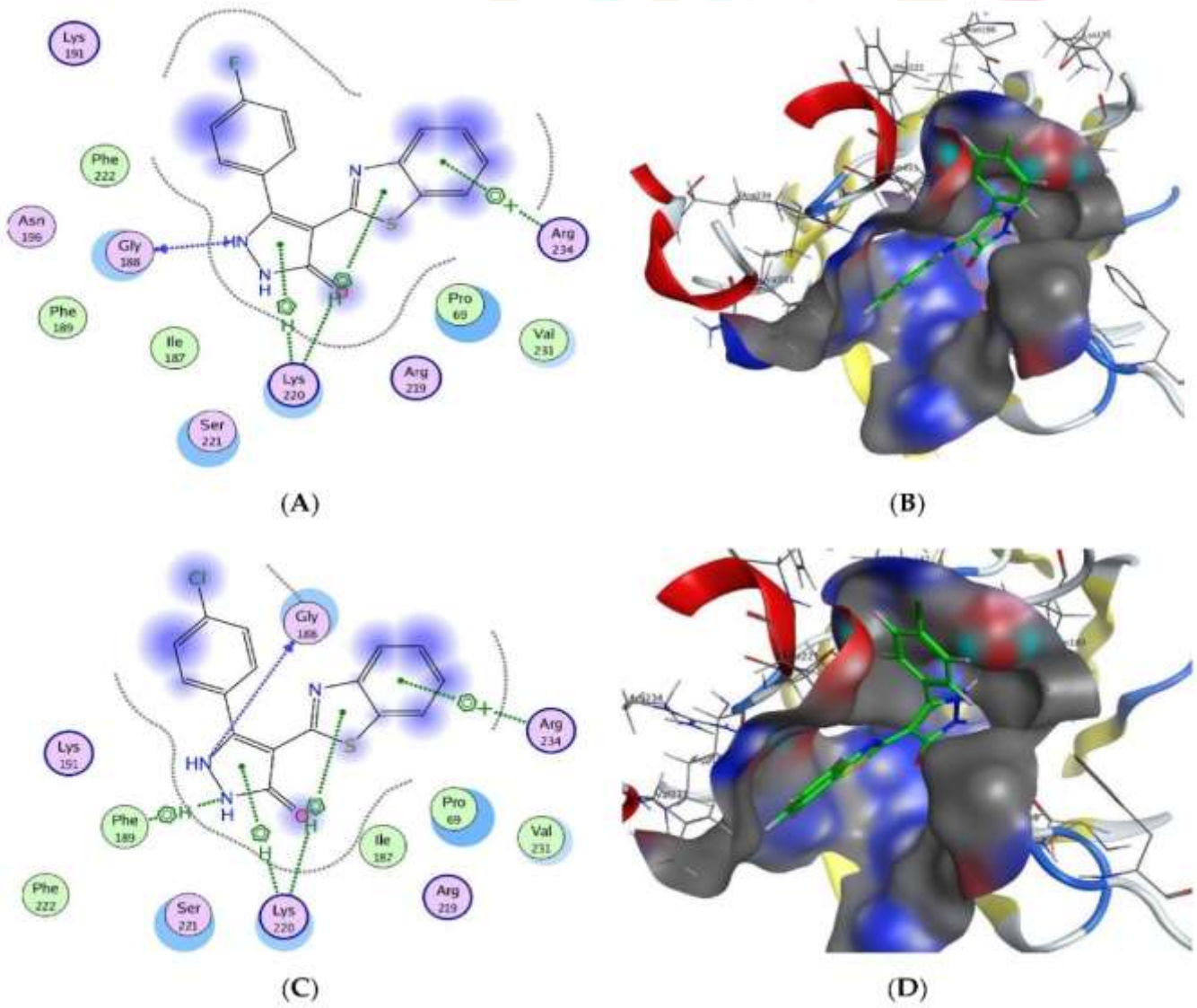


Fig.3: Docking poses of compounds

Combinatorial chemistry:-

Introduction:-

Combinatorial chemistry involves chemical synthesis techniques that enable the production of a vast array (from tens to thousands or even millions) of compounds within a single process. These compound libraries can be created as mixtures or as sets of individual compounds.

This method allows for the simultaneous synthesis of numerous structurally diverse molecules.

It is also known as matrix chemistry. Combinatorial chemistry is one of the modern approaches aimed at minimizing the time and expenses linked to the development of effective and competitive new medications.

➢ Utilizing this innovative technology, pharmaceutical firms can swiftly identify new drug candidates and reduce expenditures in preclinical development.

➢ Combinatorial chemistry can be applied in the synthesis of small molecules as well as peptides.

➢ It offers a potentially rapid pathway to new pharmaceuticals, catalysts, and a variety of compounds and materials.

➢ This technique was developed in the late 1960s through the 1980s and early 1990s to facilitate simultaneous applications to many molecules.

Combinatorial technologies :-

The introduction of new methodologies for generating collections of structurally related compounds (libraries) through combinatorial strategies has rejuvenated random screening as a model for drug discovery, igniting considerable enthusiasm about the potential for discovering new and valuable drugs within short timeframes and at reasonable costs (Figure 1). Nevertheless, the emergence of this new domain in drug discovery has not diminished the significance of traditional medicinal chemistry methods, such as computer-aided rational drug design and QSAR; rather, it has spurred their evolution to integrate and complement combinatorial technologies.[32]

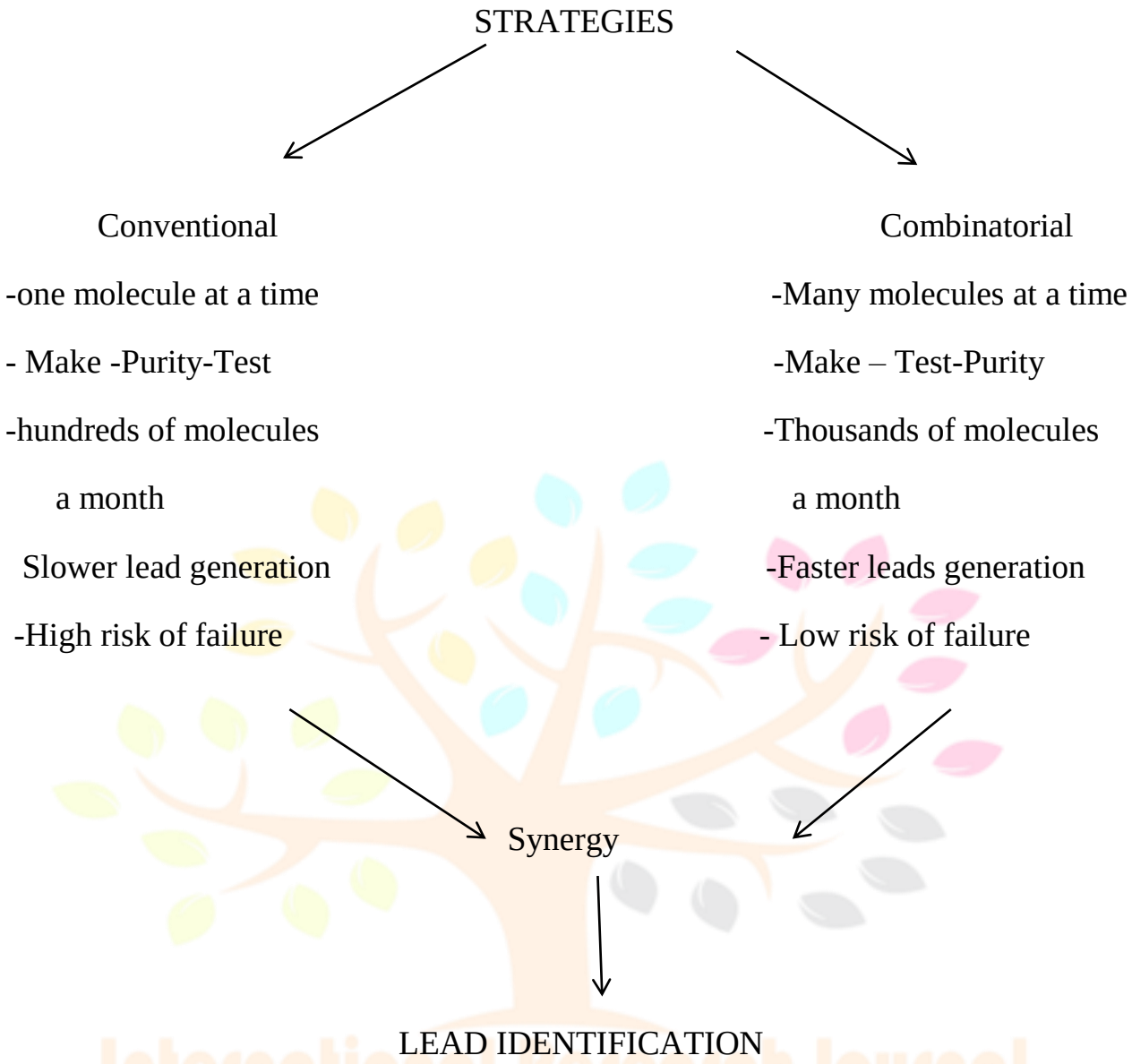


Fig.4:Principal characteristics of conventional vs. combinatorial strategy of drug discovery

Conclusion:-

Among the numerous fused heterocyclic compounds, benzothiazoles have garnered the most research focus. They can serve various functions in different pathophysiological contexts. Given their significant biological importance, a range of synthetic methods has been employed to develop effective drug candidates that incorporate this powerful scaffold with diverse substitutions. The anticancer, antihyperglycemic, antiprotozoal, antiviral, and antibacterial characteristics of benzothiazole derivatives have attracted the attention of researchers for an extended period. This article illustrates the current role of benzothiazoles in medicinal chemistry by examining findings from SAR studies and the binding conformations of these heterocycles with different targets. Utilizing this knowledge, new and varied

benzothiazole compounds can be synthesized to address pathophysiological conditions that are currently challenging to treat.

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