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**Review Paper**

# Benzimidazole Derivatives in Modern Medicinal Chemistry: Synthetic Innovations and Biological Potential

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## ABSTRACT

Benzimidazole is a privileged heterocyclic scaffold that has attracted considerable attention in medicinal chemistry owing to its broad spectrum of biological activities and favourable pharmacological properties. They have attracted significant attention due to their diverse pharmacological activities, including antimicrobial, anticancer, and antioxidant properties. Numerous benzimidazole derivatives have been synthesized through conventional and modern synthetic methodologies involving diverse substitution patterns, leading to compounds with enhanced potency and selectivity. The most recent computational methods, like molecular docking, density functional theory (DFT), and molecular dynamics simulation, are especially included because they can be crucial for comprehending structure–activity correlations and logical drug design. Overall, this review provides a comprehensive overview of the synthetic strategies, diverse biological activities of benzimidazole derivatives, molecular docking and various software's serving as a valuable resource for researchers engaged in medicinal chemistry, pharmaceutical sciences, and drug discovery

## INTRODUCTION

Heterocyclic compounds are characterized by the presence of at least one heteroatom within their cyclic rings of atoms. Nitrogen, oxygen, and sulfur are the heteroatoms that occur most frequently [1]. Research interest in heterocycles is growing as a result of its medical, anti-microbial and industrial applications. Heterocycles are the most important traditional division of organic chemistry and they are also the subject of most scientific investigation [2]. Due to the fact that heterocyclic compounds are also common in macromolecules like enzymes, vitamins, natural products and biologically active substances, they have been considered to be an

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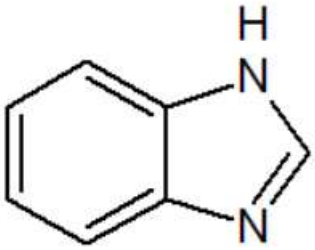
essential component in the field of medical chemistry [3].

Benzimidazole is a heterocyclic compound that serves as a building block in chemical synthesis. Benzimidazole is a bicyclic molecule with a benzene ring fused to a five membered imidazole that has two nitrogen atoms. It is often referred to as1-H benzimidazole, benzoglyoxaline [4]. Benzimidazole derivatives has been reported to exhibit various biological activities such as antiulcer [5], antifungal [6], antitubercular [7], antimicrobial [8], antimalarial [9]. Benzimidazole is a crucial pharmacophore among the several physiologically active heterocyclic compounds with a variety of pharmacological activities. Additionally, a variety of benzimidazole derivatives have been employed to cause sunburn by absorbing UV light and protecting the skin [10]. Mebendazole, telmisartan, omeprazole, enviradene, candesartan and astemizole are among the clinically authorized benzimidazole medications [11]. Benzimidazole derivatives are also reported to exhibit anticancer activities on various cell lines [12]. Thiabendazole, which operates as both antiparasitic and fungicide, was the first benzimidazole -based medication to be made accessible for clinical use [13].




**Structure of benzimidazole**

Benzimidazole and purine based nucleic acids are isostere of one another because of their structural similarity [14]. When Woolley surmised in 1944 that benzimidazole could function similarly to purines to elicit certain biological reactions, its pharmacological profile became apparent [15]. In addition, benzimidazole has a broad range of applications in material science, synthetic organic chemistry, polymer chemistry, coordination chemistry and agriculture. Because of their considerable structural flexibility, benzimidazoles seem to be able to accommodate a wide range of biological targets. This structural plasticity of bio-derived materials offers several potentials for generating new medicinal molecules [16].

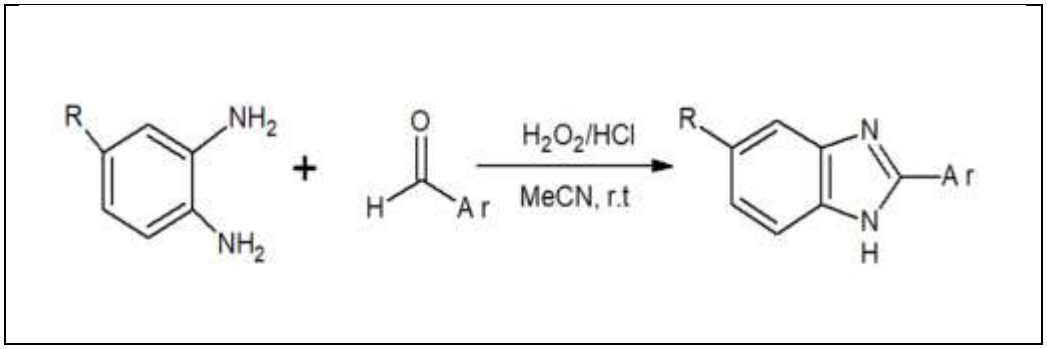
**Various Synthesis methods of Benzimidazole**

The benzimidazole was firstly synthesized by Hoebrecker in 1872 through the reduction of 2-nitro-4-methylacetanilide in the presence of tin and hydrochloric acid. Subsequently, Ladenburg in 1875 carried out the second synthesis by refluxing 3,4-diaminotoluene with acetic acid [17]. There are several methods are used for the synthesis of benzimidazole, the most straightforward technique is the condensation of o-phenylenediamine and formic acid [18]. Some of the methods for synthesis of benzimidazole is given below;

1.From o-phenylenediamine:

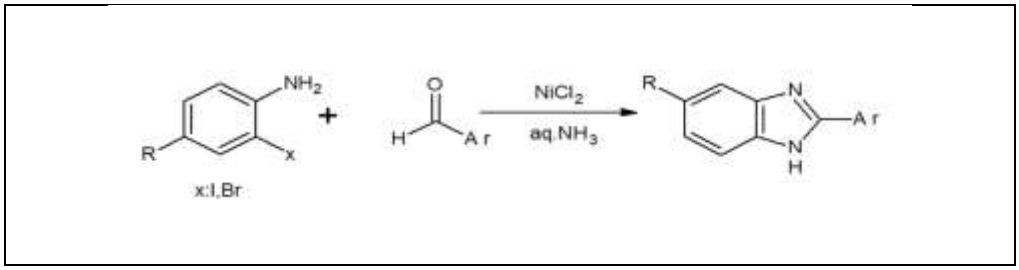
Reaction with Aldehydes

Benzimidazole derivatives were synthesized in a single pot from o-phenylenediamines and different aryl aldehydes using $H_2O_2$/HCl as catalysts in a solvent-free environment at ambient temperature or by single-step condensation in acetonitrile. These methods give high yields of benzimidazole [19].



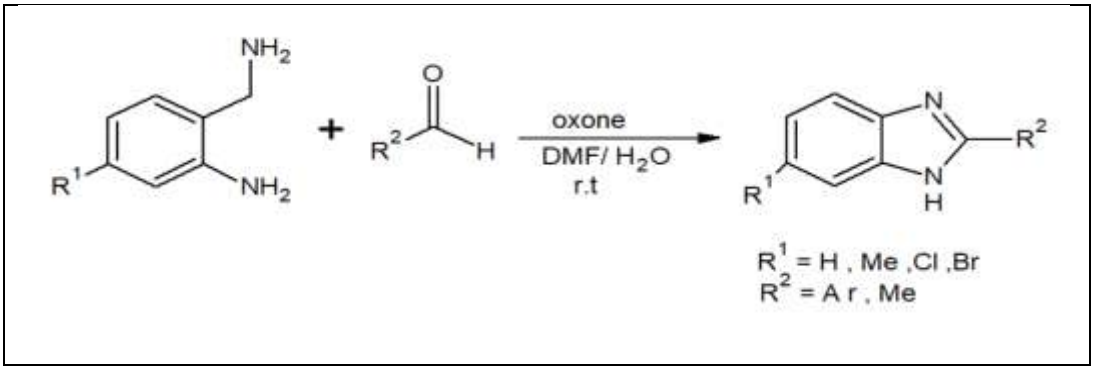

2.From 2-Haloanilines:

This method condenses 2-Haloanilines with various aldehydes using ammonia as a source of nitrogen. Nickel catalyses the reaction, which effectively creates C-N bonds and produces the benzimidazole compounds in good to high yields [20].



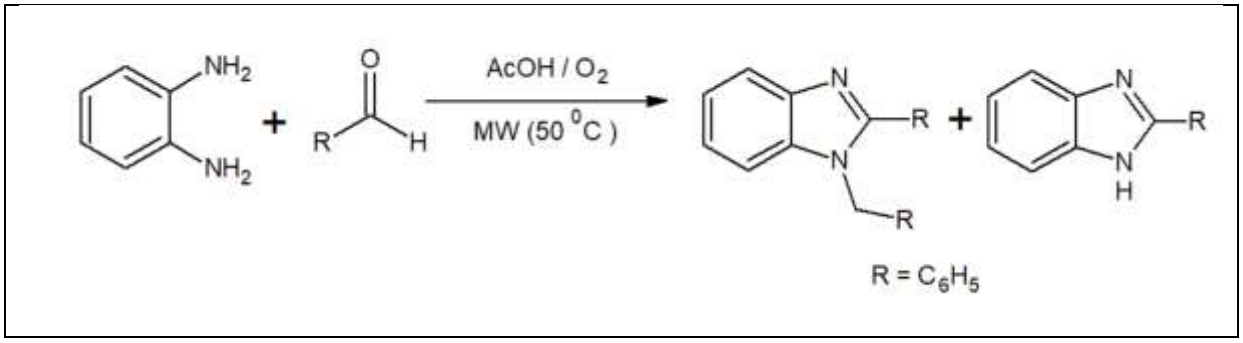

3. From 2-Aminobenzylamines:

2-Aminobenzylamine was converted into 2-substituted benzimidazoles in a single pot at room temperature using an Oxone-mediated sequential conversion method.2-Aminobenzylamine condenses with aromatic, heteroaromatic or aliphatic aldehydes to start the reaction. This produces a tetrahydro quinazoline intermediate, which is then ring-distorted with Oxone to produce benzimidazoles in excellent yields [21].



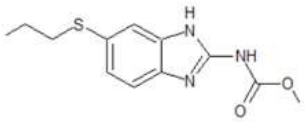

4.Synthesis using microwave:

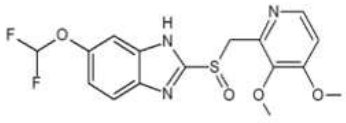
One of the most effective contemporary techniques for creating benzimidazole derivatives is the use of microwave technology. This is a green chemistry method. When acetic acid is present as a catalyst, this method has shown great efficacy in speeding up condensation reactions between ortho-phenylenediamine and aldehydes [22].

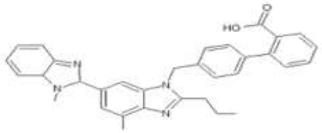


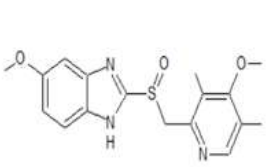

**Biological Activities of Benzimidazole Derivatives**

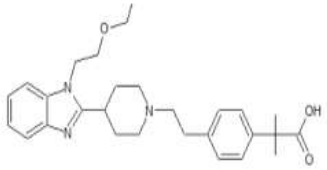
One significant nitrogen- containing heterocyclic scaffold with a variety of biological functions is benzimidazole. Benzimidazole derivatives can interact with a variety of biological targets, including enzymes, receptors, DNA and microtubules because of their structural resemblance to naturally occurring purines. Compounds with antibacterial, anticancer, antiviral, anti-inflammatory, antifungal, antitubercular, antiparasitic and antioxidant properties have been developed as a result of structural alteration on the benzimidazole nucleus. Some of the benzimidazole containing drugs are given below [23].


Albendazole


Pantoprazole


Telmisartan


Esomeprazole

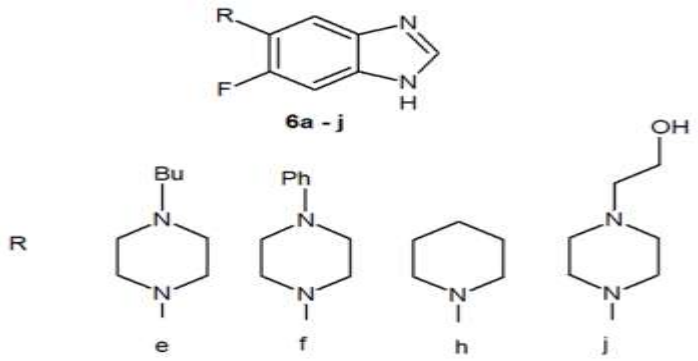

Bilastine

**Antimicrobial Activity:**

Antimicrobials have the ability to eradicate all germs or to prevent their further proliferation. Antimicrobial drugs are classified by the microbes they target.in contrast to antibiotics, which are used to treat bacterial infections, antifungals are developed specifically to treat fungal infections and prevent their spread [24].

Alghawi said et al.,2026 synthesized a series of fluoro-substituted benzimidazole derivatives **6a-j** through the condensation of o-phenylenediamine intermediates with formic acid. Using the agar well diffusion method, an evaluation of the antibacterial activity was conducted in vitro against Staphylococcus aureus, Bacillus cereus, Escherichia coli, and Klebsiella pneumoniae. The

positive control was nitrofurantoin at a concentration of 300 µg/mL. Amphotericin B was used as the reference medication at the same concentrations for antifungal screening against Aspergillus flavus, Penicillium duclauxii, and P. italicum at 20 and 50 µg/ml. The majority of substances showed moderate to strong antibacterial activity. The most effective antibacterial agent was found to be **6h** (MIC = 5.0 µg/mL). The bactericidal mechanism of action was supported by the SEM study of bacteria treated with 6h, which showed significant morphological damage, including cell deformation and membrane disintegration. Out of all the derivatives, the most effective antimicrobials were **6e, 6f, 6h,** and **6j**, which displayed inhibition zones comparable to those of common reference medications [25].




Isik and coworkers in 2024 synthesized a series of new benzimidazole – thiadiazole hybrids(**5a-i**) and evaluated their antimicrobial activity against bacterial and fungal species. The antibacterial activity was better for **5a,5b,5f** and **5h** compounds with an MIC value of 3.90µg/ ml. According to the results of the antifungal activity test, compounds **5f ,5h** demonstrated superior efficacy against Candida albicans with a MIC value of 3. 90µg/ ml. They performed molecular docking study. Density functional theory (DFT) was utilized in order to model the eight synthesized compounds. The Molecular Dynamics simulation of the compounds **5f** and **5h** were discovered to be rather stable in the 14-alpha demethylase (5TZ1) proteins active site [26].

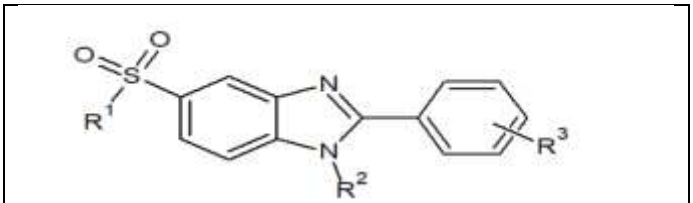
Ram A et al.,2025 designed, synthesized a series of benzimidazole derivatives and evaluated their antimicrobial and anticancer activity. Synthesis of benzimidazole derivatives was accomplished by condensation, which was then followed by cyclization. In vitro antimicrobial activity of the compounds was evaluated using the agarwell diffusion method against gram-negative bacteria such as Escherichia coli, Salmonella enterica, and Klebsiella pneumoniae, as well as gram-positive bacteria such as Staphylococcus aureus. Additionally, in vitro antifungal activity was evaluated against Candida albicans. The invitro results shows that the derivatives **1g-1k** showing encouraging antimicrobial activity. They also performed molecular docking study and showed binding interaction with bacterial, fungal and cancer targets. Molecular Electroscopic Potential (MEP) of the synthesized derivatives are showed [27].

**Anticancer activity:**

Cancer is still one of the deaths causing disease in world, it is necessary to develop effective anticancer drugs without harming normal cells.

Abbade Y et al.,2026 anticancer potential of a number of alkylsulfonyl 1H-benzo[d]imidazole derivatives was assessed in vitro against MCF-7 human breast cancer cells. The xCELLigence real-time cell analysis was used to assess the cytotoxic potential, and quantitative real-time polymerase chain reaction was used to assess the expression

levels of genes linked to microtubule organization, tumour suppression, apoptosis, cell cycle, and proliferation. AutoDock Vin was employed to conduct molecular docking against Bcl-2. After analyzing the data, it was discovered that compounds **23** and **27** exhibited the highest levels of cytotoxicity when tested against MCF-7 cells. A persistent stabilization was observed in the binding site of Bcl-2 for a period of 200 nanoseconds, as demonstrated by molecular dynamics simulations of compounds **23** and **27**[28].



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 23 | $-CH_3$ | Cyclohexyl | 4 - chloro |
| 27 | $-CH_3$ | 3,5 - difluorobenzyl | 3,4 - difluoro |

A study was conducted by Ram A et al.,2024 they covered synthesis, QTAIM, anticancer activity evaluation of pyrrole-imidazole/benzimidazole derivatives and examination of their reactivity characteristics utilizing molecular docking and DFT calculations. All the synthesized derivatives (3h-3o) were characterized by spectroscopic techniques. In vitro tests conducted on the proliferative cell line L1210 leukemia cells revealed that all of the synthesized pyrrole imidazole (**3l, 3p**) and benzimidazole (**3h-3o**) derivatives exhibited potent antileukemia activity [29].Mirgany et al.,2025 conducted a study involving synthesis, evaluation and molecular docking of benzimidazole-hydrazone derivatives as potential anticancer agents targeting Tyrosine Kinases. Biological tests were conducted to determine the cytotoxicity of the substance against cancer cell lines (HCT-116, MCF-7, and HepG2) as well as a normal cell line (WI-38). Compounds **6f** and **6h–j**, exhibited remarkable cytotoxicity, as evidenced by IC50 values ranging from 4.82 to 10.23 µM against MCF-7 cells. These values were significantly lower than those of reference medications such as sorafenib and doxorubicin. The compound **6i** shown the strongest activity against kinases such as EGFR, Her2, and VEGFR2, and the cell cycle study revealed that HepG2 cells were arrested in the G0–G1 phase [30].

Starting with the commercially available 1H-benzo[d]imidazole-2-amine, six new Benzimidazole-hydrazone derivatives were synthesized by Demirci s and team in 2024. Using xCELLigence real-time cell analysis, the anticancer properties of the produced compounds were examined against the cancer cell lines HT29 and A549. Compound **4c** had the strongest anticancer efficacy against A549 and HT29 cancer cell lines, with IC50 values of 0.0019 µM and 0.0093 µM, respectively [31].

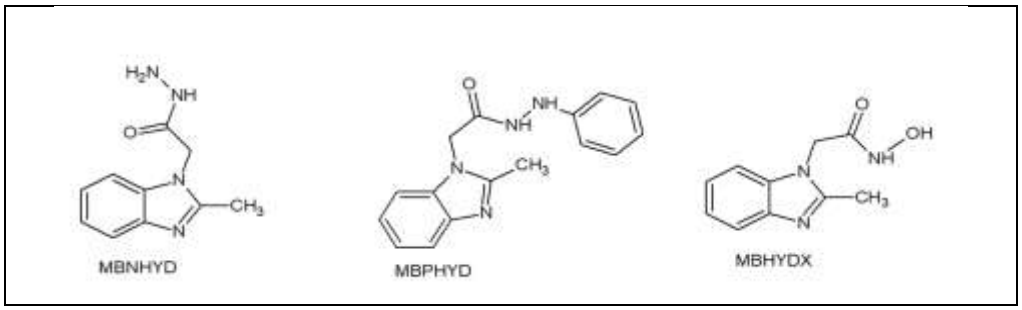
**Anti-inflammatory Activity:**

The ability of a chemical to lessen or prevent inflammation-which is typified by swelling, redness, heat, and pain-is referred to as anti-inflammatory. Since many analgesics reduce pain by addressing the underlying inflammatory processes, they also have anti-inflammatory qualities [32].

Bano s et al.,2024 conducted a study and synthesised a number of 2-substituted benzimidazole derivatives and their potential to reduce inflammation was evaluated using both in

vitro and in vivo tests. The mechanism of action of these drugs against COX enzymes and additional therapeutic targets linked to NSAIDs, including phospholipase A2, aldose reductase, and AIKRC, was clarified using molecular docking studies. While in vivo screening revealed B4, B8, and B2 to be exceptional anti-inflammatory agents, in vitro anti-inflammatory study predicted B4, B2, B8, and B7 as good agents [33].

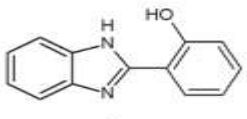
Moharana Ak and team in 2022 reports the synthesis and biological evaluation of three novel benzimidazole derivatives-MBNHYD, MBPHYD, and MBHYDX- developed to explore anti-inflammatory potential. Starting from 2-methylbenzimidazole, the authors prepared and characterized the compounds using FTIR, NMR, MS, and HPLC, confirming high purity. Toxicity assays showed that all derivatives were non-toxic in vitro (Vero cells) and in vivo (Wistar rats). Anti-inflammatory activity was assessed using carrageenan-induced paw edema in rats, where MBNHYD demonstrated the strongest effect, comparable to ibuprofen, while MBPHYD showed moderate activity and MBHYDX was weak. In silico ADME predictions indicated favourable drug-likeness, good oral bioavailability, and low off-target toxicity, with MBPHYD additionally predicted to cross the blood–brain barrier. Overall, the findings highlight MBNHYD and MBPHYD as promising scaffolds for further development of safe and effective anti-inflammatory benzimidazole-based therapeutics [34].



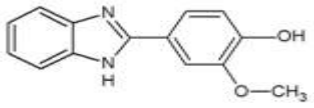

**Antioxidant Activity:**

One of the body's numerous defenses against oxidative and nitrosative damage is antioxidants [35]. The ability to suppress or stop, the oxidation of oxidizable substrates in chain reactions is known as antioxidant activity, and it is crucial for avoiding and managing a number of illnesses associated with reactive oxygen species (ROS) [36,37]. Living cells include antioxidant defense mechanisms that prevent oxidative stress-induced cell damage in a variety of disorders, preserving cellular equilibrium and life. Oxidative stress results from a shift in the balance between antioxidant defenses and oxygen-derived free radicals when antioxidant systems are compromised [37,38].

Rudrapal M et al.,2025 conducted a study involving synthesis of two benzimidazole derivatives (**3a** and **3b**), evaluation of toxicity and antioxidant activity, molecular interaction with NAD(P)H oxidase. The compounds synthesised through the condensation of o-phenylenediamine with aromatic aldehydes. Antioxidant activity was identified using DPPH assay and compound **3a** shows higher activity than compound **3b**. Molecular docking studies results that compound 3b exhibit stronger binding affinity. DFT calculations give insight into the antioxidant mechanisms of these compounds [39].



3a



3b

Bhandari et.al., conducted a study in 2022 which involved design, synthesis, molecular docking and antioxidant activity evaluation of benzimidazole-1,3,4- Oxadiazole Derivatives. The compounds were prepared via microwave assisted reactions, characterized by spectroscopic methods and tested using the DPPH radical scavenging assay alongside molecular docking against PTK2β.Results showed that compound **2A** exhibited the strongest antioxidant activity ($IC_{50}$ = 53 µg/ml) with favourable docking interactions, while compounds **3A and 4A** also demonstrated notable activity. Computational ADMET and DFT analyses supported the stability and reactivity of the most active molecules, highlighting **2A, 3A, and 4A** as promising candidates for further biological evaluation [40].

**Anti-ulcer Activity:**

About 10% of people around the world have peptic ulcer disease (PUD), which includes both gastric and duodenal ulcers. It is the most common digestive problem and its main reason is change in lifestyle [41]. Helicobacter pylori infection, excessive gastric acid secretion and decreased mucosal defense against acid secretion these are the main causes of ulcer [42].

Nalini et al.,2023 conducted a study involving design, synthesis and in-vivo anti-ulcer activity evaluation of new substituted benzimidazole derivatives. Using albino rats as the screening model and acetyl salicylic acid as the ulcer-inducing agent, aspirin-induced gastric ulcer models were utilized to investigate antiulcer activity. Compounds **R1, R2**, and **R8** were discovered to have strong inhibitory action. According to the molecular docking data, compound R8 has a maximum binding affinity of -9.3 kcal/mol for H+/K+ ATPase. Compound R8 exhibits strong activity and can be utilized as a lead molecule, according to the study [43].

**Molecular docking**

Molecular docking is a computational technique used in drug discovery to predict how ligand binds to a biological target, usually a protein receptor or enzyme. It helps identify potential drug candidates by estimating the binding mode and binding affinity between molecules [44,45]**.**

It is possible to conduct molecular docking studies between proteins and ligands, proteins and nucleotides, and proteins and other proteins. The synthesis of ligands, creation of three-dimensional protein structures, calculation of the binding energy in a protein-ligand complex, and data interpretation are all part of the molecular docking method [46]. Molecular docking, which controls the creation of stable complexes between molecules in biological systems, is based on basic concepts of thermodynamics and molecular recognition [47]. The possibilities of molecular docking have been improved by recent developments in algorithmic development and computer capacity. Prediction accuracy and computing efficiency have been significantly enhanced by the combination of artificial intelligence and machine learning techniques [48].

**Molecular Docking Software**

Some of the molecular docking software's are given below [49,50]

| software | Type | features |
|---|---|---|
| AutoDock | Open source | Uses Lamarckian Genetic Algorithm; widely used in academia |
| AutoDock Vina | Open source | Faster and more accurate than AutoDock 4 |
| Dock | Academic | One of the earliest docking programs |
| Gold | Commercial | Uses genetic algorithm; highly flexible docking |
| Glide | Commercial | High accuracy; HTVS, SP, and XP docking modes |
| MOE | Commercial | Integrated drug discovery platform |
| SwissDock | Free Web Server | Easy-to-use online docking |
| Rosetta Dock | Academic | Protein–protein docking with refinement |
| LeDock | Free | Fast and accurate docking |
| rDock | Open source | Suitable for proteins and nucleic acids |

**Discovery studio:** Dassault Systèmes BIOVIA created the software program Discovery Studio for molecular modeling and simulation. It contains a variety of tools for protein modeling, molecular docking, virtual screening, and molecular dynamics simulation analysis. Additionally, the software offers capabilities for comparing the binding modalities of several ligands to the same protein target as well as for displaying and analyzing the docking results [51].

**Chimera:** The University of California, San Francisco created the software program Chimera to see, analyze, and model molecular structures. It offers a variety of tools for running molecular docking simulations and showing the three-dimensional structures of proteins, nucleic acids, and tiny compounds. Additionally, Chimera offers tools for studying the docking results, including the ability to calculate binding energies, visualize binding poses, and create interaction maps between ligand and protein residues [49,52].

**Density Functional Theory (DFT)**

DFT in chemistry is a quantum-mechanical method that uses the electron density as the fundamental variable to compute molecular structures, energies, reaction pathways, and electronic properties with a favourable balance of accuracy and cost [53]. DFT is used in drug modeling research to examine the intricate electrical characteristics of drug delivery systems and isolated drug molecules. It is also used in conjunction with MM-based techniques to investigate drug–receptor interactions. The most extensively used and well-liked quantum theory for determining the electronic structures of atoms and molecules is DFT [54]. DFT works on the concept that a system's electronic density impacts its ground-state energy and other molecular properties. A system's density functional is represented by its ground-state energy, which maps a function to a value [55].

**Molecular Dynamic Simulation**

MD simulation visualizes the structural alterations and flexibility of docked complexes in a biophysical environment over time. MD simulation can be used to visualize the actual movement and structural changes of a protein in a biological system [56]. MD trajectories can be

analysed by calculating the compounds' root mean square deviation (RMSD) and root mean square fluctuation (RMSF) [57]. Using Newton's Laws of Motion, MD Simulation may reveal the temporal evolution of biological systems [58].

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