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PHARMACOLOGICAL PROSPECTS OF 2-AMINOBENZIMIDAZOLES: ADVANCES IN CHEMISTRY, SYNTHESIS, AND THERAPEUTIC POTENTIAL: A REVIEW

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ABSTRACT

2-Aminobenzimidazole (2-ABI) derivatives represent a promising class of nitrogen-containing heterocycles with diverse therapeutic potential. Introduction of an amino group at the 2-position of the benzimidazole ring enhances solubility, chemical stability, and biological interactions, making these compounds attractive scaffolds in drug discovery. Owing to their structural similarity with nucleotides and natural biomolecules, 2-ABIs exhibit strong affinity toward multiple biological targets through hydrogen bonding and π–π interactions. A wide spectrum of pharmacological activities has been reported, including antimicrobial, antimalarial, antiparasitic, antileishmanial, anticancer, anti-inflammatory, anticholinesterase, cardioprotective, and neuroprotective effects. Structure Activity Relationship (SAR) studies indicate that strategic substitutions on the benzimidazole nucleus markedly influence potency and selectivity, thereby guiding rational drug design. Several marketed drugs and investigational candidates incorporate the 2-ABI core, highlighting its clinical relevance. Synthetic strategies for 2-ABIs, ranging from classical condensation to modern metal-free protocols, provide efficient access to novel analogs.. Continued exploration of their molecular mechanisms and optimization of lead compounds could accelerate their progression from bench to bedside, positioning 2-ABIs as valuable scaffolds in modern pharmaceutical sciences.

Keywords: *2-Aminobenzimidazole, Pharmacological properties, Structure Activity Relationship, Scaffolds.*

INTRODUCTION

The principal objective of this study is to explore the pharmacological importance of 2-aminobenzimidazole derivatives which are emerging heterocyclic compounds in the field of pharmaceutical chemistry because of their therapeutic characteristics, and researchers are continuously studying and investigating these compounds for their extraordinary pharmacological potential.

Heterocyclic compounds are those cyclic organic compounds which have one or more atoms other than carbon (heteroatom) in their ring structure. The most common heteroatoms are nitrogen (N), oxygen (O), and sulfur (S). Heterocyclic compounds are the most important compounds in organic chemistry due to their diverse activities in biological fields. Biomolecules like deoxyribonucleic acid

(DNA), ribonucleic acid (RNA), chlorophyll, hemoglobin, vitamins, and a lot of other molecules contain heterocycles as a part of their skeleton. According to the database of FDA approved drugs, about 59% small-molecule drugs contain nitrogen heterocycle moieties [1,2,3]. They are commonly used as pharmaceutical agents, herbicidal substances, and veterinary medicinal products. They also serve as developers, corrosion preventive, antioxidants, sanitizers, copolymers, and pigment stuff. These compounds are also employed as mediums in the synthesis of other organic compounds. Some natural occurring products, for example, antimicrobials (penicillin's and cephalosporin), alkaloids (vinblastine, reserpine, and morphine) etc also contain heterocycles in their structures [4].

Aminobenzimidazoles are bipolar structure-containing heterocyclic aromatic compounds and characterized as the organic compounds in which benzene ring is combined with the imidazole ring with amino group (NH_2) attached at any position. If amino group replaced hydrogen and attached at position two of benzimidazole ring, resulting compound will be 2-aminobenzimidazole [5,6,7].

Hobrecker reported the first synthesis of aminobenzimidazole derivatives in 1872. These derivative compounds attract scientists because of their special geometrical properties and nucleophilic environments, which make them able to bind with several biological targets. The first research paper on the antibacterial properties of aminobenzimidazoles was published by Goodman and Nancy Hart in 1943 and by Woolley in 1944. For many years, these derivatives have been investigated for many therapeutic activities such as antiviral, antifungal, and anticancer activities [8].

Amination (introduction of -NH_2 group) of benzimidazole ring enhances its miscibility in polar solvents by enhancing its polarity. High solubility further enhances its bioavailability in biological systems. Benzimidazole moiety is famous for its chemical stability due to its aromatic structure. This chemical stability is essential for its strength in biological and storage conditions. Introduction of amino group in benzimidazole ring enhances its reactivity especially in hydrogen bond and π-π interactions that are responsible for binding with biological targets and playing role in biological activity of benzimidazole [9,10,11].

These compounds are commonly used in medicinal chemistry and have broad range of pharmaceutical, industrial and education importance due to their multiple activities [12]. They also have biological and clinical significance due to their similarity with nucleotides of the living system. Their heterocyclic nature and electron-rich environment make them useable not only in the field of drug discovery but also in clinical remedies with significant therapeutic efficacy. Their nucleus is also present in natural occurring compounds like Vitamin B_{12}, having structure like purine bases [13]. Many derivative compounds of benzimidazole including aminobenzimidazole, have been researched for antiviral activity against HIV, HBV, HCV, HSV, Rota virus, Herpes virus, Coxsackie, PRSV, adenovirus and mosquito larvae. They contain antimicrobial, antimalarial, anti-ulcer and anti-tumor activity. They also have corrosion inhibition characteristics [14-29].

Fig 1. Marketed drugs containing 2-Aminobenzimidazole nucleus

There are about thirty derivatives of 2-aminobenzimidazole **1** documented as drugs having various therapeutic properties such as antifungal, antiviral, antiparasitic and anti-allergic and their structural properties, synthesis and biological activities have been published [30,31]. These compounds also form complexes with metals such as zinc, copper and cobalt showing antibacterial and antifungal characteristics [32].

2. Synthesis of 2-aminobenzimidazole

2.1 Using cyanamide

2-aminobenzimidazole is obtained by ring closure of o-phenylenediamine with cyanogen bromide. The process involves the chemical reaction of o-phenylenediamine and cyanamide in the availability of protonic acid, usually at elevated temperature, resulting in the formation of 2-aminobenzimidazole (desired product).

2.2 Using Mercuric Oxide

This process of synthesis of 2-aminobenzimidazole comprising ring-closing an N-(o-amino phenyl) thiourea with mercuric oxide and desired product is obtained [33].

2.3 Halogenation of ketone with Guanadine

A new strategy of 2-aminobenzimidazole synthesis is reported in which reaction occurs between α-halogenated cyclohexanone and

guanidine. It gives facile N-bronosuccinimide (NBS) related transition metal free, viable process to produce azoles having substitution at 2-position. N-bronosuccinimide promotes direct halogenation of cyclohexyl ketone along with Oxone, which further reacts with guanidine and gives 2-aminobenzimidazoles [34].

2.4 Cascade Reaction

An efficient cascade reaction to produce 2-ABI from isoselenocyanates include the crystallization of elemental selenium (Se) from the chemical mixture much refines the purification procedure and let it to be re-utilized for synthesis of isoselenocyanates [35]. A simple method of synthesis of 2-(alkylamino) benzimidazoles involves dipeptide analog in which the guanidine functional group, (R-NH)(R'-NH)C=N-R" of an arginine has been displaced with a 2-ABI [36].

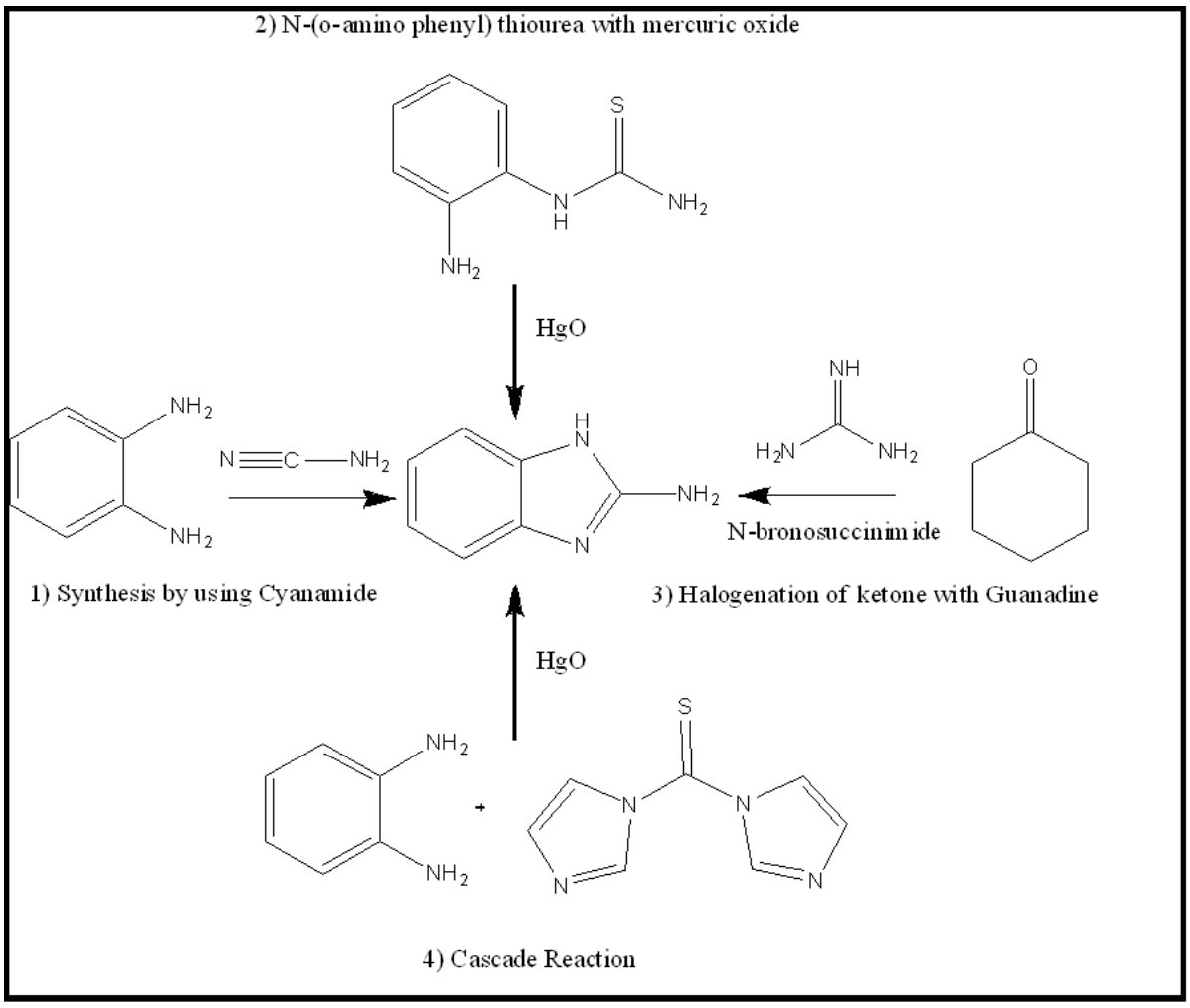


Fig 2. Different strategies for synthesis of 2-Aminobenzimidazole

3. Biological Activities

Biological activities of 2-Aminobenzimidazole reported are summarized in **Table 1.**

3.1 Antimicrobial Activity

A series of new benzimidazole derivatives having sulfides and carbamoyl esters structures, was produced using 2-aminobenzimdazole as starting material with the yield of 16.7% to 36.4%. Their architecture was described by proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR). These derivatives were investigated for their antibiotic properties and results of bioassay showed that some derivatives possess potent antifungal activity and may be used to develop potential antifungal medicines [37].

2-aminobenzimdazole derivatives are potent inhibitors of density-dependent signaling against wild-type *Pseudomonas aeruginosa*. In the study forty 1,2,3-triazole derivatives of 2-ABI were designed, synthesized, and described by Infrared (IR) spectroscopy, Nuclear magnetic resonance spectroscopy (NMR), Mass spectroscopy (MS) and elemental analysis. All synthesized derivatives were investigated for ex vivo activity of density-dependent signaling inhibition against *P. aeruginosa*. Schrodinger Glide software was used for molecular docking study of the synthesized derivatives at the target biological site, LasR receptor [38]. The study reported that 2-ABI derivatives block *Salmonella enterica* serovar *Typhimurium* biofilm formation in minute strengths (μM). Moderations at different sites of hit synthesized compound produced novel potent derivatives that block *Salmonella typhimurium* biofilm development while being harmless to bacterioplankton (bacterial component of plankton, which are microscopic organisms that drift in aquatic environments) growth [39].

3.2 Antileishmanial Activity

Leishmaniasis is an infectious disorder that impacts numerous people annually. Antileishmanial medicines are used to treat it, but they have complications such as toxicity and long course therapy. Leishmania infantum was investigated with a compound library of 1.8 million therapeutic compounds which are freely available for this motive as segment of method development. Among these compounds, a derivative of 2-aminobenzimdazole was nominated hits, which had moderate affinity, poor metabolic lability, and high lipophilicity. Further steps of synthesis were taken to introduce different molecular fragments likely to lower lipophilicity to increase clearance and other active biological compounds with improved ex-vivo characteristics and therapeutic properties against various strains of the parasite. Elevated leptoderminic activity of a compound was recorded. Among synthesized compounds, two were further used in the in-vivo acute Leishmania infantum VL mouse model. These compounds contained good in-vitro efficacy, but their potency and bioavailability were low in in-vivo models which cause complexities in use of these compounds as efficient treatments. The mechanism of action of these compounds is ongoing testing, but it was recently approved that acyl (RCO-) aminobenzimidazoles may have the kinetochore CDC-like kinase-1 (CLK1) protein kinase as the main biological target [40]. Recent research showed the activity of 2-aminobenzimidazole moiety against *Trypanosoma cruzi* and *Trypanosoma brucei*, indicating wide antiparasitic characteristics [41].

3.3 Anti-H_3 Receptor Activity

2-aminobenzimidazole derivatives have been outlined as a new class of H3 receptor antagonists which consist of 2-ABI nucleus linked to an imidazole ring structure via di- or tri-methylene spacers. These derivatives have high affinity towards the receptor that depends upon the methylene chain spacer length. 5(6)-methoxy had a sub-nanomolar binding affinity, hence indicating an extensive affinity to H_3 receptor. According to quantitative structure-activity relationship (QSAR) modeling, it was discovered that, lipophilicity (log P) and basicity (pKa) of the derivatives, is directly proportional to the compounds' receptor affinity but has a U-shaped relationship with log P. Different substitutes at position 5(6) of the benzimidazole moiety contained effect on their lipophilicity and basicity that impact their affinity towards the H_3 receptor. Intrinsically, there is a hope that derivatives of 2-aminobenzimidazole may be utilized as efficient H_3 receptor antagonists and may be specifically useful in cases where enhanced level of neurotransmitter release is required such as cognitive disorders [42].

3.4 Antimalarial Activity

The 2-aminobenzimidazole derivatives with a N1-substituted phenol are a novel series of compounds having less toxicity and potent in-vitro activity against *Plasmodium falciparum* malaria, good ligand-lipophilicity efficiency (LLE), low metabolic stability, low MW, and synthetic tractability were their attractive pharmacological properties [43].

3.5 Antiparasitic Activity

The class of 2-aminobenzimidazole derivatives was identified in a GSK (GlaxoSmithKline) compound library by using HTS (High-throughput screening) technology to generate new libraries of active compounds that have activity against trypanosomiasis and leishmaniasis [44,45,46]. Further, optimization studies as per criteria for the development of most emerging compounds, tested for ADMET (absorption, digestion, metabolism, excretion, toxicity) and antiparasitic efficacy. One derivative showed potent activity against *Trypanosoma cruzi* and *Trypanosoma brucei* and it had good permeability, no discernible toxicity on HepG2 and MRC-5 cell lines [47].

3.6 Anticancer activity

Two new small compounds containing 2-aminobenzimidazole moiety, MFBre and MFB [1-(4-chlorobenzyl)-2-(5-methyl-2-furfurylideneamino)-benzimidazole, were synthesized and their angiostatic characteristics were tested because of their capacity as a lead compound in medicinal chemistry. Results showed that the second compound had good Anti-Angiogenetic and Anti-Lymphangiogenic properties [48].

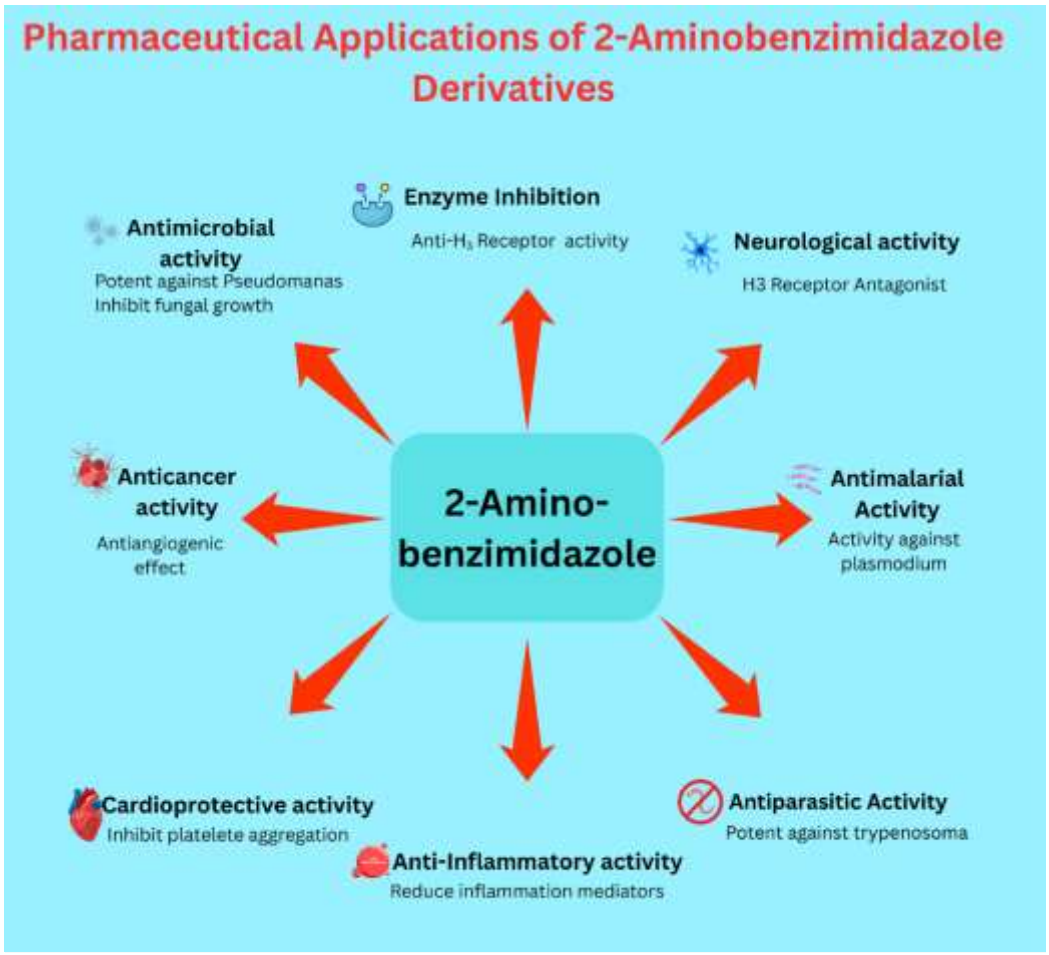


Fig 3. Therapeutic activities of 2-aminobenzimidazole

3.7 Anti-inflammatory Activity

In the research novel, acetamide derivatives of 2-aminobenzimidazole were synthesized and their anti-arthritic activity was investigated in rats. These derivatives were described by FTIR (Fourier transform infrared spectroscopy) and NMR (Nuclear magnetic resonance). Anti-inflammatory activity of synthesized compounds at different strengths (10, 20 and 30 mg/kg) were tested using Carrageen-induced paw edema model. Further, most effective strengths of these compounds were tested in complete Freund's adjuvant (CFA)-induced arthritis model. The effect on inflammatory arthritis was investigated through different tests such as Reverse Transcription quantitative

Polymerase Chain Reaction (RT-qPCR) analysis, radiographic, histopathological, and hematological analysis. The synthesized derivatives show good anti-inflammatory activity as well as they decrease level of autoantibodies in body and restore hematological specifications therefore showed improved drug profile than standard drug, methotrexate. Two compounds show string inhibitory activity against pro-inflammatory mediators and according to results, they have potent anti-arthritic activity [49].

The study reported that 2-aminobenzimidazole derivatives selectively inhibit NOD1 (Nucleotide-binding oligomerization domain-containing protein-1), which is an intracellular protein that acts as a pattern recognition receptor (PRR) in the natural immunity. Process-oriented study of Nodinitib-1 (prototypical drug) showed that 2-aminobenzimdazole derivatives change NOD1 subcellular targeting in cells by making confirmational changes of NOD1 in vitro. These derivatives give lead compounds for investigating mode regulating NOD1 activity and tools for researching the roles of NOD1 in several inflammatory and infectious disorders [50].

3.8 Anticholinesterase Activity

A series of derivatives of 2-aminobenzimidazole was prepared by using microwave irradiation method and their biological activity on acetylcholinesterase and butyrylcholinesterase, was investigated. Some of these compounds showed potent inhibitory activity and results indicated these compounds as emerging selective blockers of AChE and BuChE and beneficial in the pharmacological management of neurodegenerative disorders [51].

3.9 Cardioprotective Activity

Some halide derivatives of 2-aminobenzimidazole were synthesized and investigated for their effect on cardiovascular system. One of them exhibited potent Na^+/H^+ exchanger isoform-1 (NHE-1) inhibitory activity even better than standard drug, Zoniporidone and two compounds improved heart refractory period and decreased platelets aggregation even better than standard drugs, pentoxifylline and etmosine. One of these compounds increased heart refractory period and decreased platelets aggregation as well as suppressed glycation end products (like standard drug, aminoguanidine) [52].

3.10 Immunotropic Activity

In this study novel compounds were synthesized by reacting 2-aminobenzimidazole moiety with many acids and ketones and their biological impact on immune system was investigated in mice. One synthesized derivative decreased production of antibodies (humoral response) at specific doses but improved cell-body immunity. It reduced humoral response only at higher concentration. Another derivative also showed immunosuppressant activity. Although it had lower activity than standard drug, Cyclosporin A, it suppressed immune response in all tests efficiently [53].

3.11 Ion channel modulators

Electric potential is conducted through Ca^{2+}-activated K^+ channels that cause actional potential and take part in excitation of neurons and regulation of transmission of conductivity through synapses. Inhibitors of these channels can be proved as novel therapeutic agents for neurological and psychiatric disorders such as anxiety, depression, Parkinson's disease, and cognitive disorders. Study reveals that 2-(N-substituted)-2-ABIs are better potent inhibitors of SK channels than common inhibitors as they do not block channels' pores (but they did not displace apamin in binding investigation). These inhibitors showed first example negative modulator of channel gating for blockage of Calcium-activated potassium channels, as a mechanism of action. One of these compounds causes reversible inhibition of SK3-mediated electrical conductivity with a K_d value of 9 nM [54].

3.12 Enzyme Inhibitory activity

A series of new derivatives of 2-aminobenazimidazole were designed, synthesized and Fragment-based drug discovery (FBDD) work was done by using 2-aminobenzimdazole moiety as original fragment. FBDD has been commonly utilized in the study of aspartyl protease inhibitors, and it showed that 2-ABI make bond with aspartyl dyad (Asp 32 and Asp 228) of BACE-1 (β-site

Amyloid precursor protein Cleaving Enzyme-1). FRET (Fluorescence resonance energy transfer) assay's result showed that among twelve synthesized 2-AMI derivatives, three could cause more than 50% enzymatic potency inhibition of BACE-1 at dose of 10 µM. Molecular docking study revealed that 2-ABI could form many hydrogen bonds and fill S1/S2' pockets well [55].

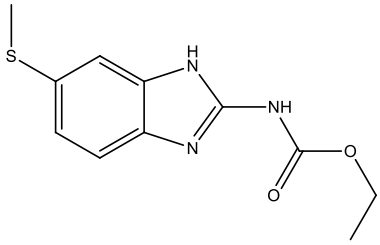
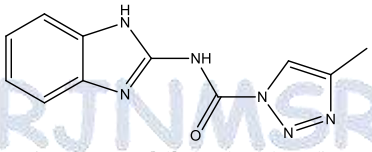
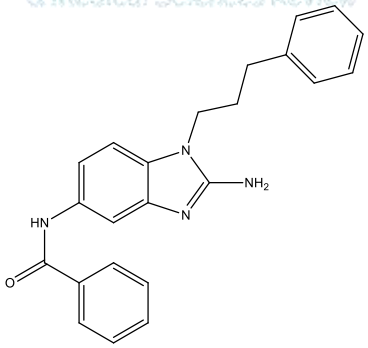
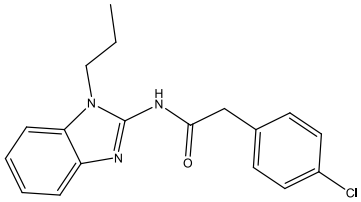
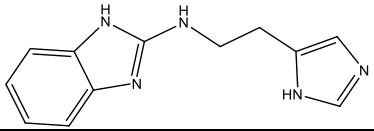
3.13 Antithyroid activity

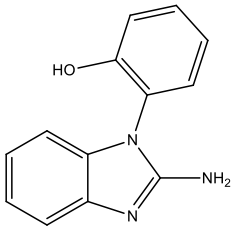
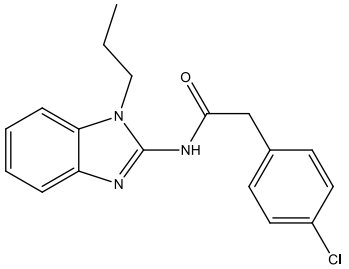
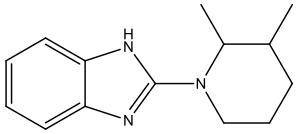
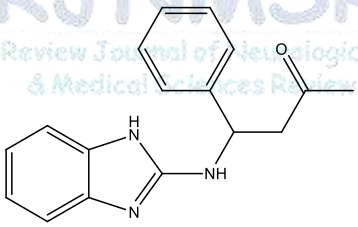
2-aminobenzimidazole derivatives along with some other imidazole ring containing compounds, also possess varying degrees of antithyroid activity [56].

3.14 Anticonvulsant activity

2-aminobenzimidazole also secured the experimental animals against hyperbaric oxygenation convulsions at various concentrations [57].

Table 1. Biological activities of 2-Aminobenzimidazole reported

Sr. No	Biological Activity Reported	Structure & Name	Citation
1.	Antimicrobial Activity	 Ethyl(6-(methylthio)-2-benzoimidazol-2-yl)carbamate	37
		 N-(1H-benzo[d]imidazol-2-yl)-4-methyl-1H-1,2,3-triazole-1-carboxamide	38
		 N-(2-amino-1-(3-phenylpropyl)-1H-benzo[d]imidazol-5-yl)benzamide	39
2.	Antileishmanial Activity	 2-(4-chlorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide	40,41
3.	Anti-H_3 Receptor Activity		42

		N-(2-(1H-imidazol-5-yl)ethyl)-1H-benzo[d]imidazol-2-amine	
4.	Antimalarial Activity	 2-(2-amino-1H-benzo[d]imidazol-1-yl)phenol	43
5.	Antiparasitic Activity	 2-(4-chlorophenyl)-N-(1-propyl-1H-benzo[d]imidazol-2-yl)acetamide	44,45, 46, 47
6.	Anticholinesterase Activity	 2-(2,3-dimethylpiperidin-1-yl)-1H-benzo[d]imidazole	51
7.	Immunotropic Activity	 4-((1H-benzo[d]imidazol-2-yl)amino)-4-phenylbutan-2-one	53

4. SAR Analysis

To investigate the significance of 2-aminobenzimidazole and N1-phenol relationship, different changes were made into 2-ABI nucleus to assess its comparative significance for potency. The modifications which were made are: a) Phenol substitution, modification, and replacement; b) Amino group modification and replacement; c) evaluation of divergent scaffolds.

a. Phenol substitution, modification, and replacement

Loss of Activity: Shifting hydroxyl (-OH) to meta position, substituting with amino (-NH2), methoxy (-OCH3), hydroxymethyl (-CH2OH), fluoro (-F) groups at ortho position lose its biological activity. Expanding the ring to benzofuran/indole or introducing heteroaromatic substitutes also destroys therapeutic activity.

Position effects: Substitution at 3-, 4-, 5- and 6-position highly affect the activity.

Synergistic Disubstitution: 4,5-dimethyl has potent effect but 4,6-dimethl has comparable low effect.

Phenolic pKa correlation: A lower pKa value of the compound eliminates its activity.

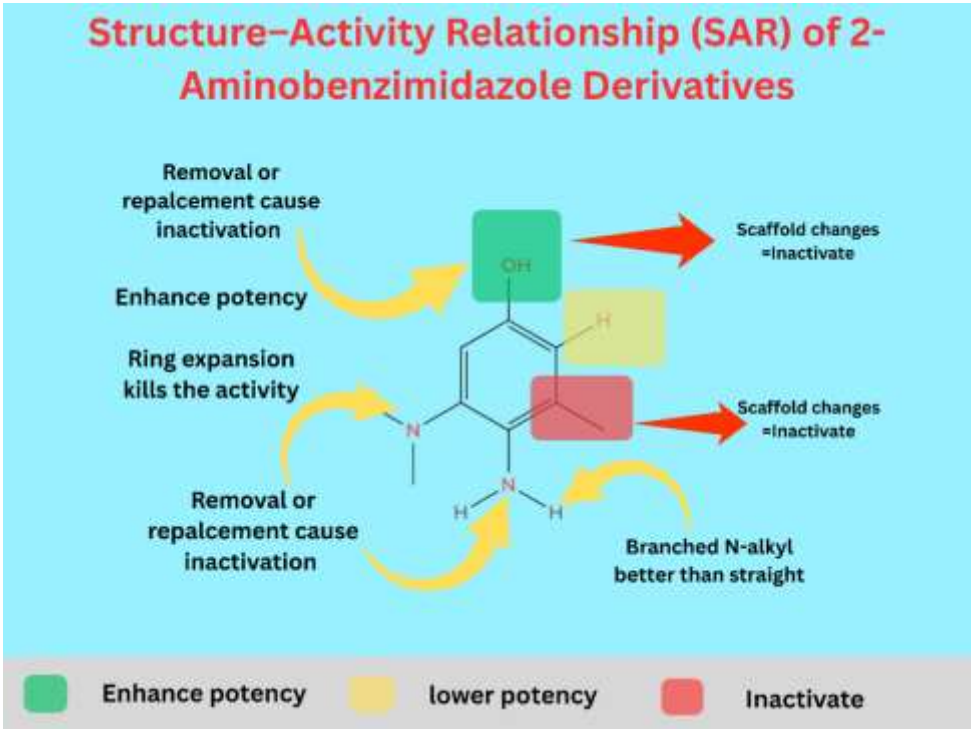


Fig 4. SAR of 2-aminobenzimidazole derivatives

b. Amino group modification and replacement

Removal: Removal or replacement of amino group with any other heteroatom, destroy the activity.

Scaffold change: If scaffold is changed it becomes inactive.

N-alkylation: Although substitution of branched chain shows better activity than straight chain, alkylation decreases the activity of parent compound.

c. Divergent Scaffolds

Scaffold variations or heteroaryl substitution eliminate therapeutic activity despite retaining basic patterns [58].

5. Discussion

2-Aminobenzimidazole (2-ABI) derivatives have emerged as an exceptionally versatile class of heterocyclic scaffolds with diverse pharmacological applications. A critical analysis of the reported literature highlights their structural adaptability, ability to form hydrogen bonds and π–π interactions, and resemblance to naturally occurring purine bases, which collectively contribute to their high affinity toward multiple biological targets.

From a synthetic standpoint, 2-ABI can be efficiently obtained through various strategies, including condensation of o-phenylenediamine with cyanamide, thiourea derivatives, or halogenated ketones with guanidine. The availability of cascade reactions and environmentally benign methods further broadens their synthetic accessibility. These approaches enable incorporation of structural diversity, which is essential for optimizing biological activity.

In terms of biological potential, 2-ABI derivatives demonstrate a remarkably broad spectrum of activities ranging from antimicrobial, antiparasitic, and antimalarial to anticancer, anti-inflammatory, and neuroprotective effects. Of particular importance is their role as quorum sensing inhibitors, enzyme blockers, ion channel modulators, and H3 receptor antagonists. Such diversity underscores the scaffold's ability to interact with targets in infectious, inflammatory, neurological, and metabolic disorders. Furthermore, the discovery of cardioprotective, immunomodulatory, and enzyme inhibitory activities positions 2-ABI as a promising nucleus for multifunctional drug design.

The SAR studies reveal that the amino group at position-2 of the benzimidazole ring is indispensable for activity, as its removal or replacement leads to a sharp decline in potency. Phenolic substitution patterns significantly influence bioactivity, with modifications at specific positions either enhancing or abolishing activity. Importantly, lipophilicity and basicity show a direct relationship with receptor affinity, particularly in H3 antagonists, while excessive alkylation or scaffold replacement tends to reduce biological relevance. These insights provide a rational framework for designing future derivatives with enhanced selectivity and potency.

Despite promising results, several challenges remain. Many reported derivatives display limited metabolic stability, poor bioavailability, or dose-dependent toxicity in in-vivo models. While some compounds show potent in-vitro efficacy, translation into clinically effective agents remains underexplored. Moreover, a lack of systematic ADMET profiling and clinical correlation restricts their progression from laboratory findings to therapeutic use.

Looking forward, the integration of computational approaches such as molecular docking, molecular dynamics simulations, QSAR, and pharmacophore modeling can accelerate the identification of potent lead molecules. Additionally, incorporation of green synthetic methods, structural hybridization, prodrug strategies, and advanced delivery systems (e.g., nanoparticles, liposomes, and polymer conjugates) may overcome pharmacokinetic limitations. The unique versatility of 2-ABI derivatives suggests they may serve as privileged scaffolds for the next generation of anti-infective, anti-inflammatory, and neuroprotective agents.

6. Conclusion

2-aminobenzimidazoles have significant importance in educational field and pharmaceutical industry. They are attractive compounds in the field of drug design, discovery and development, and various researchers are studying them, and hence large data is available on their in-vivo and ex-vivo activities. Their methods of synthesis are also simple. In contrast to many other emerging heterocyclic compounds which have more than one step synthesis, they have one-step synthetic methods with high yield. These derivatives are emerging compounds in the field of medicinal chemistry due to having strong pharmacodynamic and pharmacokinetic characteristics. They show several biological activities such as antibacterial, antifungal, antimalarial, antiparasitic, anti-helminthic, anticonvulsant, anti-ulcer, anti-inflammatory, antileishmanial, anticholinesterases, anticancer, antithyroid, anti H3 receptor, immunotropic, cardioprotective, enzyme inhibiting and ion channels modulating activities. They are encouraged to use various diseases including neurodegenerative, cardiovascular, and psychiatric. They showed activity in animals as well as humans.

Researchers are working on these compounds so that novel compounds can be synthesized by making modifications and substitutions at distinct positions. 2-aminobenzimidazole nucleus is also present in some medicines that are available in market are commonly being used. There are expectations that some most potent compounds can be proved through clinical trials in the near future.

Author Contributions:

Conceptualization, Hafiz Aamir Ali Kharl. and Maria Shafaqat ; methodology, .; validation, X.X., Y.Y. and Z.Z.; investigation, Waleed Maqbool, Maha; resources, Khaizran Fatima Kamal.; data curation, Muhammad Saad Naeem.; writing original draft preparation, Abu Sulman.; writing review and editing, Hafiz Aamir Ali Kharl.; visualization, Syeda Rimsha Gillani, Hafsa Sehar.; supervision, Hafiz Aamir Ali Kharl.; project administration, Amina Afaq.. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest:

The authors declare no conflict of interest.

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