A REVIEW ON: THE DIFFERENT BENZIMIDAZOLE DERIVATIVES ACTIVITIES IN THE DIAGNOSIS AND TREATMENT OF DISEASES

[1]Dr. D.P. Kawade,, [2]Mrs. Gitanjali Gadpayle

[1]Associate Professor, [2]Student

Department of Pharmaceutical Chemistry,

Priyadarshini J. L. College of Pharmacy, Nagpur, India

Abstract

This review's main goal is to provide the results of studies on the benzimidazole derivative. Benzimidazole derivatives were created and tested for cytotoxicity and antiviral activity against a panel of ten RNA and DNA viruses in cell-based experiments. Also review on antifungal activity of selected benzimidazole compounds and synthesis and antimicrobial activity of some new benzimidazole derivatives. More recently, selected benzimidazole derivatives were shownto be active in vitro against two protozoan parasites, Trichomonas vaginalis and Giardia lamblia, and clinical studies with AIDS patients have suggested that microsporidia are susceptible as well. The benzimidazole methylcarbamate drugs, commonly used as anti-helmitics, have been suggested to have anticancer activity, but progress has been stalled by their poor water solubility and poor suitability for systemic delivery to disseminated cancer. The in vitro effects of novel benzimidazole derivatives with thiosemicarbazide and triazole moieties at the N1 position on rat liver microsomal NADPH-dependent lipid peroxidation (LP) levels were determined by measuring the formation of 2-thiobarbituric acid reactive substance. Overview on the anti-diabetic studies of novel benzimidazole-pyrazoline hybrid molecules and and anti-inflammatory evaluation of novel benzimidazole derivatives.

Index Terms: *Benzimidazole, Antiviral, Antifungal, Antiprotozoal, Anticancer, Antioxidant activity.*

I. INTRODUCTION

Benzimidazole has isosteric relationships with indole and purine nuclei, which are found in a variety of essential biological components and bioactive chemicals. This heterocycle might be a favoured substructure that interacts with many proteins and enzymes. Indeed, the benzimidazole ring is present in a variety of essential medications utilised in many therapeutic domains. [1] Among the antiviral benzimidazoles, an important position is held by 2-aryl/heteroarylbenzimidazole derivatives, either endowed with activity against Coxsackie Virus B3 or targeting specific hepatitis C virus enzymes. Thus, N-(2-fluorophenyl)-2-(2-pyridyl)benzimidazol-4-carboxamide shows an IC50 value of 1.69 lM against Coxsackie Virus B3,5 while 1-cyclohexyl-2-heteroarylbenzimidazole-5-carboxylic acids and their amido derivatives inhibit the HCV NS5B polymerase at nanomolar concentrations [2]

For its use in chemotherapy, a wide range of benzimidazole compounds have been developed. Compounds called oxyadiazoles have demonstrated biological action against bacteria and parasites. Additionally, the existence of basic Mannich side chains in a medication can solve the issue of water insolubility by causing hydrochlorides to form. Additionally, several heterocyclic moieties, such the triazole nucleus, have been shown to be fungicidal and antibacterial. [3,4] Microtubules are a characteristic feature of eukaryotic cells. They are major components of the mitotic spindle and, in some cells, the cytoskeleton and flagella or cilia. Microtubules form by polymerization of tubulin, a dimeric protein composed of aand ,-tubulin subunits, each approximately 440 amino acids long. Each subunit binds one molecule of GTP, and polymerization is followed by hydrolysis of the P-tubulin GTP. The mechanisms that control the rapid polymerization and depolymerization of spindle microtubules before and after mitosis are unclear. Most studies of microtubules have been limited to those isolated from mammalian brain, in which microtubules are abundant in the cytoskeleton. Microtubules involved in mitosis are much more difficult to isolate. [5] Free radicals, including superoxide radical (Oz2 2), nitric oxide (NOz), hydroxyl (OHz) and peroxyl (ROz 2) have been implicated in a number of disease processes, including atherosclerosis, rheumatoid arthritis and carcinogenesis.1 It has also been reported that pathogenesis and symptoms of inflammatory processes are accompanied and/or initiated by the production of reactive oxygen species (ROS). [6]

Drugs with antioxidant and free radical-scavenging characteristics are being investigated for the prevention and/or treatment of disorders that are directly connected to the body's inability to produce enough antioxidants. [7]

II. ANTIVIRAL ACTIVITY OF BENZIMIDAZOLE DERIVATIVES:

The 2-phenylbenzimidazole derivatives synthesized in this work were evaluated for antiviral activity against ten RNA and DNA viruses. Among single-stranded, positive RNA viruses (ssRNA+), we considered a Retrovirus (Human Immunodeficiency Virus type 1, HIV-1) two Picornaviruses (Coxsackie Virus type-2, CVB-2 and Poliovirus type-1, Sabin strain, Sb-1), a Flavivirus (Yellow Fever Virus, YFV) and a Pestivirus (Bovine Viral Diarrhea Virus, BVDV). Among single-stranded, negative RNA viruses (ssRNA) a Paramyxoviridae (Respiratory Syncytial Virus, RSV) and a Rhabdoviridae (Vesicular Stomatitis Virus, VSV) were selected as representatives. Among double-stranded RNA (dsRNA) viruses, a Reoviridae family member (Reo-1) was included. [8] AZT (30 -azido-thymidine), NM 108 (20 -C-methyl-guanosine), NM 176 (20 -C-ethynyl-cytidine), Ribavirin, NM 299 (6-azauridine), M 5255 (mycophenolic acid), and ACG (acyclovir) were used as reference inhibitors of ssRNA+ , ssRNA and DNA viruses, respectively. Fifty-six of the 76 tested compounds exhibited antiviral activity against one or more viruses; in particular, 17 compounds exhibited a selective activity against a single virus, while 20, 11, 7, and 1 molecules were active against two, three, four, and six viruses, respectively. [8]

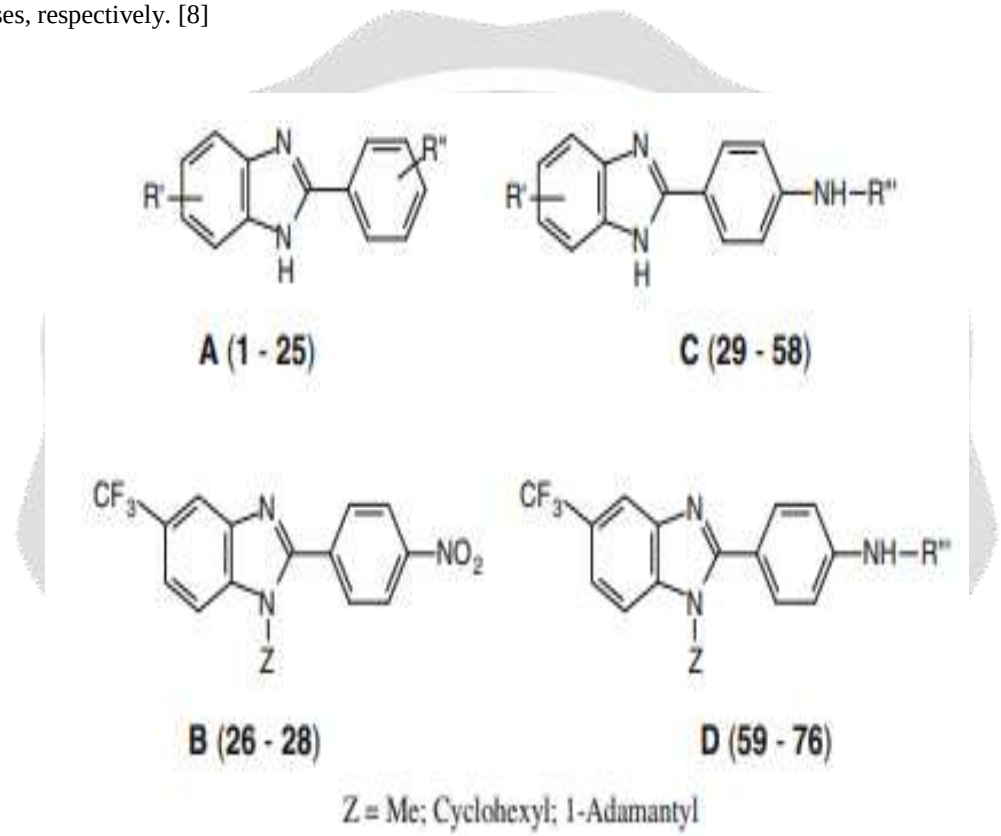

Figure 1: Structures of the investigated 2-phenylbenzimidazole derivatives [8]

III. ANTIFUNGAL ACTIVITY OF SELECTED BENZIMIDAZOLE COMPOUNDS:

The strong antifungal activity-i- (butylcarbamoyl)-2-benzimidazole carbamic acid, methyl ester. The degradation product was identified as 2- benzimidazole carbamic acid, methyl ester; limited tests showed that it has an antifungal activity similar to that of Benlate. Benlate, CTR-6669, and parbendazole are closely related benzimidazole carbamates, with CTR-6669 having the simplest structure; Benlate contains the butylcarbamoyl group in the 1 position of the ring, whereas parbendazole has a butyl group in the 5 (6) position. Thiabendazole, on the other hand, is not a carbamate but instead contains the 4'-thiazolyl ring. [9]

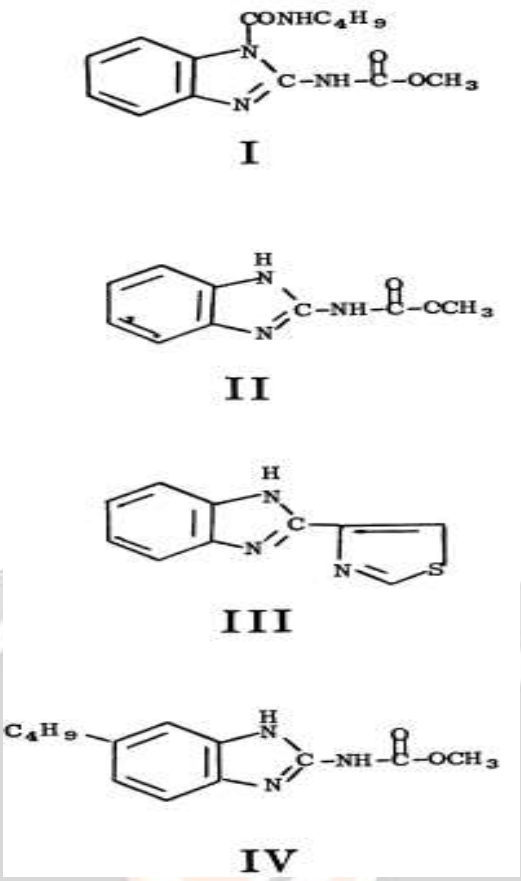

Fig. 2. Structures of the four benzimidazole compounds used in the antifungal tests. (I) Benlate; (If) CTR-6669; (1I1) thiabendazole; (IV) parbendazole. [9,10]

IV. SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW BENZIMIDAZOLE DERIVATIVES:

The 3-(2-methylbenzimidazol-1-yl)propanoic acid hydrazide , when compound was treated with carbon disulphide and potassium hydroxide, 5-[2-(2-methylbenzimidazol-1-yl)ethyl]-[1,3,4]-oxadiazole-2(3H)- thione was obtained, (Scheme 1) One of the earliest discoveries concerning the utility of Mannich bases as intermediates in drug synthesis was made by Burckhalter and co-workers. Similarly, compound 2 was allowed to undergo the Mannich reaction with different secondary amines namely, diethylamine, morpholine or N-methylpiprazine and paraformaldehyde in absolute ethanol to give compounds 3a-c respectively. (Scheme 1). A benzimidazole incorporated into a triazole moiety was synthesized by the reaction of 2 with hydrazine hydrate (99%) in absolute ethanol which afforded 1-[(1-amino-2-mercapto-1,3,4-triazol-5- yl)ethyl]-2-methylbenzimidazole. A number of arylidine hydrazones incorporated into the parent benzimidazole were also synthesized. Thus condensation of compound 4 with aromatic aldehydes, namely, p-methoxy benzaldehyde and o-chlorobenzaldehyde in absolute ethanol afforded the corresponding Schiff's bases. On the other hand, reaction of 4 with acetic anhydride in the presence of glacial acetic acid leads to the formation of monoacetyl derivative 6. (Scheme 1). [11]

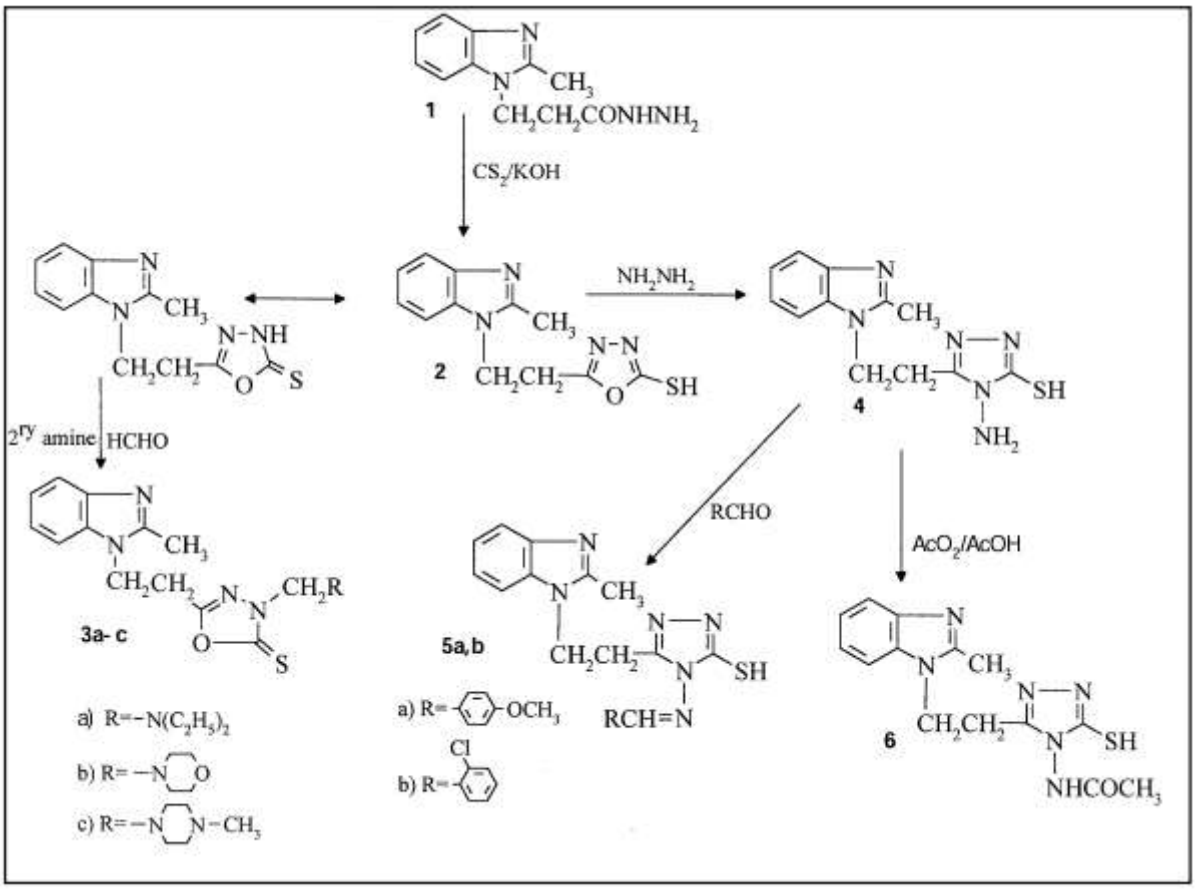

Figure 3. Scheme 1 [11]

Carbohydrazide 1 was also allowed to react with ethyl acetoacetate and acetylacetone to give the corresponding methylpyrazolone derivative 7 and dimethylpyrazole derivative 8 respectively. (Scheme 2, Tables 1 and 3). Condensation of compound 1 with aromatic and heterocyclic aldehydes in absolute ethanol afforded the corresponding Schiff's bases 9a-f. Also, the cyclocondensation of some substituted Schiff's bases with thioglycolic acid and thiolactic acid afforded the corresponding thiazolidinone 10a-c and methylthiazolidines 11a-c respectively (Scheme 2). [12]

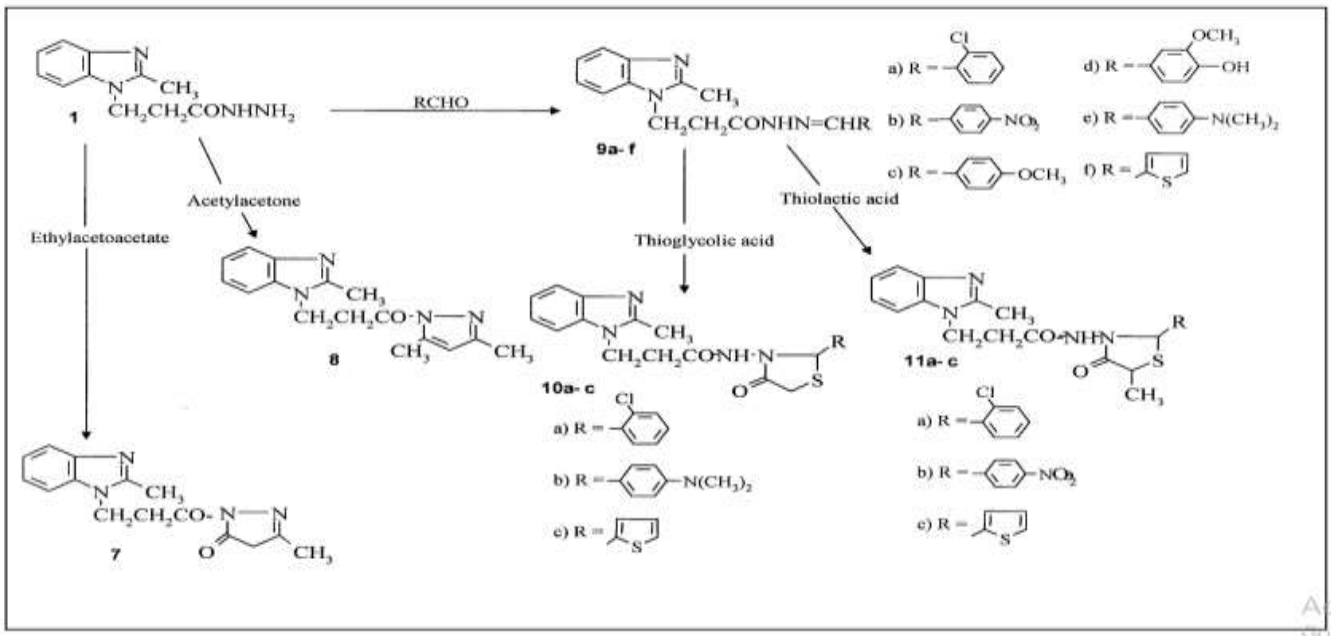

Fig. 4 : Scheme 2. [12]

1) Biological Screening. Antimicrobial activity test:

The disc diffusion technique was used with various modifications for the produced compounds, with Gentamycine and Ampicelline serving as references. The compounds were tested against one strain of Gram +ve bacteria (Bacillus cereus), one strain of Gram -ve bacteria (Escherichia coli), one strain of yeast (Saccharomyces cerevisae), and one strain of fungi. (Aspergillus niger). Whatman No. 1 filter paper discs of 5mm diameter were autoclaved for 15 minutes at 121°C. The sterile disks were impregnated with different compounds (600 µg / disk). Agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5 °C for 1 h. to permit good diffusion and then transferred to an incubator at 37 °C for 24 h. for bacteria, and at 28 °C for 72 h. for yeast and fungi. The inhibition zones caused by the various compounds on the microorganisms were examined. The results of the preliminary screening test are listed in Table 1. The antibacterial and antifungal activity of compounds 1, 2, 3a, 4, 5b, 8, 9a, 10a,c and 11a,c were tested. From the data obtained in Table 1, it is clear that compound 2 was found to be highly active against Bacillus cereus but, slightly active against Escherichia coli. Compounds 4 and 9a were found to be moderately active against Bacillus cereus while compounds 3a and 10c were found to be slightly active against Bacillus cereus. But all the tested compounds were found to be inactive against Saccharomyces cerevisae and Aspergillus niger. Also, compounds 1, 5b, 8, 10a and 11a were found to be inactive against all microorganisms used. [13]

IV. ANTIPROTOZOAL ACTIVITIES OF BENZIMIDAZOLES AND CORRELATIONS WITH 13-TUBULIN SEQUENCE:

In this study, we examined the susceptibilities of T. vaginalis and G. lamblia to 14 anthelmintic and antifungal benzimidazole derivatives. Furthermore, susceptibilities were examined for three unrelated protozoans not previously examined: the parasitic amoeba Entamoeba histolytica, the free-living amoeba Acanthamoeba polyphaga, and the kinetoplastid Leishmania major. To investigate the molecular basis for these results, partial P-tubulin sequences from these organisms (and from the AIDS-associated pathogens Cryptosporidium parvum, Encephalitozoon hellem, and Encephalitozoon cuniculi) were analyzed for the presence of five amino acid residues previously implicated in benzimidazole susceptibility. This analysis indicated that Glu-198 and, in particular, Phe-200 are correlated with benzimidazole susceptibility. [14]

1) Materials and Methods:

The source of organisms, culture conditions, and procedures for assessing drug susceptibility for G. lamblia WB, T. vaginalis 30236 and Tvl:MCP, E. histolytica 200:NIH and HM1:IMSS, and L. major 1S were as previously reported. T. generously gave G. lamblia H/7. Nash and was cultured and assayed identically to G. lamblia WB. A. polyphaga CDC:0187:1 was cultured aerobically at 23°C in proteose peptone-yeast extract-glucose medium (28). To assay susceptibility of this organism, benzimidazoles were diluted into 200 p1 of medium containing 200 trophozoites in microtiter wells and cells were counted microscopically after 48 h. To estimate toxicity to mammalian cells, Vero (African green monkey kidney) cells were cultured in Dulbecco's modified Eagle's medium with 10% fetal bovine serum at 37°C in 5% CO2. Benzimidazoles were added to microtiter wells containing 2 x 104 cells in 200 RI of medium. After 48 h of incubation, cells were counted microscopically. [15]

Drug concentrations limiting growth to 50% of control levels (IC50) were calculated for all species by plotting percent control vs log concentration. The following benzimidazoles were generously provided by the firms listed: albendazole sulfoxide, parbendazole, and oxibendazole. T vaginalis 30236 cells were exposed to nocodazole, mebendazole, or fenbendazole at concentrations of 0.04, 0.2, 1, or 5 ug/ml for a range of times to assess if the drug had lethal action. Other circumstances were as already mentioned. Final DMSO dosages were 0.1%; DMSO alone was given to controls. Cultures were well mixed after drug exposure, and then 2-pI aliquots were taken and diluted into 2 ml of drug-free media (the final benzimidazole concentration was.5 ng/ml). [15]

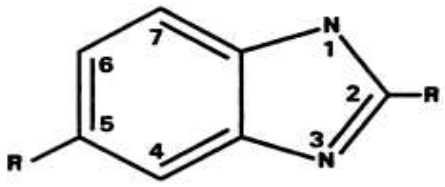

Figure 5: Structure of benzimidazoles. [15]

2) Prediction of benzimidazole susceptibility from Beta-tubulin sequence:

The partial ,B-tubulin sequences from the microsporidia E. hellem and E. cuniculi and the apicomplexan C. parvum (11). These intracellular protozoan parasites normally cause inapparent or self-limiting infections but have been implicated in severe intestinal or systemic infections in immunocompromised individuals, including AIDS patients. These infections do not respond to treatment with a wide variety of conventional antimicrobial agents. The identification of new agents is hampered by the lack of routine in vitro culture systems for both the microsporidia and C. parvum. On the other hand, in clinical studies of AIDS patients, intestinal infections with the microsporidian E. bieneusi responded favorably to treatment with albendazole. It was of interest therefore to analyze the ,B-tubulin sequences from E. hellem, E. cuniculi, and C. parvum to predict their benzimidazole susceptibility or

resistance (E. bieneusi itself was not available for study). Both of the microsporidia and C. parvum possess a single ,-tubulin gene copy (11, 18a). C. parvum ,-tubulin lacks both Glu-198 and Phe-200 and is thus predicted to be benzimidazole resistant. E. hellem and E. cuniculi 13-tubulins are very similar to each other over the region analyzed. In addition to Phe-167 and Arg-241, both ,B-tubulins include Glu-198 and Phe-200. [16,17]

V. ADVANCES OF BENZIMIDAZOLE BASED ANTICANCER AGENTS:

Benzimidazole-based compounds have drawn a lot of interest since they have strong cytotoxic potential. Many anticancer medications based on benzimidazoles have been granted US FDA worldwide clearance over the past ten years. Abemaciclib, Selumetinib, and Binimetinib recently received permission to treat a variety of cancers with genetic mutations. Here, we've covered various recently authorized, in-development, and upcoming anticancer medications that are benzimidazole-based. [18]

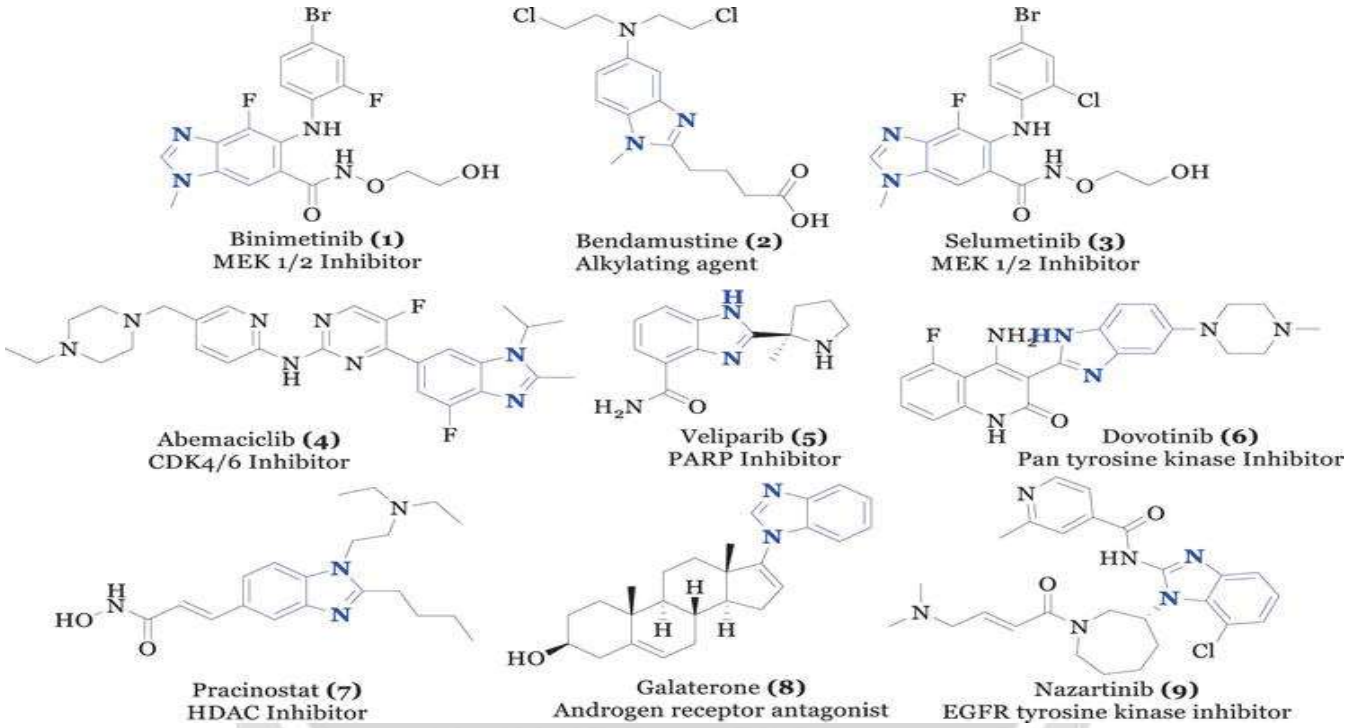

Figure 6: Benzimidazole based clinically approved anticancer agents. [18]

1) Benzimidazole based hybrid derivatives as potent anticancer agents:

A novel hybrid derivatives of benzimidazole-thiazolidinedione as potent cytotoxic agents. Target compound 34 demonstrated potent inhibitory activity against A549, DU-145, MDA-MB-231 and PC-3 cancer cell line with an IC50 value of 11.46 μM, 31.41 μM, 29.18 μM and 39.87 μM respectively. Compound 34 have shown cell cycle arrest in G2/M phase of A549 cells in a dose dependent manner. Furthermore, compound 34 also demonstrated cell shrinkage of A549 cells along with chromatin condensation and horse shoe shaped nuclei formation. [19]

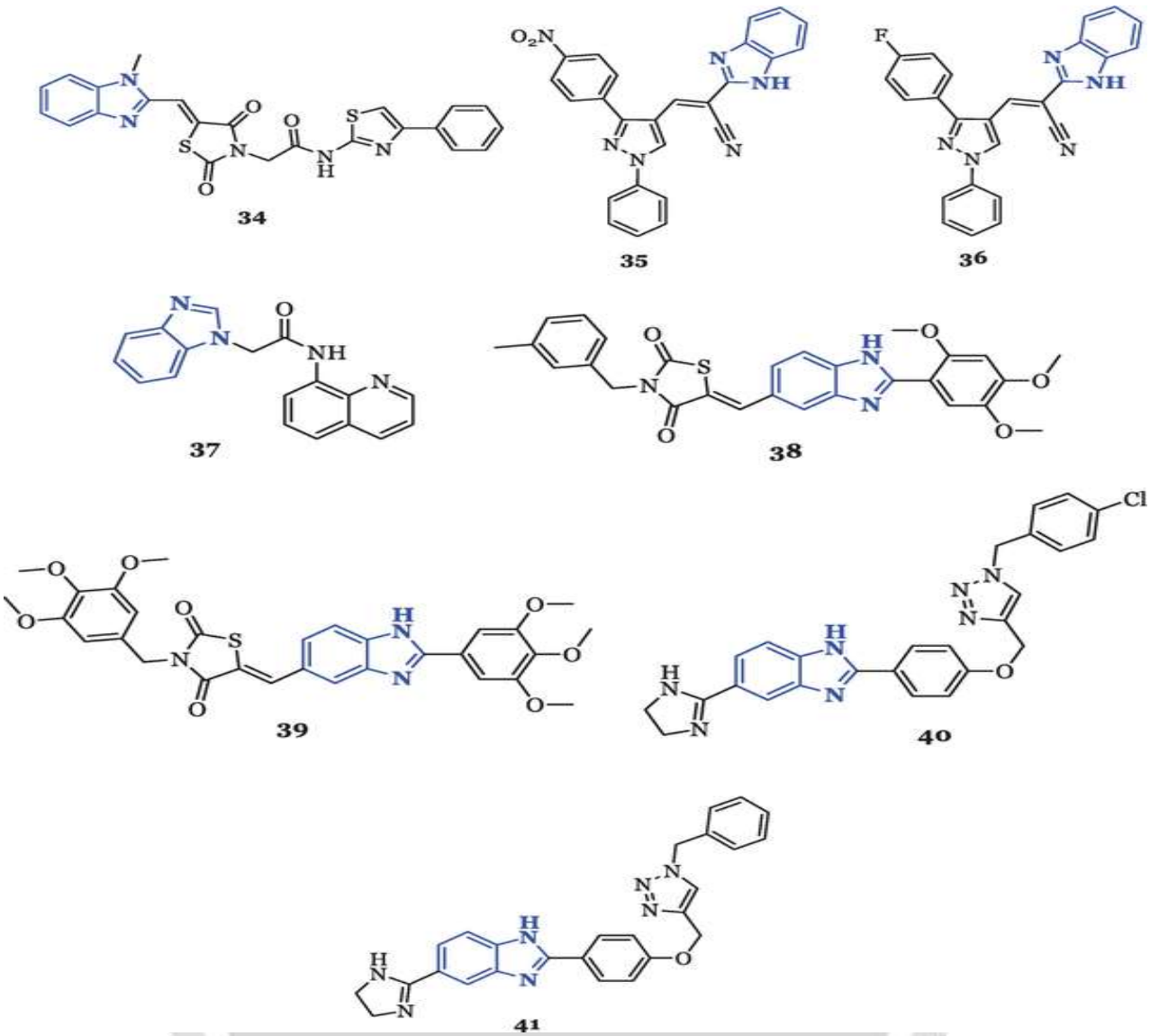

Fig. 7. Examples of benzimidazole containing hybrid derivatives as potent anticancer agents. [19]

VI) SYNTHESIS AND ANTIOXIDANT PROPERTIES OF NOVEL BENZIMIDAZOLE DERIVATIVES:

The free radical scavenging properties of the compounds were also examined in vitro by determining the capacity to scavenge superoxide anion formation and the interaction with the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). The compounds showed a significant effect in the above tests except to scavenge superoxide anion formation. [20]

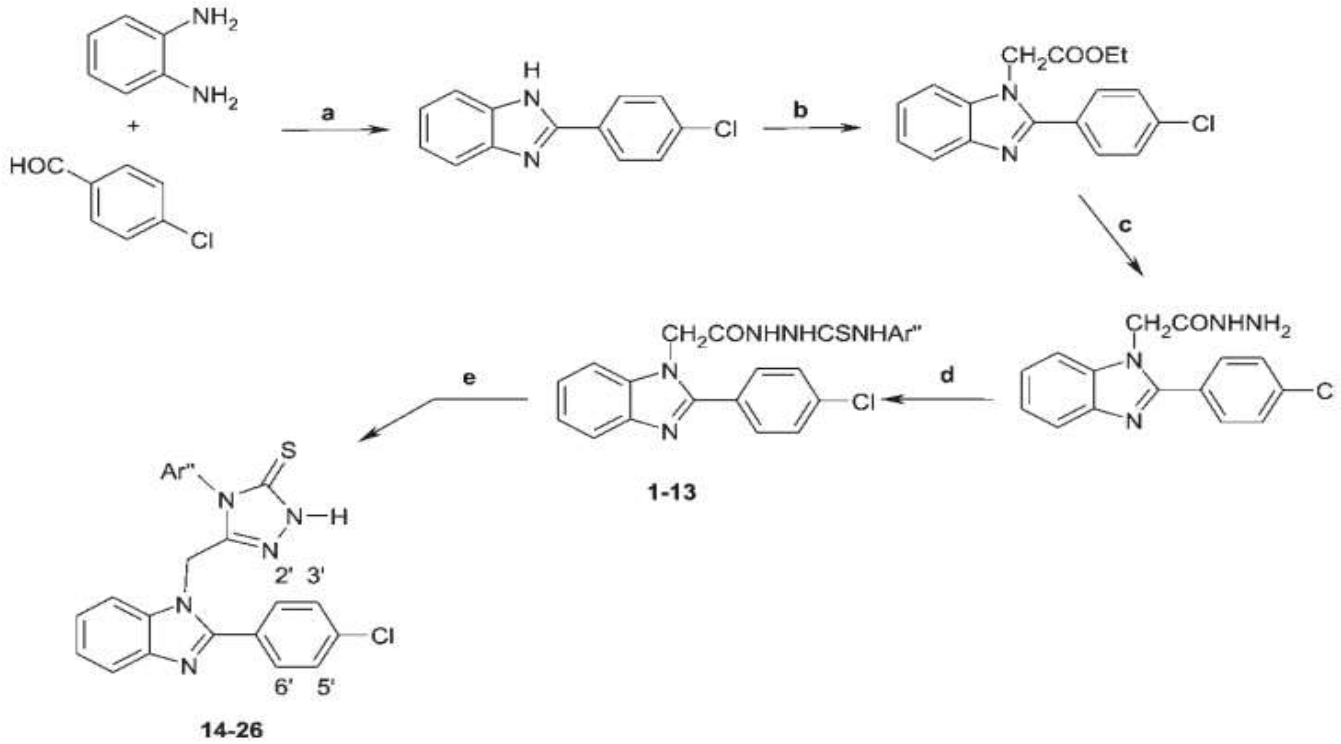

Fig.8: Synthetic route for the preparation of compounds 1–13 and 14–26. Reagents a: Na2S2O5 b: ClCH2COOEt/KOH-DMSO c: NH2NH2H2O/EtOH d: appropriate phenylisothiocyanate/EtOH e: NaOH. [20]

1) Antioxidant Activity Studies:

i) Assay of Lipid Peroxidation:

Male albino Wistar rats (200–225 g) were used in the experiments. Animals were fed with standard laboratory rat chow and tap water ad libitum. The animals were starved for 24 h prior to sacrifice and then killed by decapitation under anesthesia. The livers were removed immediately and washed in icecold distilled water and the microsomes were prepared. NADPH-dependent LP was determined using the optimum conditions determined and described previously.30 NADPH-dependent LP was measured spectrophotometrically by estimation of thiobarbituric acid reactant substances (TBARS). Amounts of TBARS were expressed in terms of nmol malondialdehyde (MDA)/mg protein. [21,22] Lipid peroxidation was determined spectrophotometrically at 532 nm as the thiobarbituric acid reactive material. Compounds inhibit the production of malondialdehyde and therefore the produced color after addition of thiobarbituric acid is less intensive. A typical optimized assay mixture contained 0.2 nM Feþþ, 90 mM KCl, 62.5 mM potassium phosphate buffer, pH 7.4, NADPH generating system (consisting of 0.25 mM NADPþ , 2.5 mM MgCl2, 2.5 mM glucose-6-phosphate, 1.0 U glucose-6-phosphate dehydrogenase and 14.2 mM potassium phosphate buffer pH 7.8) and 0.2 mg microsomal protein in a final volume of 1.0 ml. [23]

ii) DPPH Free Radical Scavenging Activity:

The free radical scavenging activities of these compounds were tested by their ability to bleach the stable radical 2,2,diphenyl-1-picrylhydrazyl (DPPH). This assay has often been used to estimate the anti-radical activity of antioxidants. Because of its odd electron DPPH gives a strong absorption bound at 517 nm in the visible part of the spectrum. To 1.0 ml of methanolic solution of DPPH (100 mM) was added 0.1 ml of the test compounds and BHT dissolved in dimethylsulfoxide (DMSO). Absorbance at 517 nm was determined after 30 min at room temperature and the scavenging activity were calculated as a percentage of the radical reduction. Each experiment was performed in triplicate. DMSO was used as a control solution and BHT as a reference compound. The radical scavenging activity was obtained from the equation: Radical scavenging activity % = {ODcontrol – Odsample)/ ODcontrol}*100. [24]

VII) ANTI-DIABETIC STUDIES OF NOVEL BENZIMIDAZOLE-PYRAZOLINE HYBRID MOLECULES:

The pyrazoline-benzimidazole hybrids 5a-i were evaluated for their anti-diabetic activity via α-glucosidase enzyme inhibition assay (table 4). The compounds 5d, 5f and 5h showed 85.05%, 81.94%, 66.44% and 89.48% inhibition with IC50 values of

50.06µM, 149.5µM and 78.01µM, respectively. The results showed that the compound 5d exhibited better enzyme inhibition activity with IC50 of 50.06µM as comparison to acarbose (IC50 =58.88 µM) as a positive control. [25]

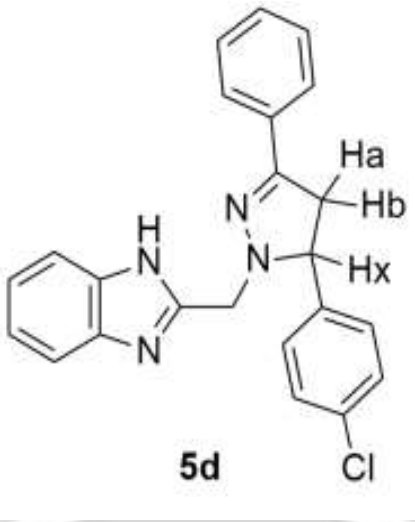

Fig. 9: Structure of compound 5d [25]

VIII) ANTI-INFLAMMATORY EVALUATION OF NOVEL BENZIMIDAZOLE:

A series of benzimidazole derivatives were synthesized and screened for anti-inflammatory activities, and showed excellent inhibition of the expression of inflammatory cytokines in LPS-stimulated macrophages. [26]

CONCLUSION:

Benzimidazole have the potential to be highly effective in the various diseases such as More recently, through the high-throughput screening of about 50,000 compounds, 16 hit compounds have been identified and found to block viral infection with low cytotoxicity, Antifungal Activity of Selected benzimidazole Compounds. A wide variety of benzimidazole derivatives have been described for their chemotherapeutic importance antiprotozoal activities correlations with beta-tubulin sequence. Many benzimidazole-containing compounds as anticancer agents are studied and available, involving various mechanisms in inhibiting mutated cancerous cells, in which kinases inhibitors play a significant role. In short, we herein reported the synthetic methods for the structural hybridization of benzimidazole heterocyclic ring systems; Compound 5d exhibited potent activity comparable to the reference (acarbose). The presented review mainly focuses on benzimidazole and their advances; the pivotal information catered here can be regarded as noteworthy and crucial by medicinal chemists for drug design, discovery and development of novel, potent and safe, target-based anticancer agents, antiviral, antifungal and other activities.

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