International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 35-53 www.ijprajournal.com ISSN: 2249-7781

Bezimidazole -The Drug of Choice

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Date Of Submission: 05-05-2021 Date Of Acceptance: 20-05-2021

ABSTRACT: Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. This review is summarized to know about the chemistry of different derivatives of substituted benzimidazoles along with their pharmacological activities.

Keywords: Substituted Benzimidazoles, Chemistry, Pharmacological activities ,Animalscreening.

I. INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole[1].Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds with respect to their inhibitory activity as well as their selectivity.Bezimidazole is an

important group of compound that has found practical applications in a number of fields like analgesic[2], anti-inflammatory[2],antibacterial[3],antifungal[4],antiviral[5], antihelmenthic[5], anticonvulsant[6],anticancer[7],antiulcer[8]and antihypertensive[9].Historically, the first benzimidazole was prepared in 1872 by Hoebrecker[10] , who obtained 2,5(or 2,6)-dimethylbenzimidazole by the reduction of 2-nitro-4- methylacetanilide.

In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, show easy interactions with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in man

II. DIFFERENT SUBSTITUENTS OF BEZIMIDAZOLE DERIVATIVES

1-Substituted Bezimidazole Derivative

Fischer and Veiel[11] reported the synthesisof1-methylbenzimidazole by the reaction of ortho-phenylenediamineswith formic acid. Antihelmintic activity was carried out by using Indian adult earthworms, Pheretimaposthuma. The time of paralysis and time of death of worms signifies the potency of the 1-methyl bezimidazole derivatives

Noha et al[12] reported the synthesis of 1-triazole bezimidazole derivative by reaction of aromatic aldehydes with 1,2,4-triazole derivatives to give a series of some new Schiff bases[13]. All of the derivatives show good anti-fungal activity on (Candida albicans) during the biological screening along with mild anti bacterial activity. Derivatives also show excellant anti-tumour activity against breast carcinoma (MCF-7) and colon carcinoma

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 35-53 www.ijprajournal.com ISSN: 2249-7781

(HCT116) cell lines.. In order to confirm the obtained biological results they also carried out docking calculations.

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Ramesh et al[38] described the synthesis of a 2- phenylbenzimidazole-1-acetamide derivatives by the reaction of ortho-phenylenediamine and phenyl-acetamide. The anti-helminticactivity study was carried out by using Indian adult earthworms, Pheretimaposthuma. Observations were made for the time taken to paralysis and death of individual worms. Out of various title compounds tested, few of these derivatives were found to exhibit better to paralyze worms whereas other compounds exhibited better to cause death of worms compared to the standard anthelmintic drug albendazole. The better activity was attributed to the presence of the electron withdrawing polar group at the fourth position of 2-phenyl ring of benzimidazole-1- acetamide

Soni B et al[39] reported synthesis of anovel series of N'-(substituted benzylidene)-2-[2-(substituted phenyl)-1H-benzimidazol-1-yl]acetohydrazide.Using ortho-phenylenediamine,benzaldehyde, potassiumhydroxide, DMF, sodium bisulfite, chloroacetoacetate,hydrazine and different aromatic aldehyde.The synthesized derivatives were screened for analgesic activity by tail flick method in mice and anti-inflammatory activity by carrageenan induced rat paws edema method. From the results it was found that most of the compounds show significant analgesic and anti-inflammatory activity

Patel and co-workers[40]reported the synthesisof variety of 2-(aryl)-1-(1H-benzimidazol-1-yl)ethanone and 2-(aryl)-1-(2-methyl-1Hbenzimidazol-1-yl) ethanone. All the synthesized compounds were screened for cyto-toxic activity by cell viability assay method using two human cell line VERO and NCI. Most of the tested compounds exhibited significant cyto-toxic activity after 48 h which were compared with standard drug doxorubicin. Among all the compounds screened, two compounds were found to be the most potent in the series with 78.34%and 79.90% inhibitions in NCI after 48 h. From the study it wasconcluded that the cyto-toxicity of the all synthesized molecules significantly increased as nitrogen function increase

SudheerBabu et al[41] reported the synthesis of 1-methyl-2-indole(benzimidazole)benzamine by the reaction of ortho-phenylenediamine, substituted aniline, glycine formaldehyde and different aromatic amine and sand bath for 180-190c and the yield ranges from 52-76% The synthesized compounds were screened for their in-vivo anti-inflammatory activity by carrageenan paw edema method

Gupta et al[42] reported a series of biologically active 1-phenyl-2-piperazine benzimidazole derivatives .Various novel benzimidazoles were synthesized by the reaction of ortho-phenylenediamine with the derivatives of benzoic acid in presence of 4N hydrochloric acid followed by the reaction with piperazine and formaldehyde to produce corresponding Mannich bases. All the title compounds were evaluated for their anti-helmintic activity by the identification of paralyzing and death time using mebendazole as standard drug at a concentration of 2 mg/ml. In addition all the compounds were evaluated for antibacterial activity against gram positive bacterial strains like Bacillus subtilis and Streptococcus aureus, and gram negative bacterial strains like Escherichia coli and Pseudomonas aeruginosa by disc diffusion method using ciprofloxacin (50 µg/ml) as standard drug. The compounds were found to possess various degree of anti-helmintic and antibacterial activity. The results of anit-helmintic and anti-bacterial studies indicated that significant activity of the newly synthesized

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Volume 6, Issue 3 May - June 2021, pp: 35-53 www.ijprajournal.com ISSN: 2249-7781

benzimidazole derivatives was found in derivatives with piperazine and N-methyl piperazine in combination with para-chloro and ortho-nitro benzoic acid

Sanahanbi et al[43] reported the synthesis of some Schiff's Bases of 4 amino-5-[(2-methyl-1H-benzimidazol-1-yl)methyl] -4H-1,2,4-triazole-3-thiolderivatives.Using carbohydrazide,ethanol,aromatic aldehyde and carbon disulfide.All the synthesized compounds were evaluated for their anti-helmintic activity against Indian earthworms (Pheretimaposthuma) and utilized for in- vitro anti-helminthic assay as per standard protocol

AnilReddy[44]reported, that2-amino(phenyl)methyl-N,N-di-methyl-1-Hben zimidazol amine was synthesized by ortho-phenylenediamine and phenyl glycine were stirred in HCl and refluxed for 4 h, then cooled at room temperature The pH was adjusted to 7.2 using sodium hydroxide pellets. The resulting brown solid was filtered and washed with water dried in vacuum and re-crystallized from acetone

Anna et al[47]reported the synthesis of 1-amino-2-piperazine benzimidazole by the condensation of 2- benzylaminobenzimidazoles with selected secondary amines such as morpholine, piperidine, N-methyl-piperazine ,N-phenyl-piperazine, 1-(2pyridyl)piperazine ,1(2-methoxyphenyl)piperazine, 1-(2-pyrimidinyl) piperazine, and formaldehyde in ethanol by The pyrimido-benzimidazole derivatives have been synthesized in the reactions of Schiff base with selected compounds containing active methylene group such as acetylacetone, benzoylacetone, and malononitrile. All compounds were screened against the cells of MV4-11 human leukemia and then the most active of them were tested towards human T47D breast and A549 lung cancer cells as well as normal mouse fibroblasts (BALB/3T3). The most active compound against the cancer cell-line,4-amino-3-cyano-2-(4-hydroxyphenylene) -1,2-dihydropyrimido[1,2
benzimidazole (IC_{50} 0.23±0.05 µg/ml against MV4-11 cells) show very low cyto-toxicity towards mouse fibroblasts. Cisplatin was the control drug (IC_{50} 0.04±0.01 µg/ml).

Arfa et al[48]reported the synthesis of 2-(2′-pyridyl)1- bezoylbenzimidazole by reaction of ortho-phenylenediamine, pyridine and substituted bezaldehydesand investigated their cyto-toxic effect.The structure of the synthesized analogs were characterized and evaluated for their cyto-toxic effect. When comparing the active derivatives, it was found that the compound containing unsubstituted phenyl moiety possessed lesser activity as compared to the substituted phenyl ring. It was also shown that substitution of different groups at the phenyl ring imparted varying degrees of cyto-toxic potentials such as addition of chloro group at paraposition to the phenyl ring made the compound more potent. Similarly, derivatives possessing nitro group at orthoand metaand metaposition loosed their potency. Substitution at the phenyl ring played a major role in determining the biological activity of the derivatives. The tested compounds exhibited the cyto-toxicity in the following order chloro>phenyl>nitro>hydroxyl

1,5 DI SUBSTITUED BEZIMIDAZOLE DERIVATIVE

Von Walther[49]reported the synthesis of 1-phenyl-5-nitroben- bezimidazole by the reaction between ethyl orthoformate and 4-nitro-2-amino-diphenylamine.

Von Pinnow[50] reported the reduction of o-nitrodimethyl- anilines. Thus, 3-nitro-4-dimethylaminotoluene on reduction with tin and dilute hydrochloric acid gives some 1 ,5-dimethylbenzimidazole

III. SUBSTITUTED BEZIMIDAZOLE DERIVATIVE

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Rekha et al[14] reported the synthesis of 6-chloro-5-fluoro-2-phenyl amine benzimidazole derivative by reacting 6-chloro-5-fluoro1H-benzo[d]imidazol-2-amine with various aromatic aldehyde and nickel nitrate using methanol as solvent. The novel 2-substituted benzimidazole was evaluated for their in vitro and in vivo antiinflammatory activity by BSA (Bovine serum albumin) method and mercury displacement method, respectively. All of the synthesized compounds showed good in vitro and in vivo anti-inflammatory activity. However the anti-inflammatory activity of the synthesized compounds was found to be less than that of respective standard drug at tested dose level

Manish et al[14]reported the synthesis 2-substituted benzimidazole derivatives.N-[4-(1H-benzimidazol-2-yl)-phenyl]-acetamide. The synthezised compounds were evaluated for mean paralysis and mean death time. Various new 2-substitutedbenzimidazole derivatives were synthesized, characterized, and tested for their anthelmintic activity . The anthelmintic assay was performed in vitro, using adult earthworm (Eiseniafetida). N-[4-(1H-benzimidazol-2-yl)-phenyl]-acetamide,N-[4-(1H-benzimidazol-2-yl)-phenyl]-2-chloro acetamide, and furan-2-carboxylic acid-[4-(1H-benzimidazol-2-yl)- phenyl] amide exhibited excellent anthelmintic activities which are comparable to that of standard albendazole.

Komal P et al[15] reported the synthesis of 2-chloromethyl-1H-benzimidazole by condensing 2- chloromethyl-1H-benzimidazole with different aromatic amines andheterocycle. using DMF, potassium carbonate and reflux for 16 hr.

Shrutiet al[16] made an attempt to synthesize novel cinnolinebenzimidazoles and evaluated them as therapeutic agent for their potential anthelmintic activity. Substituted cinnolinebenzimidazole was synthesized by a multi-step synthesis. Initially, diazonium salt was prepared by the reaction of substituted anilines with mixture of concentrated hydrochloric acid and cold saturated solution of sodium nitrite at 0-5 °C. Latter, 3-chlorophenyl hydrazono (cyno) acetamide was prepared by the reaction of cyanoacetamide with sodium acetate and alcohol. In the subsequent step 7-chloro-4-aminocinnoline-3-carboxamide was obtained by the treatment of 3-chlorophenylhydrazono (cyno) acetamide with anhydrous aluminium chloride and chlorobenzene in presence of nitrogen gas. In the last step substituted-4-(p-aminobenzimidazole) cinnoline-3-carboxamide was synthesized by a reaction of substituted-4-aminocinnoline-3-carboxamide with ortho-chlorobenzimidazole in DMF. All the synthesized compounds were evaluated for their anthelmintic activity against Indian earthworms (Pheretimaposthuma) and utilized for in vitro anthelminthic assay as per standard protocol

Rangaswamy and co-workers[17]designed, synthesized, and identified novel antiproliferative agents that can potently targetcancer. They reported the synthesis of the new series of N-Substituted-2-(2-butyl-4-chloro-1H-imidazole-5-yl)-1Hbenzo[d]imidazole derivatives and evaluated their antitumor activity against HeLa cell lines. They identified the lead compound in the series and tested its antiproliferative and antiangiogenic properties against Ehrlich ascites tumor (EAT) bearing mice. From the study it was identified that 2-(2-butyl-4-chloro-1-heptyl-1H-imidazol-5yl)-1H-benzo[d]imidazole as a lead compound with the inhibitory concentration 50 % of 25.3 µM. The lead compound significantly decreases the angiogenesis in peritoneum of EAT bearing mice. From the study it concluded that benzimidazoles suppress the cell proliferation, peritoneal angiogenesis, and ascites volume

Keerthanaet al[18] reported a series of novel dithiocarbamates with benzimidazole and chalcone. The was designed, synthesizedand evaluated for their antimitotic activity In general it was found that acyclic amines showed less potency comparedtocyclicgroups.Twocompoundsofthisserie

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 35-53 www.ijprajournal.com ISSN: 2249-7781

sdisplayed themostpromisingantimitoticactivitywithIC_{50}of1.66 µMand1.52 µM, respectively.

Selvam etal[19]reportedthe synthesis of 2-substituted benzimidazole derivatives by using ortho-phenylenediamine, PABA,ethanol,aldehydes,chloroacetyl chloride and tertiary amine. All the synthesized compounds were evaluated for their in-vitro anti-helmintic activity against Indian earthworms (Pheretimaposthuma) and utilized for

In-vitro anthelminthic assay as per standard protocol

Kalirajan et al[20]reported the synthesis differentmannich bases of 2-substituted banzimidazoleslike 2-(1H-benzo[d]imidazol-2-yl) benzoic acid and 2-methyl benzimidazole .Against various gram positive, gram negative bacteria and various fungal stains, the compounds were screened for their antimicrobial activity and anti-fungal activity by cup-plate method. With that of standard (ampicillin and ketoconazole) many compounds showed comparable activity. By HRBC membrane stabilization method the compounds were also evaluated for their in vitro anti-inflammatory activity. When compared with standard drug Ibuprofen thesynthesized compounds show highly significant activity, with percentage of inhibition to the inflammatory response ranging from 64 to 77 %

Kuldeep Kumar[21] reported the synthesis of 2-(2-butyl-4-chloro-1-heptyl-1H-imidazol-5yl)-1H-benzimidazole derivatives from microwave irradiation method by condensation of 2-nitro-aniline with different carboxylic acids (aliphatic,aromatic andhetrocyclic),selenium chloride, acetic acid using All of the derivatives show good anti-fungal activity (Candida albicans) during the biological screening along with mild anti bacterial activity

Karna et al[22] reported the synthesis of triazole by treatment of 2-(4-azidophenyl)-1H-benzimidazole with different alkynes, sodium ascorbate, and $Zn(OTf)_2$. The compounds were screened for cyto-toxicity assay and achieved good results. A series of new benzimidazole-linked 1,2,3- triazole congeners were synthesized through cyclization of terminal alkynes and azide.These synthesized congeners were evaluated for their cyto-toxicity against five human cancer cell lines. Benzimidazole linked 1,2,3-triazole derivatives have shown promising activity with IC_{50} values ranging from 0.1 to 43 µM . Among them,2-(3-Chloro 4-azidophenyl)-1H-benzo[d]imidazole showed in-vivo anti-cancer activity with standard drug

Aruna et al[23] synthesized a series of N-(2-(1-benzo[d]imidazol2-yl) phenyl)-substituted benzamines by using ortho-phenylenediamine and salicylic acid. Initially 2-(1Hbenzo[d]imidazol-2-yl) phenol was synthesized which on bromination yielded 2-(2-bromo phenyl)-1H-benzo[d]imidazol-2- yl which on further reaction with aniline derivatives yielded title compounds. The halogen substituted derivative [fluorine, chlorine and bromine] show good in-virto anthelmintic activity and it was performed on Phaeritimaposthuma species of earth worms by the identification of paralysing and death time using Mebendazole as standard.

DavoodAzarifar et al[24] reported the green synthesis of various 2-aryl-1-(arylmethyl)-1H-benzimidazoleby reaction of acetic acid-promoted condensation of ortho-phenylenediamine with aldehydes in air under microwaveirradiation. Derivatives exhibited excellent in vitro anthelmintic activities and in-vitro anti-microbial activity which are comparable to that of standard albendazole and procaine penicillin respectively

Abhay et al[25] reported the synthesis of new series of 2-substituted benzimidazolederivative by Schiff bases reaction and its azetidinone and

International Journal of Pharmaceutical Research and Applications
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thiazolidinone derivatives were synthesized from ortho-phenylenediamine and para-amino benzoic acid. The synthesized compounds were screened for in-vitroanti-bacterialactivity (Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Salmonella typhi), in-vitroanti-fungal (Candida albicans and Aspergillusniger) activity by disc diffusion method, analgesic activity was studied by tail flick method and antiinflammatory activity by carrageenan induced paw oedema method. The synthesized compounds showed significant activity of antibacterial, antifungal, analgesic and anti-inflammatory activity comparable to that of Ciprofloxacin, Ketoconazole, Paracetamol and Aspirin, respectively.

vaidehi et al[26]reported the synthesised of 2-substituted benzimidazoles successfully by condensation of ophenylenediamine with substituted acids in presence of ring closing agents like polyphosphoric acid / HCl. The present work has demonstrated the use of a simple Cyclo-condensation method of ring closing agents for synthesis of 2-substituted benzimidazoles All the synthesized compounds were screened for in-vitro anti-helmintic activity by exposing the adult Pheritimaposthuma to different concentrations of synthesized compounds using albendazole as standard drug. The potent active compounds of this series possess electron releasing groups like methyl, aryl, and amine on C-2 of benzimidazole ring.

Mita D. Khunt et al[27]reported the synthesis the benzimidazolederivative by reacting ortho-phynlene-diamine with several aldehydes using a green solvent PEG_{400} and got good yields of benzimidazoles.All the synthesized compounds were screened for in-vitro anti-helmintic activity by exposing the adult Pheritimaposthuma to different concentrations of synthesized compounds using albendazole as standard drug

Jayanti et al[28] performed microwave assisted reaction of benzimidazolylchalconesderivatives into 2-substituted pyrazolines. The synthesized compounds were screened for their in-vivo anti-inflammatory activity by carrageenan paw edema method and in-vitro anti-microbial activity by agar well diffusion method against diclofenac sodium and ciprofloxacin and ketoconazole, respectively.

Hollan et al[29]reported the synthesis of imidate by reacting of [ester(trichloroacetimidate)] with ortho-phenylene diamine or its salt gives the 2-trichloromethyl benzimidazole at room temperature, and this is an important precursor for 2carboxylic benzimidazoles.

Sreena et al[30]reported the synthesis of some substituted benzimidazole derivatives and screened their anthelminitic activity. Ortho-phenylenediamine was condensed with acids in presence of polyphosphoric acid and solvents like water and dilute hydrochloric acid to synthesizebenzimidazole derivatives. All the synthesized compounds showed significant in-vivo anti-helmintic activity. Among the synthesized compounds 2-phenylbenzimidazole showed potential anthelminitic activity (0.931±0.231 and 1.317±0.149 min for paralysis and death, respectively) when compared with the standard piperazine citrate.

Rithe et al[31] reported various 2-substituted benzimidazole derivatives and it synthesized by condensation of ortho-phenylenediamine (0.01 mole) and different aromatic carboxylic acid (0.01 mole) in the presence of ammonium chloride as catalyst at 80c· temperature under reflux for 4 hrs and it show potential anti-helminitic activity

Saber[32]reported the synthesis of2-substituted benzimidazoles under microwave irradiation by solvent-free conditions and it catalyzed by alumina, silica gel and zeolite HY.

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The derivatives synthesized by reacting with ortho-phenylenediamine (2 mmol) with aromatic, aliphatic and heterocyclic carboxylic (2 mmol) and 50 mg of Alumina or Silica gel or Zeolite were mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5- 9 min at 160-560 W 80-90°c

The synthesized compounds were screened for their in-vivo anti-inflammatory activity by carrageenan paw edema method and in-vitro anti-microbial activity by agar well diffusion method against diclofenac sodium and ciprofloxacin and ketoconazole, respectively

Birajdar et al[33]reported the synthesis of abenzimidazole derivative through oxidative cyclization of ortho-phenylenediamine and different aldehydes using dioxane dibromide, as a user-friendly reagent. This is a new, convenient and facile methodology for the synthesis of 2-substituted-1H-benzimidazole.The synthesized compounds were screened for their in-vivo anti-inflammatory activity by carrageenan paw edema method

Shivkumar et al[34]reported the of synthesis 3-aryloxy methyl-4-[2-(benzimidazolylthio) acetamide]-5-mercapto-1,2,4-triazoles by reaction between aryloxyacid,hydrazides with alcoholic KOH and CS_2

Dubeyetal[35]reported the confirmation of 2-(thiomethyl-2'-benzimidazolyl) benzimidazole and its derivatives and the synthesized compounds were tested for anti-ulcer activity. Lowest energy which on cyclised with 2-(benximidazolylthio)methyl acetic acid hydrazide. Anti-bacterial study of synthesized compounds reveals that none of the compound showed promising activity, hence there was a need for further structural modification to improve the efficacy of the compounds. From the results of anti-fungal activity ,it was found that, methyl group containing compound produced good activity which indicates the vital role of methyl group in antifungal activity,

Srinivasulu et al[36]reported the one-pot synthesis of 2-substituted benzimidazole [halogen derivatives] from ortho-phynelyenediamine and halogen substituted aldehydes were developed under zinc triflate in ethanol solvent at reflux temperatureIn-vitroanti-bacterial study of the synthesized compounds reveals that none of the compound showed promising activity

Gurusamyet al[37]reported a synthesis of novel series of 2-substituted benzimidazole derivatives. The synthesis is carried out by reacting 2-chloro methyl benzimidazole with substituted primary aromatic amines . The synthesized derivatives were screened for analgesic activity by tail flick method in mice and anti-inflammatory activity by carrageenan induced rat paws edema method. From the results it was found that most of the compounds show significant analgesic and anti-inflammatory activity

2,5 DISUBSTITUTED BENZIMIDAZOLE DERIVATIVE

Von Niementowski[51]reported the reaction of esters and ortho-phenylenediamines to give benzimidazoles. Equimolecular amounts of 3,4-diaminotoluene dihydrochloride and ethyl formate when heated in a sealed tube for 3 hr. at 225°C. give 84 per cent of 5(or 6)-methylbenzimidazole hydrochloride. The product was not further alkylated by the ethyl chloride formed. Ethyl acetate under the same conditions gives only a poor yield of 2,5(or 2,6)-dimethylbenzimidazole, and poor yields of benzimidazoles would probably be obtained from esters of acids of higher molecular weight. A good yield of 2-methylbenzimidazole may be obtained by allowing a mixture of o phenylenediamine and ethyl acetate to stand

Chu et al[52] reported that the anticancer mechanism of a compound,

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2-chloro-N-(2-p-tolyl1H-benzo[d]imidazol-5-yl) acetamide toward breast cancer. It further reported that this compound potently inhibited both EGFR and HER_2 activity by reducing EGFR and HER_2 tyrosine phosphorylation and preventing downstream activation of PI3K/Akt and MEK/Erk pathways in vitro and in vivo. They also showed that compound inhibited the phosphorylation of FOXO and promoted FOXO translocation from the cytoplasm into the nucleus, resulting in the G1-phase cell cycle arrest and apoptosis. Moreover, this derivative potently induced apoptosis via the kinase -mediated death receptor 5 up regulation in breast cancer cells. The antitumor activity of this derivative was consistent with additional results demonstrating that it significantly reduced tumour volume in nude mice in vivo. Analysis of the primary breast cancer cell lines with HER_2 over expression further confirmed that this analog significantly inhibited Akt Ser_{473} and Bad Ser_{136} phosphorylation and reduced cycline D_3 expression

Ladenburg and Rugheimer[53]synthesized the 2-phenyl-5 (or 6)-methylbenzimidazole by heating 3,4diaminotoluene with acetophenone at 180°C. for some time. The methyl group is the one that is eliminated preferentially

Sugumaran et al[54] synthesized a series of 2,5-disustituted benzimidazoles by nitration of 2-alkyl/aryl benzimidazoles by using conc. HNO_3 and conc. H_2SO_4. The

Synthesis of a new series of amino methylated 5-nitro-1H-benzimidazole,6-nitrobenzoxazole2(3H)-ones and 4-nitroisoindoline1,3-diones show anti-leishmanial and anti-microbial activity. The synthesized compounds were evaluated for their anti-bacterial activity against gram negative bacterial species such as E. coli, and gram positive species such as Staphulococcusaureus, and S. Epidermidis

Gaur et al[55] synthesized different substituted β-benzimidazolyl-α-methyl crotonic acid-anilids, β-benzimidazolyl α-methyl crotonic acid amides, βbenzimidazoleyl methyl butyramids and β-benzimidazolyl α-methyl butyranilides . The synthesized compounds were analyzed for anti-helmintic activity. It was found that the meta-chloroderivative showed maximum activity while para-methoxy derivative showed minimum activity.

Tangedaetal[56] reported the synthesis of a series of new benzimidazoledithiocarbamates.It was synthesized by ortho-phenylenediamine, carbametes and thioacetic acid and it evaluated for antitumor activity against three cancercelllines(A-549,MDA-MBandHT-29)Thesynthesizedcompoundswerefurthersubjectedtothemolecular properties studies using different softwares viz., Molecular inspiration software, and ALOPGPS 2.1 program. Toxicity parameters were calculated using Osiris Software 2.1. All compounds are nontoxic; fulfill the solubility requirements and passing oral bioavailability criteria.Amongtheseries,compoundwithbenzylaminosidechain with 5-methyl group exhibited potent in vitroantitumor activity withIC_{50}valuesof3.38±1.9µg/mlwhencomparedtocisplatinwith IC_{50}of10.7±1.5µg/mlagainstMDA-MBcelllines

Pinnow[57]reported the synthesis of4-chloro-2-aminodimethylaniline when heated with excess acetic anhydride at 145-160°C. gives 1,2-dimethyl-5- chlorobenzimidazole.All the synthesized compounds were evaluated for their anti-helmintic activity against Indian earthworms (Pheretimaposthuma) and utilized for in- vitro anti-helminthic assay as per standard protocol

Chakravarti et al[58] reported the synthesis of 2-disubstituted pyridinyl) benzimidazoles and 1H-bemzimidazoles as anti inflammatory agent as well as anti-helmiticbenzimidazoles . Using thermodynamic, electronic, and spatial descriptors, for each category of compounds the quantitative structure activity relationship analysis was

International Journal of Pharmaceutical Research and Applications
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performed. By leave-one-out cross validation method the resulting QSR equations were validated. Significant correlation ship was found between anti -inflammatory activity and electronic parameter and spatial parameters.

Katarzyna[59] reported the synthesis of aseriesofnew benzimidazolederivatives.It wassynthesizedandtestedin vitroforpossibleanticanceractivitytheireffect of proliferation into selected tumour cell lines at normoxia and hypoxia conditions was determined by WST-1 test. Additionally, apoptosis test (caspase 3/7 assay) was used to check the mode causedbytheagentsofcelldeath.Fouroftheexaminedc ompounds showed a very good anti-proliferative effect and three of themwere specificforhypoxiaconditions.Screeningtestofcaspas e-dependent apoptosis proved that exposure to A549 cells for 48 h test compoundspromotedapoptoticcelldeath

Raiford, L.C and Coppo[60]reported the reaction between beta-keto esters and ortho-phenylenediarnines under basic conditions a analogous to 2-benzimidazoleacetone have been obtained

Hager[61]reeported the synthesis of 5-amino-2(3H)-benzimidazolone by reducing 2,4-dinitro- phenylurethan with tin and hydrochloric acid

Billeter and Steiner[62]reeported the synthesisof 2(3H)-benzimidazolethione and 5-methyl- 2(3H)-benzimidazolethione by the action of thiophosgene on ortho-phenylenediamine and 3,4-diaminotoluene, respectively. 3 4-Diaminobenzenearsonic acid and thio- phosgene gave a 78% yield of 2(3H)-benzimidazolethioned-arsonic acid

Cibaltd[63] reported the synthesis of bezimidazole derivative by reacting trichloroacetyl-4-methyl-2-nitroaniline with tin and hydrochloric acid undergoes hydrolysis to 3,4-diaminotoluene dihydrochloride and trichloro-acetic acid. Salicyloyl-o-nitroaniline is converted to 2-(o-hydroxyphenyl)-benzimidazole and Crotonoylamino-3-nitrotoluene to yields 3-propenylde-methylbenzimida- zole. The double bond is not reduced in the reaction

Green and Day[64]reported the synthesis of 2-phenyl-5-methylbenzimidazole in about 80% yield from 3-benzalamino-4-acetaminotoluene and from 4-benzala- mino-3-acetaminotoluene by heating with nitrobenzene and alcoholic potassium hydroxide solution. The synthesized compounds were analyzed for anti-helmintic activity. It was found that the metaderivative showed maximum activity while para derivative showed minimum activity.

Janssen Pharmaceutica[65]synthesizedmebendazole, methyl-[5-(benzoyl)-1H-benzoimidazol-2-yl]carba mate was a derivative of benzoimidazole, which was made by reacting 3,4-diamino benzophenone with N-methoxycarbonyl-S-methylthioure .The exact mechanism of action of mebendazole was not conclusively known, but it seems likely that it causes irreversible inhibition of the uptake and utilization of glucose by the parasite and stops the formation of ATP, thus causing glycogen depletion and subsequent death of the parasite. Mebendazole is used for treatment of enterobiasis,ascariasis,ankylostomiasis,strongyloidi asis,trichocephaliasis,trichuriasis, and mixed helminthoses. It was used twice a day over the course of 3 days in doses of 100 mg,resulting in complete recovery in 90–100% of patients. Synonyms of this drug are vermox, mebutar, panfugan, and many others.

Weiming et al[66] synthesized 2-[3-(4-morpholino)propylthio]-5-(diflurомethoxy) benzimidazole derivatives by reacting morpholine with flurомethoxybezimidazole The synthesized compound show better anti-inflammatory effect

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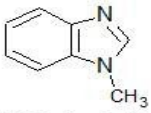
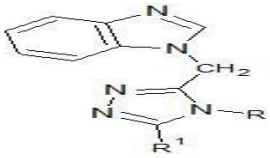
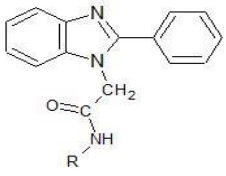
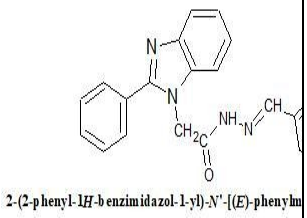
than Aspirin and better analgesic activity than Indomethacin and lower gastric ulcer

Sandeepet al[67] reported a series of new 5-ethoxy-2-substituted benzimidazole derivatives.It was synthesized from ortho-phenylenediamine and ester . These derivatives were tested for anti-inflammatory activity by using carrageenan induced rat paw edema method. Most of the obtained compounds exhibited anti-inflammatory activity, especially some of the compound showed significant activity when compared with that of ibuprofen used as standard drug

Mono Substituted Bezimidazole Derivative [table 1]

S. No	Compound	Structure	Activity	References
01	1-Methyl benzimidazole	 1-methyl-1*H*-benzimidazole	Antihelmenthic	Fischer and Veiel
02	1-Triazole bezimidazole derivative		Antihelmenthic	Noha et al

1,2Di-Substituted Bezimidazole Derivative [table-2]

S. No	Compound	Structure	Activity	Referencs
01	2 phenylbenzimidazole-1-acetamide		Anti-helmenthic	Ramesh et al
02	N'-(substituted benzylidene)-2-[2-(substituted phenyl)-1H-benzimidazol-1-yl]acetohydrazide.	 2-(2-phenyl-1*H*-benzimidazol-1-yl)-*N*'-[(*E*)-phenylm	Anti-imflamatory	Soni B et al

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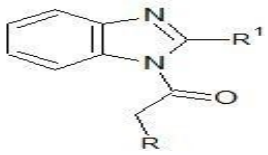
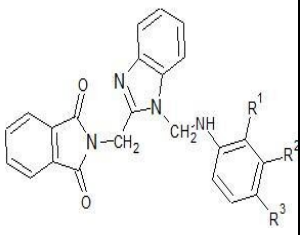
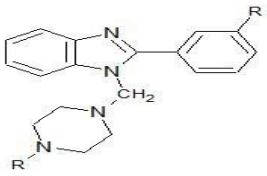
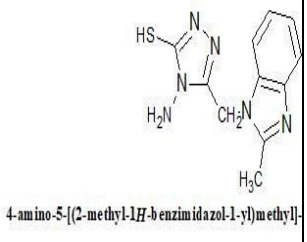
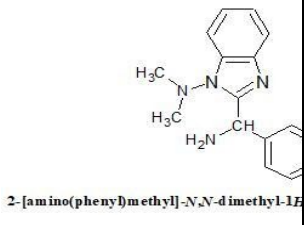
03	2-(aryl)-1-(1H-benzo[d]imidazol-1-yl) ethanone and 2-(aryl)-1-(2-methyl-1Hbenzo[d]imidazol-1-yl) ethanone		Antihelmenthic	Patel and co-workers
04	1,2-disubstituted benzimidazoles		Anti-helmenthic	SudheerBabu et al
05	1,2-disubstituted derivative		Anti-helmentic	Gupta et al
06	Schiff's Bases of 1,2-methyl benzimidazole derivatives	 4-amino-5-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]-	Anti-viral	Sanahanbi et al
07	1,2 benzimidazole	 2-[amino(phenyl)methyl]-*N*,*N*-dimethyl-1*H*	Anti-thelmentic	Anil Reddy
10	2-amino-1H-benzimidazole		Anti-helmentic	Anna et al

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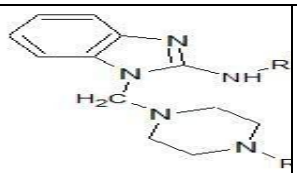
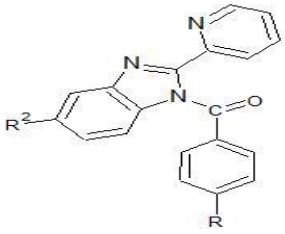
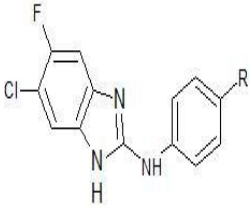
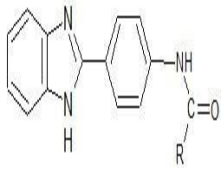
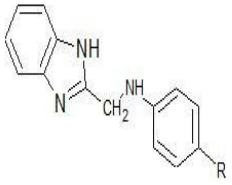
				
11	2-(2′-pyridyl) benzimidazole		Anti-helmenthic	Arfa et al

2 - Substituted Benzimidazole Derivative [table-3]

Sno	Compound	Structure	Activtity	Reference
01	2substituted benzimidazole derivative		Anti-imflammatory	**Rekha et al**
02	2-substituted benzimidazole derivatives		Anti-helmenthic	**Manish et al**
03	2-chloromethyl-1Hbenzimidazole		Anti-helmenthic	**Komal P et al**

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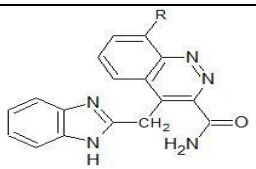
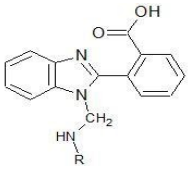
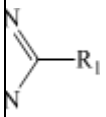
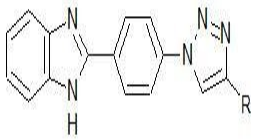
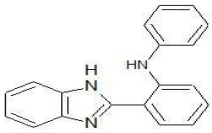
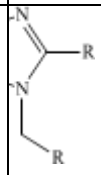
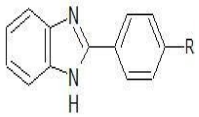
04	cinnolinebenzimidazoles		Anti-helminthic	**Shruti et al**
06	2-(1H-benzo[d]imidazol-2-yl) benzoic acid		Anti-microbial	**Kalirajan et al**
07	2-substituted benzimidazole derivatives		Anti-helmintic	**Kuldeep Kumar**
08	Triazole derivative		Anti-cancer	**Karna et al**
09	N-(2-(1-benzo[d]imidazol2-yl) phenyl)-substituted benzamines		Anti-helminthic	**Aruna et al**
10	2-aryl-1(arylmethyl)-1H - benzimidazoles		Anti-helminthic	**DavoodAzarifar et al**
11	2-substituted benzimidazole		Anti-fungal. Anti-microbial	**Abhay et al**
12	2-substituted benzimidazoles		Anti-helminthic	**B.N.B.vaidehi et al-**

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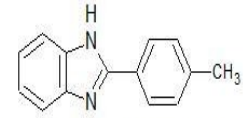
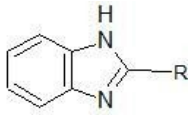
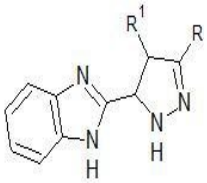
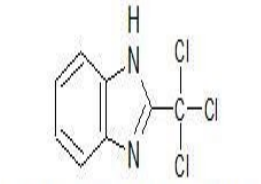
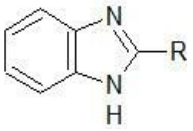
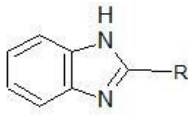
		 2-(4-methylphenyl)-1*H*-benzimidazole		
13	2-substituted benzimidazoles		Anti-helminthic	**Mita D. Khunt et al**
14	2-substituted pyrazolines		Anti-helminthic	**Jayanti et al**
15	2-trichloromethyl benzimidazole	 2-(trichloromethyl)-1*H*-benzimidazole	Anti-viral	**Hollan et al**
16	2-benzimidazole derivatives		Anti-helminthic	**Sreena et al**
17	2-substituted benzimidazole derivatives		Anti-helminthic	**Rithe et al-**
18	2- benzimidazoles		Anti-viral, anti-helminthic	**Saber**

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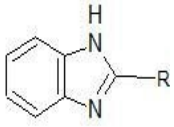
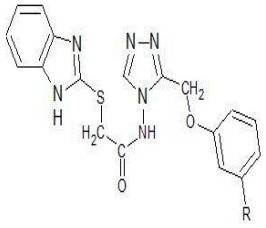
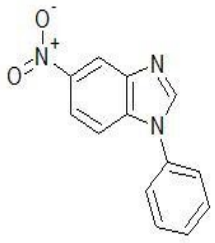
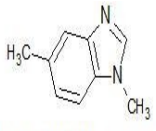
				
20	3-aryloxy methyl-4-[2-(benzimidazolylthio) acetamide]-5-mercapto-1,2,4-triazoles		Anti-fungal	**Shivkumar et al**

1, 5 Di- Substituted Bezimidazole derivative [table-3]

S no	Compound	Structure	Activity	Reference
01	1-phenyl-5nitroben- zimidazole	 5-nitro-1-phenyl-1*H*-benzimidazole	Anti-viral	**Von Walther**
02	1,5-dimethylben zimidazole	 1,5-dimethyl-1*H*-benzimidazole	Anti-fungal	**Von pinnow**

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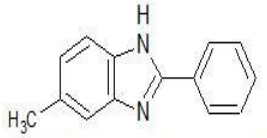
2,5 Di-Substituted Benzimidazole Derivative[table-5]

	S.no	Compound	Structure	Activity	Reference
	01	5-methyl-1-H benzimidazole	 5-methyl-2-phenyl-1*H*-benzimidazole	Anti-helminthic	**Von Niementowski**

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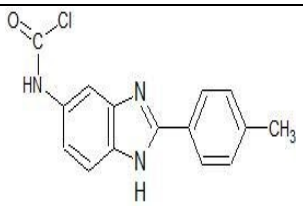
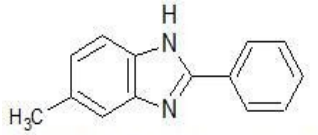
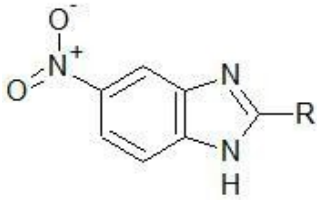
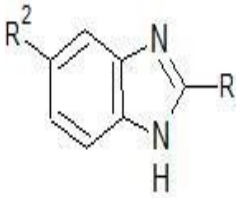
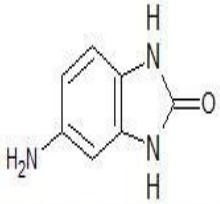
	02	2-chloro-N-(2-p-tolyl1H-benzo[d]imidazol-5-yl) acetamide		Anti-cancer	**Chu et al**
	03	2-phenyl-5 methylbenzimidazole	 5-methyl-2-phenyl-1*H*-benzimidazole	Anti-viral	**Ladenburg and Rugheimer**
	04	2,5-disustitutedbenzimidazoles)		Anti-microbial	**Sugumaran et al**
	07	2,5disubstituted derivative		anticancer	**Katarzyna**
08		5-amino-2(3H)-benzimidazolone	 5-amino-1,3-dihydro-2*H*-benzimidazol-2-	Anti-viral	**Hager**

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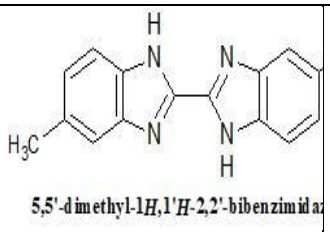
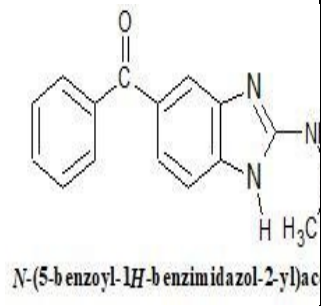
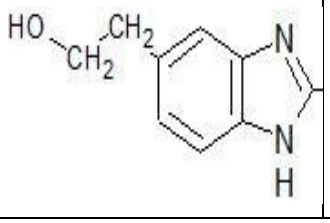
09	2-(o-hydroxyphenyl)-benzimidazole	 5,5'-dimethyl-1*H*,1'*H*-2,2'-bibenzimida	Anti-viral	**CIBA LTD**
10	methyl-[5-(benzoyl)-1H-benzoimidazol-2-yl]carbamate	 *N*-(5-benzoyl-1*H*-benzimidazol-2-yl)ac	Anti-helmintic	**Janssen Pharmaceutica**
11	5-ethoxy-2-substituted benzimidazole		Anti-imflamatoy	**Sandeep et al**

IV. CONCLUSION

The benzimidazole ring is an important pharmacophore in modern drug discovery. Attention has been gradually more given to the synthesis of benzimidazole derivatives as a source of new biological agents[68]. The benzimidazole derivatives are source for further medicinal research, and allow them to interact easily with the biopolymers, possess pharmacological activity with lower toxicities[69].Changes in the benzimidazole structures have offered high biological activities that have proven useful for the development of new medicinal agents having improved potency and lesser toxicity[70]. The present review highlights the various synthesized benzimidazoles and their derivatives possessing various activities such as analgesic, anti-inflammatory, anti-helmentic, anti-tubercular ,anti-viral, anti-fungal, anti-diabetic , anti-cancer and anti-oxidant

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Volume 6, Issue 3 May - June 2021, pp: 35-53 www.ijprajournal.com ISSN: 2249-7781

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