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

Review on design synthesis of new Benzimidazole and Benzothiozole fused ring derivatives for anti cancer an anti microbial activity

[1]Junaid Tantray,[2] Mohd Zaid,[3]Ramesh Kumar, [4]Hanief Chaudhary, [5]Dr. Sourabh Kosey, [6]Dr. Akhilesh Patel, [7]Yashir Ansari, [8]Vikas Kumar

[1] Assistant Professor,[2] M. Pharma,[3] Pharm D
Dept of Pharmacology & Pharmacy Practice,
[1]NIMS Institute of Pharmacy NIMS UNIVERSITY RAJASTHAN JAIPUR INDIA

Abstract : Over the course of more than a century, researchers have researched the characteristics of benzimidazole and its derivatives. Substitutes and intermediates for the synthesis of compounds with potential as pharmacological or biological agents include benzimidazole derivatives. Antiulcer, anticancer, and anthelmintic species are just a few of the therapeutic areas where substituted benzimidazole derivatives have found use. This article provides a systematic assessment of recent advancements in benzimidazole-based molecules across the entire spectrum of medicinal chemistry as anticancer agents.In order to assist medicinal chemists in creating an SAR on benzimidazole drugs/compounds, this review will be further helpful for the researcher based on substitution pattern around the nucleus.A bicyclic molecule of the heterocyclic class is benzothiazole (BTA). BTA derivatives have a wide range of biological effects, including those against cancer, inflammation, tumours, viruses, bacteria, proliferative cells, diabetes, convulsions, tuberculosis, leishmaniasis, histamine, and fungi, among others. The metalloenzyme carbonic anhydrase was significantly inhibited by the BTA scaffolds (CA). In this review, a thorough literature assessment over the previous 10 years reveals that BTA derivatives are primarily used as anticancer medicines. These substances work against different cancer cell lines by a variety of methods, some of which have not been well researched or understood. On the other hand, more research has been done on how BTA derivatives might block tumour-associated CAs, and these substances may be used as anticancer leads for the developmentof treatments for tumours that are under-oxygenated.

Key words: Benzimidazole, synthesis, pharmacological activity, antitubercular, anticancer, Benzothiazole; anticancer agent; drug targets; scaffold; carbonic anhydrase inhibitor

INTRODUCTION

A heterocyclic aromatic organic chemical is benzimidazole. This bicyclic molecule can be thought of as benzene and imidazole's aromatic rings fused together. It is a solid with no colour. Benzimidazole. We created and characterised benzimidazole derivatives. The in vitro antibacterial and anticancer properties of synthesised compounds was examined1. For in vivo and in vitro antitubercular efficacy, the produced compounds were tested. The most effective antibacterial compound discovered was number 10 2. Chemotherapy has revolutionized the treatment of infectious 55 diseases since the discovery of antibacterial dyes by Ehrlich earlier 56 in the 20th century and paved the way to a great victory for human 57 health and longevity3. The emergence of resistance against currently used antimicrobial drugs led to a revitalized interest of the 59 researchers in infectious diseases to develop new chemical entities 60 to combat them [4].

It is a prized structure in medicinal chemistry and a significant pharmacophore. This bicyclic molecule, which is formed when benzene and imidazole combine, is in nature. is a popular moiety today that has several pharmacological characteristics. N-ribosyl-dimethylbenzimidazole, which functions as an axial ligand for cobalt in vitamin B12, is the most prevalent benzimidazole chemical in nature.

Many years have passed since Benzimidazole was first used2. With the substitution of fluorine, propylene, tetrahydroquinoline, and cyclized compounds in various benzimidazole derivatives in 1990, compounds with increased stability, bioavailability, and significant biological activity were produced5. 3,4 It was also demonstrated that the activity is increased by the substitution of an electron-donating group on pyridine. In 1991, benzimidazole derivatives were created by derivatizing benzimidazole at the N-H position with an electron-donor group and replacing it with a long chain of propyl, acetamido, thio, thiazole-amino, and tetramethyl piperidine on pyridine, which had good antiulcer activity[6]

Due to the resistance to several antimicrobial medicines (B-lactam antibiotics, macrolides, quinolones, and vancomycin), infectious microbial illnesses are currently an issue on a global scale. An important worldwide health issue is the wide variety of clinically significant species of microorganisms[7]. Making proper use of the antibiotics that are currently on the market is one strategy to combat this problem. The other is the creation of brand-new anti-microbial substances.[8]To combat the establishment of resistance and, ideally, cut the length of therapy, there will always be a critical need to discover new chemotherapeutic drugs9.

Because of their structural resemblance to purines, benzimidazoles have an antibacterial effect. This effect is explained by their competition with purines, which prevents the synthesis of bacterial nucleic acids and proteins. [10]

Anti-cancer activity: 1, 3-diarylpyrazinobenzimidazole derivatives have been synthesised and their anti-cancer properties have been studied. To do this, 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles were produced by reacting 2-bromoacetophenones with 2-aryloylbenzimidazole derivatives in acetone. The compound was created by reacting the resultant substance with ammonium acetate in acetic acid. The synthesis and evaluation of 1-(4methoxyphenethyl)-1H-benzimidazole-5carboxylic acid derivatives is another approach that has been reported. The compound methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3nitrophenyl)-1H-benzimidazole-5-carboxylate induced maximum cell death in leukemic cells with an IC(50) value of 3 microM. [11]

Antibacterial and antimicrobial effects: According to a literature review, 2-substituted benzimidazole derivatives are proven to be pharmacologically more effective than other benzimidazole derivatives; as a result, the design and synthesis of 2-substituted benzimidazoles are a viable area of research. [12]. It is recognised that this group is present in a number of commonly used antibacterial medications, including thiazide, furacilin, and furazolidone[13]. Due to their chemotherapeutic significance in the creation of novel anti-microbial drugs, hydrazones have attracted a lot of interest in recent years, and numerous research [14]have been published. There are a number of 1, 2-disubstituted-1Hbenzimidazole-N alkylated-5-carboxamidine derivatives that have extremely effective antibacterial properties against S. aureus and methicillin resistant S. aureus. [15]With MIC values of 0.78 to 0.39 g/mL against these species, the study found the best activity. Various benzimidazoles that have been chloro- and dichloro-substituted also have antibacterial procedures16.

Antimicrobial and antifungal activities: Isoxazolyl substituted compounds were tested for action against Gram positive organisms such Bacillus mycoides and staphylococcus aureus[17], as well as Gram negative species like E. coli and Proteus vulgaris. We looked into certain benzimidazole compounds with hydrazone moiety to see whether they would have any antibacterial or antifungal properties. The majority of the test substances were found to be significantly efficient against the gram-negative bacterial strains Proteus vulgaris, Staphylococcus typhimurium, Klebsiella pneumoniae, and Pseudomonas aeruginosa18. By using a microwave-assisted technique, certain fluroquinolones substituted benzimidazole derivatives have been reported. According to reports, the produced chemicals are Norfloxacin [8] and Ciprofloxacin [7] derivatives.[19]

Numerous microbial illnesses will soon be incurable due to the growing threat posed by antimicrobial resistance to human health [20]. In order to overcome microbial resistance, new tactics must be developed that block the virulence factors of microbes, such as quorum sensing (QS). The generation of virulence factors, the emission of bioluminescence, adhesion, motility, competence, biofilm formation, and sporulation are only a few of the physiological processes that QS regulates [21]. Through the disruption of QS, QS inhibitors are used to treat persistent resistant bacterial infections[22]and are crucial in the fight against resistant infections [23]. As a result, the focus of present research is on creating and synthesising novel antimicrobial compounds with anti-QS action.

Heterocyles are significant pharmcophores and play a key role in the creation of special chemical compounds with pharmacological properties. Broad range therapeutic agents are reported to contain five membered heterocyclic, which play a significant role in the processes of drug discovery and drug development[24].Benzothaizole (BTA), a fused benzoheterocyle found in many naturally occurring chemicals, is what gives these products their medical, pharmacological, and pharmaceutical uses[25]. BTA is found in both terrestrial and marine compounds, and it exhibits a variety of biological activity.The thiazole ring and a benzene ring fuse to generate the BTA nucleus in[26]. The pharmacological characteristics of the medication used to treat amyotrophic lateral sclerosis in[27]. Medical chemists were interested in riluzole (Figure 1) in the direction of biologically active benzothiazole[28].

Cancer is the most prominent, notably complex and lethal disease which became a serious concern of today's medical science. It poses a great challenge to medical scientific community for development of drugs, medicines and procedures for safer treatment and cure of cancer disease[29]. These neoplasm tumour cells are diversified, heterogeneous cells with rapid proliferative properties. These neoplasm malignant tumours, have potential to invade or spread to other parts of body through blood stream and lymphatic system[30]. The plethora of research mentioned in the present review of last decade on anticancer potential of BTA derivatives will be helpful in future drug discovery and drug development for the treatment of lethal cancer disease.

With 1.15 million new cases of breast cancer in 2002, it was by far the most prevalent cancer in women, accounting for 23% of all female cancers. When both sexes are taken into account, it comes in second overall. In industrialised nations—roughly 361,000 in Europe (27.3% of malignancies in women) and 230,000 in North America (31.3%)—more than half of all cases are diagnosed. Most developed nations have high incidence rates, with North America having the highest age-standardized incidence (except from Japan, where breast cancer ranks third behind colorectal cancer and stomach cancer) (99.4 per 100,000). Although less prevalent, breast cancer is still the most common cancer in eastern Europe, south America, southern africa, and western Asia. in these areas is female[34]. There is an urgent need for novel, cheap chemotherapeutic drugs to combat the threat of rising resistance and unaffordable therapy among breast cancer survivors.

Modern researchers' preferred heterocyclic moiety is benzimidazole, also called as benzimidazole or benzoglyoxa line[31]. It is a versatile heterocycle with a wide range of biological activities thanks to the presence of imidazole, a biologically active pharmacophore, including antihistaminic [32],antiulcer, antitubercular[33], antioxidant [34]anti-HIV[35], antiinflammatory[36] ,analgesic[37] ,antimicrobial[38],antiprotozoal, antitrichinellosis[39],antihypertensive[40]

In response to the aforementioned findings and as part of our ongoing research on benzimidazole derivatives [41]we now present the creation, testing for antibacterial activity, antitubercular activity, and anticancer activity of a novel line of benzimidazole derivatives

RESEARCH METHODOLOGY

Without additional purification, analytical grade chemicals that were purchased from commercial sources were used. Hi-media Laboratories provided the media for the antimicrobial activity tests. From IMTECH, Chandigarh, we obtained microbial type cell cultures (MTCC) for antibacterial activity. Using the KBr pellet technique and the OPUS 7.2.139.1294 spectrophotometer software, infrared (IR) spectra were acquired and represented in cm1. In deuterated DMSO downfield to tetramethylsilane standard, the proton nuclear magnetic resonance (1 HNMR) and 13CNMR spectra were recorded on a Bruker Avance III 600 spectrum analyzer (at 600 and 150 MHz, respectively), and chemical shifts were recorded as The open glass capillary method

was used to determine the melting points, which are uncorrected. TLC was used to confirm the reaction's progress spots were seen in an iodine chamber after being observed on silica gel-G plates. At Panjab University in India, the LCMS data were collected using a Waters Q-TOF micromass (ESI-MS). On a CHNN/CHNS/O analyzer (Flash EA1112N series, Thermo Finnigan, Italy), elemental analysis for synthetic derivatives was carried out.

1)Benzimidazole derivative-

1.1) Antimicrobial agents-

Due to growing global concern over the worrisome rise of antibiotic-resistant microorganism infections, the quest for chemicals with anti-bacterial action has taken on increased relevance in recent years. As a result, substances with antimicrobial properties are considered as a whole under the title of "antimicrobials" in the current review. Al-Tel and colleagues described the synthesis of benzimidazolepyridine/pyrimidine derivatives and their evaluation of their antibacterial effects on various bacterial and fungi strains. As compared to amoxicillin and cefixime, some of the motifs had strong antibacterial action. The compounds 16(a,b) with a halogen substituent on the benzimidazole rings and bromine at the phenyl moiety residing on the imidazopyridine ring shown strong antibacterial activity [42]. Fang et al. created benzimidazole-containing bis-azole compounds and tested them for their in vitro anti-microbial properties. strains of bacteria and fungi. With a MIC value of 4 g/mL, compound [43]had outstanding effectiveness against P. aeruginosa, which were 16 -fold more powerful than the standard medication, chloramphenicol. Dihalobenzyl groups, as opposed to monohalobenzyl ones, are more beneficial for boosting antibacterial and antifungal effectiveness, according to SAR[44]. Jubie and colleagues described the synthesis of ciprofloxacin and norfloxacin Mannich bases employing different benzimidazoles as microbiological agents and microwave irradiation. In comparison to the standards norfloxacin and ciprofloxacin at 50 and 100 g/mL, all of the benzimidazole substituted norfloxacin derivatives 18(a-c) and ciprofloxacin derivatives 19(a-c) had considerable activity[45]. The antimicrobial activity of thiadiazolo-thiazolidinones (20) containing benzimidazole was produced and tested. SAR research reveals halogen substitutes anti-microbiological effect[46]. For the purpose of testing the in vitro antibacterial activity, Mungra et al. described the synthesis of benzimidazolequinoline hybrids. Compound (21) exhibited activity against the Gram-positive bacterium B. subtilis that was comparable to that of conventional ampicillin [47] .Conjugates of benzimidazole and thiazolidinone were created, and their antifungal properties were assessed. Comparable to regular carbendazim 52the compound [48]has an antifungal effect on P. nicotianae and B. elliptica. The creation of benzimidazole-thiazol-2-amine compounds was reported by Reddy and colleagues, and their antibacterial activity was assessed. When compared to the control (Streptomycin), compounds (23) and (24a) showed approximately equal inhibitory action against B. subtilus. The most active compounds are 24(a,b), which were more effective than fluconazole against F. oxysporum[49]. Rohini and colleagues reportedarylbenzimidazole-quinazoline as antibacterial agents. Among the substances examined It is possible that the presence of heterocyclic isoquinolyl, pyridyl, and nitro substituted aryl groups at the C6 position of the benzimidazo[1,2-c]quinazoline moiety in compounds (25c), (25i), and (25j) accounts for their most effective inhibitory action against test organisms[50]. Benzimidazole derivatives with nitro substitutions were produced and tested for antibacterial activity in vitro. The antibacterial activity is enhanced by a nitro group in the aromatic ring.

2)Antiinflammatory and analgesic agents-

Different approaches are used to develop new non-steroidal anti-inflammatory medications, including selective COX-2 inhibition and inducible nitric oxide synthase inhibition (iNOS)[51]. By generating nitric oxide as a byproduct, iNOS contributes to both acute and ongoing inflammation.inflammatory mediator that is cytotoxic Numerous chemical substances formed from various heterocyclic nuclei have been shown to suppress or stop the inflammatory process at various stages[52]. The search for benzimidazole-derived anti-inflammatory drugs predates the development of contemporary medical chemistry. The anti-inflammatory action of numerous benzimidazole derivatives has been reported by a large number of research organisations, although no such molecule has yet reached the clinics[53].

Derivatives of 2-methylaminobenzimidazole were created and tested for analgesic andanti-inflammatory effects on carrageenan- and acetic acid-induced writhing in mice and paw oedema in rats. In comparison to the reference drug Nimesulide (100% at 50 mg/kg b.w), compounds 56(a,b) demonstrated potent analgesic (89% at 100 mg/kg b.w.) and antiinflammatory (100% at 100 mg/kg b.w.) activity[54]. According to SAR research, the chloro group in the aniline ring's meta position boosts its analgesic and anti-inflammatory properties[55]. Gaba et al. created sulfonyl benzimidazole derivatives and tested them for their anti-inflammatory, analgesic, and stomach ulcerogenic properties.Compounds 57(a-c) showed moderate to good analgesic and anti-inflammatory efficacy.

The SAR investigation reveals the acidic nature of some compounds and/or the reduction of molecules from the -NO2 group to the -NH2 group, which may reduce oxidative stress [56]. Various phenyl pyrazolo benzimidazolesThe quinoxaline derivatives 58(a-c) were created as anti-inflammatory and antioxidant compounds. The compounds (58a) (92.5%), (58b) (93.0%), and (58c) (93.3%) in particular showed good free radical scavenging activity and compounds same compounds showed good inhibition of edoema volume with 91.5, 92.6, and 93.1% inhibition [57]. All the compounds demonstrated significant antioxidant and antiinflammatory activity. Analgesic and anti-inflammatory activity was tested on a number of N-Mannich bases of benzimidazole derivatives. At 40 mg/kg, 2-Styryl benzimidazole (59) and compound (60) were shown to be equally potent to paracetamol and more potent than diclofenac [58]. Hybrids of benzimidazoles, azetidinone, and thiazolidine were created, and their analgesic and anti-inflammatory properties were tested. In this major action caused by thiazolidinones, the derivatives have demonstrated good analgesic and anti-inflammatory efficacy.At a dose of 200 mg/kg, it was discovered that 62(a, b) was comparable to diclofenac (25 mg/kg) [59].Compounds produced and tested as anti-inflammatory drugs with antiulcerogenic activity included benzimidazole-pyride hybrids and benzimidazole-polyhydroxy sugar linked compounds. The results were compared to omeprazole and diclofenac, respectively. Comparable to diclofenac (73%), compounds (63) and (64) showed dose-dependent antiinflammatory effects by reducing inflammation by 62% and 72%, respectively. The linked-position of the polyhydroxy sugar conjugated to the N-benzimidazole moiety[60] is necessary for the existence of the electron-donating methoxy groups at the 3- and 4-positions in the pyrid-2-yl moiety as well as the compound's significant anti-inflammatory activity [61]. Derivatives of benzimidazoleazetidinone have been linked to analgesic and anti-inflammatory effects.

Analgesic activity of compound 65 was found to be high (46% at 20 mg/kg).compared to the reference medicine nimesulide (20 mg/kg b.w), and anti-inflammatory (66.5% at 20 mg/kg b.w). According to a SAR investigation, compounds having substituted phenyl rings at the fourth and fifth positions of the azetidinone ring had increased analgesic and anti-inflammatory activity [62]. In

LPS-stimulated macrophages, benzimidazole and imidazopyridine derivatives demonstrated good suppression of the production of inflammatory cytokines. The release of TNF- and IL-6 was suppressed by compound (66) in a dose-dependent manner, and hepatic cells did not exhibit any cytotoxicity]. Figure 6 depicts the chemical structures of benzimidazole derivatives that act as analgesics and anti-inflammatory drugs, and Table 2 lists some of them.

3) Antitubercular agents-

The most common infectious disease that results in death worldwide is still tuberculosis (TB), a contagious infection brought on by Mycobacterium tuberculosis (MTB)[63]. More than 150 million people will become ill from TB between 2002 and 2020, according to the WHO's estimates, and 36 million people will pass away from the disease[64]. Novel medications that can shorten this lengthy treatment duration and target multidrug-resistant TB strains are critically needed[65]. The following is a discussion of the vast variety of TB actions that benzimdiazole and its derivatives exhibit. After being created, styryl-2-benzimidazole derivatives were tested for their in vitro antitubercular, antibacterial, and antifungal activity against MTB H37Rv. Compounds 73(a-e) displayed greater antitubercular activity, and compounds 73(b,c) demonstrated antimicrobial agent efficacy[66]. FromWhen compared to compounds with nitro substituents, SAR compounds' activity has been significantly boosted by the inclusion of the bromo group on the aromatic ring[67]. Synthesized compounds of triazole-benzoimidazole were tested for their ability to inhibit mycobacterial growth. Against mycobacteria, compounds 74 (a–c) demonstrated promising efficacy. According to a SAR research, substances containing fluorine replacements at the phenyl ring had higher antimycobacterial action [68]. Triazole-benzoimidazole derivatives with flouro substitutions were created and tested for their antibacterial and antitubercular efficacy against the MTB H37Rv strain in vitro. Fluorine and chlorine compounds 75(a–c) and others with electronegative atoms showed good efficacy (up to 96% inhibition at 6.25 g concentration)[69]. Alkyl substituted benzimidazoles have been synthesised by Pandey et al., and their antitubercular effectiveness against the virulent strains of MTB H37Ra and virulent strainvarying amounts of MTB H37Rv. When comparing the activity of the imidazole and benzimidazole derivatives 76(a,b), the imidazole substituent performs well[70].

The antimycobacterial activity of substituted 2-polyfluoroalkyl and 2-nitrobenzylsulphanyl benzimidazoles against MTB, M. kansasii, M. kansasii, and M. avium was produced and tested. In example, the 5,6-dichloro-2-nonafluorobutylbenzimidazole (77), the 5-halogeno 78(a-c), the 4,6-dihalogeno (78d), and the 2-(3,5-dinitrobenzylsulphanyl)benzimidazoles all demonstrated significant antimycobacterial action (78e). According to the SAR analysis, 5,5dinitrobenzylsulfanylbenzimidazoles are halogenated with either chlorine,All mycobacterial strains were highly actively inhibited by bromine or iodine 78(a-c)[71].

The antimycobacterial efficacy of alkylsulfanyl-benzimidazole derivatives against MTB and nontuberculous mycobacteria was investigated after their synthesis. In terms of effectiveness against M. kansasii and M. avium, the compound with, 3,5-dinitro derivative (79), outperformed the standard isoniazide[72]. The conjugated benzimidazole-oxadiazole compounds were created and tested in vitro.MTB H37Rv-specific antituberculosis activity. Compound (80), which is comparable to regular pyrazinamide and has a methoxy (-OCH3) group attached to the N-phenyl acetamide moiety, displayed the maximum level of inhibition (99%) against MTB H37Rv at a constant concentration level (6.25 g/mL)[73]. Trisubstituted benzimidazoles exhibited strong antituberculosis action against MTB, according to Kumar and colleagues. With MIC values between 0.5 and 6.1 g/mL, compounds 81(a) through (d) exhibit excellent activity against clinical MTB strains [74]. The antimycobacterial activity of derivatives of substituted benzimidazoles was produced and tested against MTB H37Rv. Particularly compound (82), which was most active with an IC50 of 11.52 M [84], some of the benzimidazole derivatives demonstrated good activity with IC50 values of less than 15 M. The TB-fighting ability of pyrido-benzimidazole-4-carbonitrile derivatives against MTB H37Rv was excellent. Compound (83) displayed comparable in vitro behaviors[75]as demonstrated against the weak control strain[73]. The anti-TB activity of 5-nitrofuran or 5-nitrothiophene-benzoimidazole-5-carbohydrazide derivatives was produced and tested on sensitive MTB[76].

In comparison to INH (0.063 g/mL) and RIF (32 g/mL), compounds (84) showed modest antimycobacterial action, with MIC values of 12.5 g/mL against MTB strain and 6.25 g/mL against MDR clinical isolates[77]. Figure 7 depicts the structures of benzimidazole derivatives used as antitubular medicines.

4) Antidiabetic and anticonvulsant agents –

Diabetes mellitus (DM), which affects the metabolism of carbohydrates, lipids, and proteins as a result of insulin shortage or insulin resistance, is a non-communicable disease and one of the most difficult obstacles to overcome[78]. Recurrent seizures, which characterise epilepsy as one of the most prevalent and severe neurological illnesses, are caused by a brief electrical disturbance in the brain brought on by an imbalance between excitatory and inhibitory neurotransmitters[79]. The present multi-drug therapy is not effective in about one-third of patients[80]. Recent antiepileptic medications such as phenytoin, carbamazepine, and sulfamate topiramate (TPM) have been clinically effective against various types of seizures [81] the following is a discussion of some anti-diabetic and anti-convulsant properties of benzimidazole and its derivatives. a number ofMaximal Electroshock (MES) model and the oral glucose tolerance test were used to screen for the in vivo anti-convulsant efficacy of 4-thiazolidinones 85(a-j) and 1,3,4-oxadiazoles 86(a-j) containing benzimidazole moiety (OGTT). Compounds 86(a,b), and 87(d,e) shown outstanding anti-diabetic activity, whereas compounds 85(a-c) and (85e) demonstrated significant anti-convulsant effects[82]. The compounds with hydroxyl groups (-OH) displayed extremely promising properties, according to SAR analyses [83]. A group of substituted benzimidazole derivatives 87(a-e) were created and tested for their potential anticancer, antidiabetic, and antiasthmatic properties. These compounds showed some reliable findings in both in vitro and in vivo investigations on testing organisms[84].

The anticonvulsant activity of the nitro-benzimidazole derivatives was produced and tested against the MES and PTZ elicited by electrical and chemical stimulation in mice. the majority of the chemicals demonstratedPentylenetetrazole (PTZ) and maximal electroshock (MES)-induced convulsions are inhibited. The compound (88) shown the highest level of activity in both convulsion models [80]derivatives of substituted benzimidazoles produced byAlkyl, acyl, and sulfonylation reactions, as well as sonogashira couplings[85]. The potential antibacterial, anti-asthmatic, and anti-diabetic properties of all the compounds have been evaluated; however, compounds 89(a,b), (90f), and 91(a-d) completely inhibited both S. aureus and S. typhimurium[86].

The only organism that completely inhibited compound (90a) and compound (91e) was S. typhimurium. These substances were also investigated for potential anti-asthmatic activities against PDE-IV and for potential antidiabetic actions against DPP-IV and PTP-1B [87]. Kwak et al. created benzimidazole compounds with a phenylcyclohexyl acetic acid group as DGAT-1 inhibitors.In a four-week study using the DIO mouse model, compound (92) demonstrated good in vivo efficacy [88]. Carbazole-based carboxylic acidsacids created by Ushiroda and colleagues were tested for their ability to reduce cholesterol and act as an anti-diabetic.

Peroxisome proliferator-activated receptor (PPAR) (partial agonist) activity of compound (93) was strong. In an animal model, the sodium salt of (93) showed strong efficacy in decreasing blood glucose and lipids without leading to appreciable weight gain, a known adverse consequence of PPAR full agonists [89]. Figure 8 depicts the structures of benzimidazole derivatives used as anti-diabetic and anticonvulsant medications.

5) Antioxidant agents-

Healthy tissues are maintained in part by the homeostatic equilibrium between reactive oxygen species (ROS) and endogenous antioxidants. When under oxidative stress, human bodies produce too much ROS, which damages different cell components (including DNA, lipids, and proteins) and leads to cell death and health issues [90].

A growing body of research demonstrates that oxidative damage brought on by ROS promotes the onset of many diseases, including myocardial infarction, cancer, neurological diseases, and inflammation[91]. As a result, the development of various forms of antioxidants for use in medical therapy is of particular scientific interest. Antioxidants are essential for defending living things against excessive ROS[92].

It has been observed that pyrimido-benzimidazole analogues and benzimidazole Schiff bases are inhibitors of lipid peroxidation and lipoxygenase (LOX) (LPO). Each and every one of the evaluated derivatives inhibitedwhereas the majority of them were found to have higher activation than the reference chemical trolox, lipid peroxidation[93]. The most effective compounds were found to be the pyrimidobenzimidazoles (95a), (95e), and (95f), as well as the Schiff bases (94e), (94h), and (94i). Compound (94i), followed by (94f), was identified as a LOX inhibitor within the subset of Schiff bases, whereas compounds (95a) and (95g) were discovered to be the most effective of the 3-oxo-pyrimido[1,2- a]benzimidazole group[94]. The anti-oxidant lipid peroxidation levels (LP assay) and microsomal ethoxyresorufin O-deethylase activity of the produced oxyadiazole-benzimidazole derivatives 96(a,b), (97) were examined (EROD assay). When compared to standard BHT (65%), some of these compounds (96b), (97) had slightly inhibitory effects (28%) on the lipid peroxidation levels at 10-3 M concentrations. The more active compound was determined to be (96a).having an IC50 value of 2.0 10-4 M [95]than caffeine on the EROD assay. Kerimov and colleagues have described the synthesis of benzimidazole derivatives (98, 99) and screened them for their antifungal, EROD, and lipid peroxidation (LP) levels. Compounds 98c (52%), 98e (58%) and (98h) (43%) at 10-3 M concentration were found to significantly lower the liver microsomal LP level in male rats. The microsomal EROD enzyme activity was more effectively reduced by compounds (98c) (100.0%), (98h) (100.0%), (99c) (98.0%), and (99h) (100.0%) than by the targeted inhibitor coffee (85%) [96]. It has been observed that trifluoro benzimidazole derivatives with a 1,2,4-triazole moiety have antioxidant and anti-lipase activity. The best antilipase activity was displayed by compound (101d), which also exhibited very good scavenging activity [97]. Oxadiazole were found to contain a benzimidazole moiety.both synthetic andMicrosomal NADPH-dependent suppression of lipid peroxidation levels (LP), microsomal ethoxyresorufinodeethylase activity (EROD), and DPPH radical scavenger effects were used to assess the antioxidant capabilities of the compounds. The most active chemical among the ones tested was discovered to be [98]Figure 9 depicts the structures of benzimidazole derivatives that act as antioxidants.

6) Antiprotozoal and antitrichinellosis agents-

In developing nations, parasitic illnesses brought on by protozoa continue to be a serious public health issue. Giardia intestinalis and Entamoeba histolytica, the causes of giardiosis and amebiosis, respectively, are two significant intestinal protozoa[99]. The World Health Organization (WHO) estimates that 280 million cases of giardiasis occur each year. It's interesting to note that G. intestinalis is the most frequently identified flagellate in the gastrointestinal system [100]. In order to gain access to new SAR properties that may enable the optimization of benzimidazole derivatives as antiprotozoals, expanding the library of benzimidazole derivatives continues to be of utmost relevance[101].

Trichomonas vaginalis, Entamoeba histolytica, Giardia intestinalis, and Leishmania mexicana were among the protozoan parasites that were tested in vitro using trifluorobenzimidazole derivatives. The first three demonstrated nanomolar activity.test for protozoa. Additionally, the substances were examined in vivo and in vitro against the worm T. spiralis[102]. The best in vitro antiparasitic profile was demonstrated by compound(s) (103a,b) against all parasites. Compounds (103a) exhibit good action against the adult phase in the in vivo model against T. spiralis at 75 mg/kg[94]. Trichinella spiralis larvae were resistant to Trichinella 104(ad) reported bis(benzimidazol-2-yl)amines as antitrichinellosis agents. Compounds 104(a-d) displayed an antitrichinellosis action that was five times stronger than albendazole. Compounds 104(a-d) at oral dosages of 50 and 100 mg/kg mw were 100% efficacious when tested in vivo on the intestinal phase of the T. spiralis[103].

To test their effectiveness against the protozoa T. vaginalis, G. intestinalis, and E. histolytica, sulfanyl-benzimidazole compounds were created. In the nanomolar range, all tested compounds displayed good activity.Compound (105c) was the most effective against G. intestinalis among them and was both more flexible and potent than metronidazole [104]. A range of benzimidazole derivatives have been produced by Pérez-Villanueva et al. and tested for their ability to combat trichinellosis. Particularly compounds 106(a,b), which have trichomonicidal action, showed stronger activity against T. spiralis larvae than any other benzimidazole derivative. In order to create compounds with high activity, the substituents at the 2- and 6-positions are crucial[105]. Linear biphenyl benzimidazole diamidines were produced as a series of antiprotozoal compounds. The compounds have in vitro IC50 values between 3-37 nM against T. brucei rhodesiense, indicating strong activity[106].

These substances demonstrated IC50 values ranging from 0.5 to 23 nM, showing greater activity versus P. falciparum. In the STIB900 model for acute African infection, compounds demonstrated moderate to good in vivo efficacy.Trypanosomiasis Nitazoxanide-benzimidazole hybrids were created and tested in vitro against Entamoeba histolytica, T. vaginalis, and Giardia intestinalis. Against the three protozoa, all the produced compounds were active and shown considerable action, especially against E. histolytica, where the IC50 values ranged between 3-69 nM[107].

With values for all three protozoa less than 87 nM, chemicals (108) and (109) stood out in the overall analysis[108]. Figure 10 depicts the structures of benzimidazole derivatives used as antiprotozoal and antitrichinellosis drugs.

7) Anticancer agents-

One of the main health risks that the vast majority of people worldwide face is cancer. Different anticancer medications described for the treatment of different types of malignancies work through various processes[109]. However, because these drugs don't discriminate between normal and pathological cells, their main adverse effect is cytotoxicity toward normal cells [110]. Several benzimidazole compounds have powerful anticancer effects and are discussed as contemporary anti-tumor medications[111].

The cytotoxic and/or growth-inhibitory properties of 2-arylbenzimidazoles and pyrazino-benzimidazole derivatives were produced and tested in vitro against several cancer cell lines. The anti-cancer action of compounds (110) and (111) is remarkably effective. Compounds containing methoxy or halogen have higher activity levels than substitutes [112]. Benzimidazolesoxothiazolidine (112) and benzimidazoles thioxothiazole 113(a,b), 2-[(4-fluorobenzylidene 114(a,b) and cyclo-alkylidene) cyanomethyl] benzimidazoles 115(a,b), 2-[(4- or 5-oxothiazolidin-2-ylidene, 4-substituted thiazoly The most effective compounds with broad spectrum activity against all three cell lines were the 2-thiazolylbenzimidazole derivative (113a), benzylidene cyanomethylbenzimidazole (114a), and oxothiazolidin-2-ylide-necyanomethylbenzimidazole (118a) [113]. In vitro cytotoxic activity of benzoimidazol-phenylpyrimidine-5-carbonitriles against twelve cancer cell lines was tested after they were created. The most effective synthetic chemical against cervical cancer was 120(a-e) (KB),Leukemia (U937), CNS cancer (SF-268), and melanoma (G 361), in that order [114]. Moriarty et al. described the synthesis, analysis, and evaluation of comparable ring-fused systems, as well as 2-aryl and 2-pyridinyl ring substituted benzimidazolequinones. The best level of selectivity for human cancer cell lines overexpressing reductase enzymes was demonstrated by the most conjugated naphthyl fused system (121a). The resonance stabilisation of the chemically reduced intermediates was responsible for this selectivity. Contrarily, substances with pyridinyl rings and those with 2-aromatic substitutes were more hazardous to normal human fibroblast cell lines (GM00637). In particular, all tested human cell lines were extremely hazardous to 2-naphthyl substituted benzimidazolequinone (121b) (0.04-0.07 M) [115]. The derivatives (122) and (123) and different [1,2-a] alicyclic-ring fused benzimidazolequinones were produced after the aziridinyl substituent was added. When it comes to the later compounds, the aziridinylWhen a quinone analogue (123) or mitomycin C (MMC) towards the PD20i cell line is substituted by a methoxy group, cytotoxicity towards the cell line defective in FANCD2 is reduced [116]The first diazole analogue (125) of MMC, which was later published by the same group, was proven to be much more cytotoxic toward the human breast cancer cell lines MCF-7 and HCC1937 than against the healthy cell line (GM00637)[117]. In contrast to MMC, it has been proposed that the cellular response to aziridine drugs including benzimidazoles may be mediated by distinct mechanisms[118]. Preparing Schiff bases with a benzimidazole substitution allowed researchers to assess how well various human cancer cell lines and healthy human fibroblasts proliferated.

126(a,b) demonstrated the strongest antiproliferative effect and a potent cytotoxic effect among synthetic compounds.micromolar doses had a concentration-dependent impact on the HeLa and MCF-7 cell lines [125]. Anaplastic lymphoma kinase has been specifically and powerfully inhibited by 2-acyliminobenzimidazoles (ALK). When dosed qd, compound (127) significantly reduced tumour size in an NPM-ALK-driven murine tumour xenograft model.(Once every day). In preclinical[119], compounds (127, 128) exhibit excellent potency and PK properties. The efficacy of pyrazole-benzoimidazole-5-carboxylates (129) to inhibit 60 different human tumour cell lines was investigated during their synthesis. With exceptional values in panels of Non-Small Cell Lung Cancer, Melanoma, and Leukemia, Products 129(a,b) displayed the strongest activity against a variety of cancer cell lines, with GI50 ranges of 1.15-7.33 M and 0.167- 7.59 M, respectively. The anticancer activity increases from SAR when 2-oxo-1,2-dihydroquinolin-3-yl is present in the structure[120]. Thiazolylbenzimidazole derivatives were created, and their anticancer effectiveness against the SMMC-7721 and A549 cell lines was tested. The majority of substances demonstrated effective antitumor properties, while substance (130) shown exceptional in vitro anticancer activity comparable to taxol. replacement of the flexible from SARReplace the basic side chain with a phenyl group to slightly reduce cytotoxicity, and replace the 2-diethylamino-ethyl side chain with a hydrophilic cyclohexyl ring to significantly reduce activity against SMMC-7721 and A549 cells. The anticancer efficacy of the amide groups was greatly influenced by their hydrophilic property [121]. Two cancer cell lines—human colorectal cancer cell line HT-29, breast cancer cell line MDA-MB-231, and normal spleen cells—were produced, and their cytotoxic activity was examined. The clearly discernible antiproliferative activity of 131(a,b) and (131c) against the human colorectal cancer cell line HT-29 was determined, and the computed IC50 were respectively 9.26, 0.56, and 0.013 nM[122].

Triazolo-thiadiazole and oxadiazole-containing benzimidazoles (133) were created and assessedits antitumor efficacy in vitro against NCI 60 cell lines The compounds (132a, b), and (133), together, have a wide range of anticancer effects on tumour cell lines. According to SAR, benzimidazoles with an oxadiazole ring exhibit stronger anticancer activity than those with a triazolo-thiadiazole nucleus.

2. BTA derivatives as anticancer agents-

2.1. Fluorinated derivatives of benzothiazole as anticancer agents-

In order to test their anti-tumor properties against cancer cell lines like MDA-MB-468 (mammary gland/breast tissues originating from metastatic location) and MCF-7 (human breast adenocarcinoma), Aiello et al. synthesised fluorinated 2-aryl benzothiazole derivatives. With GI50 values of 0.57 and 0.4 mM against MCF-cell line, respectively, the fluorinated BTA derivatives 1 (3-(5-fluorobenzo[d]thiazol-2-yl)phenol) and 2 (4-(5-fluorobenzo[d]thiazol-2-yl)phenol) displayed the best activity. This is in contrast to BTA derivatives containing alkoxy, methyl sulphonyl, and ethy (Figure 2)[123]. Kumbhare and others afforded the N-bis-benzothiazole and benzothiazolyl thiocarbamide derivatives and screened for cytotoxic activities against two human cell lines U-937 (human macrophage cell line), THP-1 (human leukaemia monocytic cell line) and B16-F10 (mouse melanoma cell line). The thiourea containing benzothiazole derivative 3 (Figure 3) demonstrated the best antiproliferative activity against the U-937 cell line as compared to standard drug Etoposide. The IC50 values of compound 3 were higher (16.23 ± 0.81 mM)), (4847.73 ± 2.39 mM)) and (34.58 ± 1.73 mM)) as compared to standard compound etoposide IC50 values (17.94 ± 0.89), (18.69 ± 0.94) and (2.16 ± 0.11 mM)) against U-937, B16-F10 and THP-1 cell lines respectively.

Benzothiazole-containing mannich base arylimidazo derivatives were synthesised and tested, according to Kumbhare et al for their effectiveness against HepG2, MCF -7, and HeLa cells in combating cancer lines. These synthetic mannich base BTA scaffolds all demonstrated cytotoxicity against all examined cell lines, with the exception of the pyrrolidine-based Imidazo benzothiazole derivative 4 (Figure 3) showed an increase in the levels of caspase-3, one of the distinctive characteristics of apoptosis. The substance 4 shown anti-cancer properties and demonstrated to be superior to other compounds as an antiproliferative agent against the HepG2, MCF-7, and HeLa cell lines when evaluated at Concentrations of 4.0 mM. The addition of a fluorine atom at position 7 of derivative 4 improved, according to the SAR studies. The cytotoxic effects. The compound 4 could possibly result in the treatment for cancer, in particular hepatocaricinoma The BTA scaffold 4's potential for anticancer action is encouraging for the creation of novel anti-cancer therapeutics, which will be a beneficial addition to the arsenal's paclitaxel, Drugs containing cisplatin and doxorubicin[124].

2.2. Imidazole based benzothiazole derivatives as anticancer agents-

Yurttas et al. produced compounds of 2-(4-aminophenyl)BTA that had heterocyclic rings substituted, and they assessed their anticancer effectiveness against 60 human tumour cell lines. Figure 8 shows the BTA derivatives 13 (2-(1H-benzo[d]imidazol-2-ylthio)-N-(4-(benzo[d]thiazol-2-yl)-3- chlorophenyl) acetamide) and 14 (N-(4-(benzo[d]thiazol2-yl)phenyl)-2-(1-phenyl-1H-benzo[d]imidazol-2-yl Tumour cell lines the heterocylic substitutions have an impact on these BTA derivatives' activity and antitumor potential, with derivative 14 having antitumor potential that is comparable to that of standard medications and derivative 13 having less activity than derivative 14. According to the heterocyclic substitution, the overall anticancer potential of 2-(4-aminophenyl) benzothiazole derivatives was benzimidazole imidazole > benzothiazole > benzoxazole[125].

By treating modified anilines with KSCN to get the required benzothiazole derivatives, Singh et al. reported the synthesis of imidazole-based benzothiazoles and evaluated their anticancer properties. Comparing compound 15 (Figure 9) to the reference medication doxorubicin, which has an IC50 value of 10 mM, revealed that it exhibits outstanding anticancer efficacy[126].

2.3. Piperazine based benzothiazole derivatives as anticancer agents-

Al-Soud et al. described the synthesis of BTA derivatives incorporating sulphonamide, piperazino-arylsulfonamide, and arylthiol scaffolds and assessed their anti-proliferative potential against various cell lines, including CCRF-SB (Human Acute B-Lymphoblastic Leukemia), DU-145 (Human Prostate Cancer Cell Lines Express Androgen Receptor), HepG-2 (skin melanoma). The antiproliferative activity of derivative 16 (N-(2-(4-(benzo[d]thiazol-2-yl) piperazin-1-yl)-2-oxoethyl)-4-chloro-benzenesulfonodithioamide) against the human derived DU-145 cell line was shown in Figure 10, whereas derivative 17 (N-(2-(4-(benzo[d]thiazol-2-yl) pipe 8 and 9 mM, respectively, are used (Figure 10). Due to the addition of chloro and dichloro phenyl groups, derivatives 16 and 17 displayed antiproliferative potential, whereas their replacement with hydrogen, methoxy, nitro, trifluoromethyl, and methyl groups resulted in a reduction in the antiproliferative potential of BTA derivatives[127].

Gurdal et al. created BTA compounds with piperazine moieties and tested their cytotoxicity on HUH-7 (Heptacellular), MCF-7 (Breast), and HCT-116 cancer cell lines (Colorectal). All of these derivatives' GI50 values showed that they had good potential against the aforementioned cell lines, but the pyridine-containing derivative 18 (Figure 11) stood out for its remarkable cytotoxic activity, with GI50 values of 7.9 mM, 9.2 mM, and 3.1 mM for the HCT-116, MCF-7, and HUH-7 cell lines, respectively. Hoechst staining and fluorescence activated cell sorting analysis31 were used to confirm that this derivative produced apoptosis during the arrest of the cell cycle at the subG1 phase[128].

2.4. Oxadiazole based benzothiazole derivatives as anticancer agents-

BTA and 1,3,4-oxadiazole-2-thione derivatives were synthesised by Akhtar et al., and their anticancer activity was assessed in vitro against several tumour cell lines. 19 (N-) BTA derivatives (benzo[d]thiazol2-yl) 20 (N-(benzo[d]thiazol-2-yl)-2-(1-(3,4-dichlorophenoxy)ethyl)-5-(1-(2-chlorophenoxy)propyl)-1,3,4-oxadiazol-2-ylthio)acetamide 1,3,4-oxadiazol-2-ylthio) acetamide demonstrated impressive anti-CCRF-CEM (leukaemia) cell line activity. Compounds 19 and 20 have CC50 values that were equivalent to doxorubicin (CC50 14 12 6 2 mM and 8 6 1 mM, respectively). In the hybrid structures of 19 and 20, the bromo moiety was substituted for the chloro moiety, which reduced their anti-tumor efficacy (Figure 12) [129].

2.5. Morpholine-thiourea based benzothiazole derivatives as anticancer agents-

Thiourea-based benzothiazole moiety-based derivatives were synthesised, according to Saeed et al. Using the cancer cell lines MCF-7 and HeLa cells, these novel derivatives were evaluated for their potential to treat cancer. The thiophene-based acetamide benzothiazole derivatives 21 (Figure 13), the morpholine-based thiourea aminobenzothiazole derivative 22 (Figure 13), and the morpholine-based thiourea bromobenzothiazole derivative 23 (Figures 13) were all found to be potent anticancer agents, with IC50 values of 24.15, 26.43, and 18.10 mM against the MCF-7[130].

By treating morpholine with 2-chloroacetyl chloride, Lei et al. produced the morpholine-based acetamide benzothiazole derivative 24 (Figure 14) and investigated its anticancer activity against the HCC (human hepatocellular carcinoma) cell lines HepG2 and Bel7402, reporting an IC50 value for HepG2 and Bel7402 in the millimolar range[131].

2.6. Thiophene based benzothiazole derivatives as anticancer agents-

Racane et al. produced the diamidino substituted compounds of phenyl-BTA based on furyl and thienyl and tested them in vitro for antiproliferative activity against several tumour cell lines. Derivatives 25 and 26 (diamidino- and imidazolinyl-substituted thiophene-based BTA, Figure 15) had minimal cytotoxic effects on healthy human fibroblasts and significant antiproliferative effects on the cancer cell lines MiaPaCa-2 and MCF-7. According to the experimental results, benzothiazole derivatives with thiophene and imidazole substitutions exhibited intriguing antiproliferative properties[132].

2.7. Thiadiazole based benzothiazole derivatives as anticancer agents-

Sekar et al. reported the synthesis and anticancer activities of six noval BTA derivatives. All derivatives exhibited anticancer activities from a high to a moderate activity level with the substituted thiadiazoleflourobenzothiazole 27 (Figure 16) and methoxybenzothiazole 28 (Figure 16) showing the best anti-cancer potential due to the presence of highly electronative and electron denoting pharmacophores (e.g. fluorine and methoxy moieties)[133].

2.8. Substituted pyridine based benzothiazole derivatives as anticancer agents-

Shi et al. created 20 BTA-2-thiol derivatives and tested their anti-tumor effectiveness on a variety of cell lines, including SW480 (colon adenocarcinoma), HeLa, A549, HCT-116, HepG2, and SKRB-3 breast cancer cell line. With IC50 values of 1.2 nM, 4.3 nM, 44 nM, and 48 nM, respectively, against the SKRB-3, SW620, A549, and HepG2 cell lines, the substituted bromopyridine acetamide benzothiazole derivative 29 (Figure 17) demonstrated strong anticancer activity. The mechanism of cell death in HepaG2 cells was apoptosis, which was concentration-dependent. According to these findings, BTA-2-thiols have broad-spectrum anti-cancer properties that merit further study16. According to Xuejiao et al., a substituted pyridine-based acetamide BTA derivative 30 was synthesised and its anti-cancer activity was both in vitro and in vivo evaluated. Derivative 30 showed anti-proliferative properties against a variety of human cell lines and caused HepaG2 cell lines to activate the mitochondrial apoptotic pathway. The BTA scaffold 30 emerged as a promising cancer chemotherapeutic candidate[134].

According to Kamal et al., novel phenyl pyridopyrimidinone-based BTA compounds were created and tested against the ME-180, DU-145, MCF-7, and B-16 cancer cell lines. The IC50 value for the pyridine-containing pyrimidine benzothiazole 31 (Figure 18) against ME-180 (a human cervical cancer cell line) was 4.01 mM, which demonstrated noteworthy cytotoxicity[135].

2.9. Pyrazole based benzothiazole derivatives as anticancer agents-

At a single dose of 10 mM, Gabr et al. reported the creation and testing of new BTA scaffolds against 60 tumour cell lines. The two best derivatives after additional screening at five doses were 32 (Figure 19) and 33 (Figure 19). These compounds showed intriguing anticancer activity against all sixty tumour cell lines at micromolar and submicromolar doses, with GI50 in the low micromolar to submicromolar range. The SAR research showed that both derivatives' anticancer efficacy was greatly improved by the addition of the pyrazole moiety. Additionally, the pyrimidine moiety's inclusion of 2-hydroxy ester and 3-oxopyrazole enhanced both derivatives' anti-tumor properties. Comparatively, simple BTA scafolds with pyrazole functionality were more effective against various cell lines to derivatives with a pyrimidine moiety and a pyrazole ring[136].

2.10. Pyrimidine based benzothiazole derivatives as anticancer agents-

The isoxazole pyrimidine-based BTAs were created by Kambhare et al., who then tested them for anticancer activity using the MTT assay on a variety of cell lines, including A549, Colo205, MCF-7, and U937.

Thiourea-based bromobenzothiazoles based on morpholin cell lines, in contrast to the common medication etoposide. When compared to the standard medicine etoposide, the pyridine-containing pyrimidine derivative 34 (Figure 20) showed good anti-cancer potential with IC50 values of 5.04 mM against colo205, 13.9 mM against U937, 30.67 mM against MCF-7, and 30.45 mM against A549 cell lines. The tumour protein (TP53) or p53 pathways, which control equilibrium, were triggered by the scaffold 34. between cell division and apoptosis. The SAR stated that the methoxy group (-OCH3) in the phenyl40 was what caused the derivative 34 to have the highest level of cytotoxicity against colon cancer cell lines[137].

By refluxing BTAs with bis-methylthio methylene malononitrile, Waghmare et al. created the substituted pyrimidine-containing benzothiazole derivative 35 (Figure 21), which they then investigated for anticancer efficacy against 18 different cell types. With a high percentage of growth inhibition against lung cancer, breast cancer, and kidney cancer cell lines, the scaffold 35 exhibited outstanding anticancer activity. The inclusion of two methyl and one SCH3 group in the structure of derivative 35 accounts for its strong anticancer activity[138].

The anilins created by Caleta et al. were replaced with cyano and amidinobenzothiazoles and then treated with 2-bromo-6-cyanobenzothiazole under specific reaction conditions to produce substances that have been investigated for their anticancer activity against six cancer cell lines, including diploid fibroblasts, laryngeal carcinoma (Hep-2), breast carcinoma (MCF-7), cervical carcinoma (HeLa), pancreatic carcinoma (MiaPaCa-2), colon carcinoma (SW 620), lung carcinoma (H 460), and laryngeal carcinoma (WI 38). The carbonitrile benzothiazole derivative 36 with pyrimidine as the base (Figure 21) demonstrated strong action against all cancer cell lines utilised in the study[139].

2.11. Piperidine based benzothiazole derivatives as anticancer agents-

In order to obtain the desired derivatives, Osmaniye et al. prepared BTA acylhydrazone using 4-fluorobenzaldehyde refluxed with substituted amines. They then investigated their anticancer activities against the rat brain glioma (carcinogenic C6) cell line, the human lung adenocarcinoma epithelial (A549) cell line, the human breast adenocarcinoma (MCF The piperidine-based acetohydrazide derivative 37 (Figure 22) demonstrated mild efficacy with IC50 values of 1 mM, 0.03 mM, 0.10 mM, 0.30 mM, and 1 mM against the reference drug cisplatin[140] for the A549, HT-29, MCF-7, C6, and NIH3T3 cell lines, respectively.

2.12. Secondary sulphonamide benzothiazole derivatives asanticancer agents-

According to Lad et al., a number of methylsulfonyl benzothiazoles were synthesised and evaluated for their anticancer properties using 5-ethoxybenzothiazol-2-amine. The methylsulfonyl benzothiazoles based on nitrophenyl sulphonamide 38 (Figure 23) and ter-butyl sulphonamide 39 (Figure 23) demonstrated the greatest anticancer activities against the HeLa cell line with the IG50 values of 0.22 mM and 0.6 mM, respectively44.By reacting 2-amino-6-nitrobenzothiazole with acetic anhydride, Sadhasivam et al. produced 2, 6-disubstitutedBTA. They next investigated its anticancer efficacy against the cancer cell lines MCF-7, HeLa, and MG63 (human osteosarcoma) With an IC50 of 34.5 mM for MCF-7, 44.15 mM for HeLa, and 36.1 mM for the MG63 tumour cell line, the sulphonamide scaffold-based BTA 40 (Figure 24) demonstrated modest anti-cancer action[141].

Conclusion and future aspects-

From the foregoing talks, it is obvious that the structural benzimidazole ring is significant in medicinal chemistry and that this area of study has been especially busy. For more than a century, benzimidazole and its derivatives have been known.An essential pharmacophore in the development of contemporary drugs is the benzimidazole ring. Numerous noteworthy discoveries have shown that compounds based on benzimidazoles have a wide range of potential applications as therapeutic medicines and diagnostic tools. A significant number of benzimidazole-based compounds, in particular, have recently been developed, marketed, and widely used in the clinic as anticancer, antibacterial, antifungal, anti-inflammatory, analgesic, anti-HIV, anti-oxidant, anticonvulsant, antitubercular, anti-diabetic, antileishmanial, and antihistaminic agents having minimal toxicity, high bioavailability, strong biocompatibility, and curative effects, preventing and treating a variety of disorders. All of these have strongly implied the benzimidazole derivatives' limitless potential in the medical field. Excitingly, in actively ongoing research and development, a growing number of benzimidazole compounds have been developing into clinical therapeutic candidates. All of the benzimidazole scaffold's current pharmacological actions have been covered in this article. Future research on this scaffold may yield more promising outcomes in the field of medicine because it has a wide range of potential molecular targets. This knowledge is expected to lead to the design of better molecules with improved biological properties and higher specificity, along with the development of novelsynthetic methodsFuture research on this scaffold may yield more promising outcomes in the field of molecular targets because it has a wide range of potential applicationsmedical speciality. This knowledge, together with other factors, is expected to lead to the construction of better molecules with improved biological characteristics and higher specificity.creation of innovative synthetic tactics.Benzothiazole is a pharmacophore widely used in medicinal chemistry. This review points out to a growing interest in the development of lead or hybrid structures bearing the BTA moiety as

antiproliferative and anticancer agents. The present work describes the potential of BTA scaffolds in the management of various types of cancers such as ovarian, prostate, central nervous system, renal, gastric, pancreatic, liver, breast and colon cancers. SAR studies reaveled that the anticancer activity of BTA scaffolds depends upon the nature of substituents present in these molecules, being multifactorial and not always easy to rationalise. The plethora of research on the anticancer profile of BTA derivatives mentioned in this review and their rationalisation based on the drug targets of these derivatives, when this was possible, may be useful for the development of novel such agents.

I. ACKNOWLEDGMENT

I would like to expres my gratitude to Dr. Sourabh Kosey, Dr. Akhilesh Patel and the students of Pharm D for giving their precious time and energy to this piece of work.

REFERENCES

1. Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis 773 1995;1:7–15.
2. Kent MM, Yin S. Controlling infectious diseases. Popul Bull 2006; 61: 1–20.
3. Gautam N, Garg A, Bishnoi AK, Agarwal S, Gautam DC. Antioxidant and antimicrobial assessment of synthesized and spectrally characterized new nitrophenothiazines and their sulfone analogues. Phosphorus Sulfur Silicon 778 Relat Elem 2015;190:528–36.
4. Hethcote HW. The mathematics of infectious diseases. SIAM Rev 780 2000;42:599–653.
5. Barker HA, Smyth RD, Weissbach H, Toohey JI, Ladd JN and Volcani BE. Isolation and properties of crystalline cobamide coenzymes containing Benzimidazole or 5,6Dimethylbenzimidazole. Journal of Biological Chemistry. 1960;235(2):480488.
6. Patil A, Ganguly S and Surana S. A systematic review of benzimidazole derivatives as an antiulcer agent. Rasayan J Chem. 2008;1(3):447-460
7. Kubo K, Oda K, Kaneko T, Satoh H and Nohara A. Synthesis of 2-(4Fluoroalkoxy-2-pyridyl) methyl] sulfinyl]-1H-benzimidazoles as Antiulcer Agents. Chem Pharm Bull. 1990;38(10):2853-2858.
8. Uchida M, Chihiro M, Morita S, Yamashita H, Yamasaki K, Kanbe T, Yabuuchi Y and Nakagawz K. Synthesis and Antiulcer Activity of 4Substituted 8-[(2-Benzimidazolyl sulfinylmethyl]-1, hydroquinolines and 4-tetraRelated Compounds. Chem Pharm Bull. 1990;38(6):1575-1586.
9. Grassi A, Ippen J, Bruno M, Thomas G and Bay P. A thiazolylamino benzimidazole derivative with gastroprotective properties in the rat. Eur J Pharmacol. 1991;195(2):251-9.
10. Ozkay Y, Tunali Y, Karaca H. and Isikdag I. Antimicrobial activity and a SAR study of some novel benzimidazole derivatives bearing hydrazones moiety. European Journal of Medicinal 2010;45(8):3293-3298.
11. Yun H, Baogen W, Yang J, Robinson D, Risen L, Ranken R, Blyn L, Eric SS. and Swayze E. 2-Piperidin-4-ylbenzimidazoles with Broad Spectrum antibacterial activities. Bioorg Med Chem Lett. 2003;13:3253-3256.
12. Metwally KA, Abdel-Aziz LM, Lashineel-SM, Husseiny MI and Badawy RH. Hydrazones of 2-aryl--4carboxylic acid hydrazides: synthesis and preliminary evaluation as antimicrobial agents. Bioorg Med Chem. 2006;14(24): 8675-82.
13. Spasov A, Yozhitsa L, Bugaeva I and Anisimova VA. Benzimidazole derivatives: pharmacological toxicological Spectrum activity of and properties. Pharmaceutical Chemistry Journal. 33;5:232-243.
14. Arjmand F, Mohani B and Ahmad S. Synthesis, antibacterial, antifungal activity and interaction of CT-DNA with a new benzimidazole derived Cu (II) complex. Eur J Med Chem. 2005;40(11):1103-1110.
15. Chornous VA, Bratenko MK, Vovk MV and Sidorchuk II. Synthesis and Antimicrobial Activity of Pyrazole-4carboxylic Acid Hydrazides and N-(4Pyrazoyl)hydrazones of Aromatic and Heteroaromatic Aldehydes. Pharmaceutical Chemistry Journal. 2001;35(4):203-205.
16. Rollas S, Gulerman N and Erdeniz H. Synthesis and antimicrobial activity of some new hydrazones of 4fluorobenzoic acid hydrazide and 3acetyl-2,5-disubstituted-1,3,4oxadiazolines. Farmaco. 2002;57:171174.
17. Papakonstantinou GS, Pouli N, Marakos P and Chytyroglou LA. Synthesis antimicrobial and antifungal activity of some new 3-substituted derivatives of 4-(2, 4-dichlorophenyl)5-adamantyl-1H-1,2,4-triazole. Farmaco. 2002;57:973-977.
18. Vicini P, Zani F, Cozzini P and Doytchinova I. Hydrazones of 1, 2benzisothiazole hydrazides: synthesis, antimicrobial activity and QSAR investigations. Eur J Med Chem. 2002;37:553-564.
19. Loncle C, Brunel JM, Dherbomez M, and Letourneux Y. Synthesis and antifungal activity of cholesterolhydrazone derivatives. Eur J Med Chem. 2004;39:1067-1071.

20. Salgın-Goksen U, Gokhan-Kelekci U, Goktas O, Koysal Y, Kılıc E, Isik S, Aktay G and Ozalp M. 1Acylthiosemicarbazides, 1, 2, 4triazole-5(4H)-thiones, 1, thiadiazoles and 3, 4hydrazones containing benzoxazolinones: 5-methyl-2synthesis, analgesic-anti-inflammatory and antimicrobial activities. Bioorg Med Chem. 2007;15:5738-5751.
21. Masunari A and Tavares LC. A new class of synthesis nifuroxazide analogues: of 5-nitrothiophene derivatives with antimicrobial activity against multidrug-resistant Staphylococcus aureus. Bioorg Med Chem. 2007;15:4229-4236.
22. Rajanarendar E, Ramu K, Reddy ASR and Shaik FP. Synthesis and in vitro study of novel isoxazolylbenzoimidazolyl benzamides, acrylamides and propionamides as antimicrobial agents. Ind J Chem. 2008;47:1284.
23. Jubie S, Rajeshkumar R, Yellareddy B, Siddhartha G, Sandeep M, Surendrareddy K, Dushyatha HS AndElango K. Microwave assisted synthesis of some novel Benzimidazole submitted fluoroquinolones and their antimicrobial evaluation. J Pharm Sci and Res. 2010;2(2):69-76.
24. B. Walker, S. Barrett, S. Polasky, V. Galaz, C. Folke, G. Engström, F. Ackerman, K. Arrow, S. Carpenter, K. Chopra, G. Daily, P. Ehrlich, T. Hughes, N. Kautsky, S. Levin, K. G. Mäler, J. Shogren, J. Vincent, T. Xepapadeas, A. de Zeeuw, Environment. Looming global-scale failures and missing institutions. Science 325 (2009) 1345-1346.
25. M.B. Miller, B.L. Bassler, Quorum sensing in bacteria. Annu. Rev. Microbiol. 55 (2001) 165-199.
26. 26.A.K. Bhardwaj, K. Vinothkumar, N. Rajpara, Bacterial quorum sensing inhibitors: attractive alternatives for control of infectious pathogens showing multiple drug resistance. Recent Pat. Antiinfect. Drug Discov. 8 (2013) 68-83.
27. L. Cegelski, G.R. Marshall, G.R. Eldridge, S.J. Hultgren, The biology and future prospects of antivirulence therapies. Nat. Rev. Microbiol. 6 (2008) 17-27.
28. 28.Akhtar J, Khan AA, Ali Z. Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur J Med Chem 2017;5:143–89.
29. Keri SR, Patil RM, Patil AS, Budagumpi S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. Eur J Med Chem 2015; 89:207–51.
30. Gunawardana GP, Koehn FE, Lee AY, et al. Pyridoacridine alkaloids from deep water marine sponges of the family Pachastrellidae: structure revision of dercitin and related compounds and correlation with the Kuanoniamines. J Org Chem 1992;57:1523–6.
31. Jaiswal S, Mishra PA, Srivastava A. The different kinds of reaction involved in synthesis of 2-substituted 2enzothiazole and its derivatives: a review. Res J Pharm Biol Chem Sci 2012;3:631–41.
32. Bryson M, Fulton B, Benfield P. Riluzole a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in amyotrophic lateral sclerosis. Drugs 1996;52:549–63.
33. Venkatesh P, Pandeya NS. Synthesis, characterisation and anti-inflammatory activity of some 2-amino benzothiazole derivatives. Int J ChemTech Res 2009;1:1354–8.
34. Liu Y, Wang Y, Dong G, et.al. Novel benzothiazole derivatives with a broad antifungal spectrum: design, synthesis and structure–activity relationships. Med Chem Commun2013;4:1551–61.
35. Mats ME, Shani BG, Pasternak L, et al. Synthesis and mechanism of hypoglycemic activity of benzothiazole derivatives. J Med Chem 2013;56:5335–50.
36. Bele DS, Singhvi I. Synthesis and analgesic activity of some Mannich bases of 6-substituted-2-aminobenzothiazole. Res J Pharm and Tech 2008;1:22–4.
37. Padalkar SV, Gupta DV, Phatangare RK, et al. Synthesis of novel dipodal-benzimidazole, benzoxazole and benzothiazole from cyanuric chloride: structural, photophysical and antimicrobial studies. J Saudi Chem Soc 2014;18:262–8.
38. Cai J, Sun M, Wu X, et al. Design and synthesis of novel 4- benzothiazole amino quinazolines Dasatinib derivatives as potential anti-tumor agents. Eur J Med Chem 2013;63: 702–12.
39. Delmas F, Avellaneda A, Giorgio DC, et al. Synthesis and antileishmanial activity of (1,3-benzothiazol-2-yl) amino-9- (10H)-acridinone derivatives. Eur J Med Chem 2004;39: 685–90.
40. Munirajasekhar D, Himaja M, Sunil VM. Synthesis and anthelmintic activity of 2-amino-6-substituted benzothiazoles. Int Res J Pharm 2011;2:114–7. Figure 43. Benzothiazoles with potent CA IX inhibitory action84–91. 276 A. IRFAN ET AL.
41. Yadav SP, Devprakash D, Senthilkumar GP. Benzothiazole: different methods of synthesis and diverse biological activities. Int J Pharm Sci Drug Res 2011;3:01–7.

42. Siddiqui N, Rana A, Khan AS, et al. Synthesis of benzothiazole semicarbazones as novel anticonvulsants—the role of hydrophobic domain. Bioorg Med Chem Lett 2007;17: 4178–82.
43. Shi HX, Wang Z, Xia Y, et al. Synthesis and biological evaluation of novel benzothiazole-2-thiol derivatives as potential anticancer agents. Molecules 2012;17:3933–44.
44. Leong CO, Suggitt M, Swaine DJ, et al. In vitro, in vivo, and in silico analyses of the antitumor activity of 2-(4-amino-3- methylphenyl)-5-fluorobenzothiazoles. Mol Cancer Ther 2004;3:1565–75.
45. Mortimer CG, Wells G, Crochard JP, et al. Antitumor benzothiazoles. 26.1 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW 610, NSC 721648), a simple fluorinated 2-arylbenzothiazole, shows potent and selective Inhibitory activity against lung, colon, and breast cancer cell lines. J Med Chem 2006;49:179–85.
46. Baffy G. Hepatocellular carcinoma in type 2 diabetes: more than meets the eye. Am J Gastroenterol 2012;107:53–5.
47. 47.McCutcheon M. Where have my eyebrows gone? Cengage learning. 2019. ISBN 07668393462001;5.
48. Anand P, Kunnumakara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008;25:2097–116.
49. American Cancer Society. Breast Cancer Facts & Figures 2015– 806 2016. Atlanta: American Cancer Society, Inc.; 2015. p. 1–38.
50. Wright JB. The chemistry of the benzimidazoles. Chem Rev 1951;48:397–541.
51. Sridevi CH, Balaji K, Naidu A, Sudhakaran R. Synthesis of some phenylpyrazolo 809 benzimidazolo quinoxaline derivatives as potent antihistaminic agents. E- J 810 Chem (online) 2010;7:234–8.
52. 52 Ranjith PK, Rajeesh P, Haridas KR, Susanta NK, Row TN, Rishikesan R, et al. Design and synthesis of positional isomers of 5 and 6-bromo-1- [(phenyl)sulfonyl]-2-[(4-nitrophenoxy)methyl]-1H-benzimidazoles as possible antimicrobial and antitubercular agents. Bioorg Med Chem Lett 2013;23:5228–34.
53. Arora RK, Kaur N, Bansal Y, Bansal G. Novel coumarin-benzimidazole 817 derivatives as antioxidants and safer anti-inflammatory agents. Acta Pharm 818 Sin B 2014;4:368–75.
54. Pan T, He X, Chen B, Chen H, Geng G, Luo H, et al. Development of 820 benzimidazole derivatives to inhibit HIV-1 replication through protecting 821 APOBEC3G protein. Eur J Med Chem 2015;95:500–13.
55. 55.Vasantha K, Basavarajaswamy G, Rai MV, Boja P, Pai VR, Shruthi N, et al. Rapid 823 'one-pot' synthesis of a novel benzimidazole-5-carboxylate and its hydrazone 824 derivatives as potential anti-inflammatory and antimicrobial agents. Bioorg Med Chem Lett 2015;25:1420–6.
56. Gaba M, Gaba P, Uppal D, Dhingra N, Bahia MS, Silakari O, et al. Benzimidazole derivatives: search for GI-friendly anti-inflammatory analgesic agents. Acta Pharm Sin B 2015;5:337–42.
57. 57 Wen J, Luo Y, Zhang H, Zhao H, Zhou C, Cai G. A green and convenient approach 829 toward benzimidazole derivatives and their antimicrobial activity. Chin Chem 830 Lett 2016;27:391–4.
58. Keri RS, Hiremathad A, Budagumpi S, Nagaraja BM. Comprehensive review in current developments of benzimidazole-based medicinal chemistry. Chem 833 Biol Drug Des 2015;86:19–65. doi: https://doi.org/10.1111/cbdd.12462.
59. Bansal Y, Silakari O. The therapeutic journey of benzimidazoles: a review. Bioorg Med Chem 2012;20:6208–36.
60. Yadav S, Kumar P, Clercq ED, Balzarini J, Pannecouque C, Dewan SK, et al. 4-[1- (Substituted aryl/alkyl carbonyl)-benzoimidazol-2-yl]-benzenesulfonic acids: synthesis, antimicrobial activity, QSAR studies, and antiviral evaluation. Eur J Med Chem 2010;45:5985–97.
61. 61.Al-Tel T. H., Al-Qawasmeh R. A. (2010) Post Groebkee-Blackburn multicomponent Accepted Article This article is protected by copyright. All rights reserved. protocol: Synthesis of new polyfunctional imidazo[1,2-a]pyridine and imidazo[1,2-a] pyrimidine derivatives as potential antimicrobial agents. Eur J Med Chem; 45: 5848-5855
62. Fang B., Zhou C., Rao X. (2010) Synthesis and biological activities of novel aminederived bis-azoles as potential antibacterial and antifungal agents. Eur J Med Chem; 45: 4388-4398.
63. Jubie S., Rajeshkumar R., Yellareddy B., Siddhartha G., Sandeep M., Surendrareddy K., Dushyanth H.S., Elango K. (2010) Microwave assisted synthesis of some novel benzimidazole substituted fluoroquinolones and their antimicrobial evaluation. J Pharm Sci Res; 2: 69-76.

64. Dua R., Sonwane S.K., Srivastava S.K., Srivastava S.D. (2010) Conventional and greener approach for the synthesis of some novel substituted -4-oxothiazolidine and their 5-arylidene derivatives of 2-methyl-benzimidazole:antimicrobial activities. J Chem Pharm Res; 2: 415- 423.
65. Mungra D. C., Patel M. P., Patel R.G. (2011) Microwave-assisted synthesis of some new tetrazolo [1,5-a]quinoline-based benzimidazoles catalyzed by p-TsOH and investigation of their antimicrobial activity. Med Chem Res; 20: 782-789.
66. Mobinikhaledi A., Foroughifar N., Kalhor M., Mirabolfathy M. (2010) Synthesis and Antifungal activity of novel 2-benzimidazolylimino-5-arylidene-4-thiazolidinones. J Heterocyclic Chem; 47: 77-80.
67. Reddy V.A., Reddy K. R. (2010) Synthesis and antimicrobial activity of some novel 4- (1H-benz[d]imidazol-2yl)-1,3-thiazol-2-amines. Chem Pharm Bull; 58: 953-956.
68. Rohini R., Shanker K., Reddy P. M., Ravinder V. (2010) Synthesis and antimicrobial activities of a new class of 6-arylbenzimidazo[1,2-c]quinazolines. J Braz Chem Soc; 2149- 2157.
69. Medzhitov R. (2010) Inflammation 2010: new adventures of an old flame. Cell; 140: 771- 776.
70. Grivennikov S., Greten F. R., Karin M. (2010) Immunity, inflammation, and cancer. Cell; 140: 883-899.
71. Singh P., Mittal A. (2008) Current status of COX-2 inhibitors. Mini Rev Med Chem; 8: 73-90.
72. Achar K.C.S., Hosamani K. M. Seetharamareddy H. R. (2010) In-vivo analgesic and antiinflammatory activities of newly synthesized benzimidazole derivatives. Eur J Med Chem; 45: 2048-2054.
73. Gaba M., Singh D., Singh S., Sharma V., Gaba P. (2010) Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents. Eur J Med Chem; 45: 2245-2249.
74. Sridevi C., Balaji K., Naidu A., Sudhakaran R. (2009) Antioxidant and antiinflammatory activity of some phenylpyrazolobenzimidazoloquinoxaline derivatives. J Pharma Res; 2: 1500-1503.
75. Jesudason E. P., Sridhar S.K., Padma Malar E.J., Shanmugapandiyan P., Inayathullah M., Arul V., Selvaraj D., Jayakumar R. (2009) Synthesis, pharmacological screening, quantum chemical and in vitro permeability studies of N-Mannich bases of benzimidazoles through bovine cornea. Eur J Med Chem; 44: 2307-2312.
76. Shanmugapandiyan P., Denshing K.S., Ilavarasan R., Anbalagan N., Nirmal R. (2010) Synthesis and biological activity of 2-(thiazolidin-4-one) phenyl]-1H-phenylbenzimidazoles and 2-[4-(azetidin-2-One)-3-chloro-4-phenyl]-1H-phenyl benzimidazoles. Inte J Pharm Sci Drug Res; 2: 115-119.
77. El-Nezhawy A. O. H., Biuomy A. R., Hassan F. S., Ismaiel A. K., Omar H. A. (2013) Design, synthesis and pharmacological evaluation of omeprazole-like agents with antiinflammatory activity. Bioorg Med Chem; 21: 1661-1670.
78. Chhajed S. S., Upasani C. D. (2012) Synthesis and in-silico molecular docking simulation of 3-chloro-4-substituted-1-(2-(1H-benzimidazol-2-yl)phenyl))-azetidin-2-ones as novel analgesic anti-inflammatory agent. Arabian J Chem; (In Press) http://dx.doi.org/10.1016/j.arabjc.2012.04.038
79. Chen G., Liu Z., Zhang Y., Shan X., Jiang L., Zhao Y., He W., Feng Z., Yang S., Liang G. (2013) Synthesis and anti-inflammatory evaluation of novel benzimidazole and imidazopyridine derivatives. ACS Med Chem Lett; 4: 69-74.
80. Nava-Aguilera E., Andersson N., Harris E., Mitchell S., Hamel C., Shea B., Lopez-Vidal Y., Villegas-Arrizon A., Morales-Perez A. (2009) Risk factors associated with recent transmission of tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis; 13: 17-26.
81. Kishore N., Mishra B.B., Tripathi V., Tiwari V.K. (2009) Alkaloids as potential antitubercular agents. Fitoterapia; 80: 149-163.
82. Khasnobis S., Escuyer V.E., Chatterjee D. (2002) Emerging therapeutic targets in tuberculosis: post-genomic era. Expert Opin TherTargets; 6: 21-40.
83. Smith P., Moss A. (1994) in: B. Bloom (Ed.), Epidemiology of Tuberculosis. ASM Press;Washington, D.C, p. 47.
84. Shingalapur R.V., Hosamani K.M., Keri R. S. (2009) Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles. Eur J Med Chem; 44: 4244-4248.
85. Gill C.C., Jadhav G., Shaikh M., Kale R., Ghawalkar A., Nagargoje D., Shiradkar M. (2008) Clubbed [1,2,3] triazoles by fluorine benzimidazole: A novel approach to H37Rv inhibitors as a potential treatment for tuberculosis. Bioorg Med Chem Lett; 18: 6244-6247.

86. Jadhav G.R., Shaikh M.U., Kale R.P., Shiradkar M.R., Gill C. H. (2009) SAR study of clubbed [1,2,4]-triazolyl with fluorobenzimidazolesas antimicrobial and antituberculosis agents. Eur J Med Chem; 44: 2930-2935.
87. Pandey J., Tiwari V.K., Verma S.S., Chaturvedi V., Bhatnagar S., Sinha S., Gaikwad A.N., Tripathi R.P. (2009) Synthesis and antitubercular screening of imidazole derivatives. Eur J Med Chem; 44: 3350-3355.
88. Kazimierczuk Z., Andrzejewska M., Kaustova J., Klimesova V. (2005) Synthesis and antimycobacterial activity of 2-substituted halogenobenzimidazoles. Eur J Med Chem; 40: 203-208.
89. Klimesova V., Koc J., Waisser K., Kaustova J. (2002) New benzimidazole derivatives as antimycobacterial agents. IL Farmaco; 57: 259-265.
90. Patel R. V., Patel P. K., Kumari P., Rajani D. P., Chikhalia K. H. (2012) Synthesis of benzimidazolyl-1,3,4-oxadiazol-2ylthio-N-phenyl (benzothiazolyl)acetamides as antibacterial, antifungal and antituberculosis agents. Eur J Med Chem; 53: 41-51.
91. Kumar K., Awasthi D., Lee S., Zanardi I., Ruzsicska B., Knudson S., Tonge P. J., Slayden R.A., Ojima I. (2011) Novel trisubstitutedbenzimidazoles, targeting MtbFtsZ, as a new class ofantitubercularagents. J Med Chem; 54: 374-381.
92. Yoon Y. K., Ali M.A., Wei A. C., Choon T. S., Ismail R. (2013) Synthesis and evaluation of antimycobacterial activity of new benzimidazoleaminoesters. Eur J Med Chem; (In Press) http://dx.doi.org/10.1016/j.ejmech.2013.06.025
93. Pieroni M., Tipparaju S. K.,.Lun S, Song Y., Sturm A. W., Bishai W. R.,. Kozikowski A. P. (2011) Pyrido[1,2-a]benzimidazole-based agents active againsttuberculosis (TB), multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. Chem Med Chem; 6: 334-342.
94. Camacho J., Barazarte A., Gamboa N., Rodrigues J., Rojas R., Vaisberg A., Gilman R., Charris J. (2011) Synthesis and biological evaluation of benzimidazole-5-carbohydrazide derivatives as antimalarial, cytotoxic and antitubercular agents. Bioorg Med Chem; 19: 2023- 2029.
95. Keane W.F., Brenner B.M. (2003) The risk of developing end-stage renal disease in patents with type 2 diabetes and nephropathy: The Renaal study Kidney Int; 63:1499-1507.
96. WHO data obtained from.http://www.who.int/mediacentre/factsheets/fs165/en/.
97. Schmidt D., Loscher W. (2005) Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. Epilepsia; 46: 858-877.
98. Thiry A., Dogne J.M., Supuran C.T., Masereel B. (2007) Carbonic anhy-drase inhibitors as anticonvulsant agents. Curr Top Med Chem; 7: 855-864.
99. Shingalapur R. V., Hosamani K. M, Keri R. S., Hugar M.H. (2010) Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem; 45: 1753-1759.
100. Vijayakumar K., Ahamed A.J. (2010) Synthesis, anti-tumor, anti-diabetic, and antiasthmaticactivitives of some novel benzimidazole derivatives. J Chem Pharm Res; 2: 215-224.
101. Jain P., Sharma P. K, Rajak H., Pawar R.S., Patil U. K., Singour P. (2010) Design, synthesis and biological evaluation of some novel benzimidazole derivatives for their potential anticonvulsant activity. Arch Pharm Res; 33: 971-980.
102. 102.Vinodkumar R., Vaidya S. D., Kumar B. V. S., Bhise U.N., Bhirud S. B., Mashelkar U. C. (2008) Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel Nsubstituted-2-(4-phenylethynyl-phenyl)-1H-benzimidazoles and N-substituted 2[4-(4,4- dimethyl-thiochroman-6-yl-ethynyl)-phenyl)-1H benzimidazoles. Eur J Med Chem; 43: 986- 995.
103. Kwak H. J., Pyun Y. M., Kim J. Y., Pagire H. S., Kim K.Y., Kim K. R., Rhee S. D., Jung W. H. (2013) Synthesis and biological evaluation of aminobenzimidazole derivatives with a phenylcyclohexyl acetic acid group as anti-obesity and anti-diabetic agents. Bioorg Med Chem Lett; 23: 4713-4718.
104. 104.Ushiroda K., Maruta K., Takazawa T., Nagano T., Taiji M., Kohno T., Sato Y., Horai S., Yanagi K., Nagata R. (2011) Synthesis and pharmacological evaluation of novel benzoylazole-based PPAR α/γ activators. Bioorg Med Chem Lett; 21: 1978-1982.
105. Boonstra J., Post J. A. (2004) Molecular events associated with reactive oxygen species and cell cycle progression in mammalian cells. Gene; 337: 1-13.
106. Reuter S., Gupta S. C., Chaturvedi M. M., Aggarwal B. B. (2010) Oxidative stress, inflammation, and cancer: how are they linked? Free Radical Biol Med; 49:1603-1616.

107. Dumont M., Beal M. F. (2011) Neuroprotective strategies involving ROS in Alzheimer disease. Free Radical Biol Med; 51: 1014-1026.
108. Ghouleh I. A., Khoo N. K., Knaus U. G., Griendling K. K., Touyz R. M., Thannickal V. J., Barchowsky A., Nauseef W. M., Kelley E. E., Bauer P. M., Darley-Usmar V., Shiva S., Cifuentes-Pagano E., Freeman B. A., Gladwin M. T., Pagano P. (2011) Oxidases and peroxidases in cardiovascular and lung disease: new concepts in reactive oxygen species signaling. J Free Radical Biol Med; 51: 1271-1288.
109. Zhang Y., Tocchetti C. G., Krieg T., Moens A. L. (2012) Oxidative and nitrosative stress in the maintenance of myocardial function. Free Radical Biol Med; 53:1531-1540.
110. Neochoritis C. G., Zarganes-Tzitzikas T., Tsoleridis C.A., Stephanidou-Stephanatou J., Kontogiorgis C. A., Hadjipavlou-Litina D.J., Choli-Papadopoulou T. (2008) One-pot microwave assisted synthesis under green chemistry conditions, antioxidant screening, and cytotoxicity assessments of benzimidazole Schiff bases and pyrimido[1,2-a]benzimidazol3(4H)-ones. Eur J Med Chem; 43: 986-995.
111. Ayhan-Kılcıgil G., Kus C., Ozdamar E. D., Can-Eke B., Iscan M. (2007) Synthesis and antioxidant capacities of some new benzimidazole derivatives. Arch Pharm Chem Life Sci; 340: 607-611.
112. Kerimov I., Ayhan-Kilcigil G., Can-Eke B., Altanlar N., Iscan M. (2007) Synthesis, antifungal and antioxidant screening of some novel benzimidazole derivatives. J EnzInhib Med Chem; 22: 696-701.
113. Mentes E., Karaali N., Yılmaz F., Ülker S., Kahveci B. (2013) Microwave-assisted synthesis and biological evaluationof some benzimidazolederivativescontaininga 1,2,4- triazol ring. Arch Pharm Chem Life Sci; 346: 556-561.
114. Kerimov I., Ayhan-Kılcıgil G., Ozdama E. D., Can-Eke B., Coban T., Ozbey S., Kazak C. (2012) Design and one-pot and microwave-assisted synthesis of 2-amino/5-aryl-1,3,4- oxadiazoles bearing a benzimidazole moiety as antioxidants. Arch Pharm Chem Life Sci; 345: 549-556.
115. Upcroft P., Upcroft J. A. (2001) Drug targets and mechanisms of resistance in the anaerobic protozoa. Clin Microbiol Rev; 14: 150-164.
116. Marshall M. M., Naumovitz D., Ortega Y., Sterling C. R. (1997) Waterborne protozoan pathogens. Clin Microbiol Rev; 10: 67-85.
117. Hernández-Luis F., Hernández-Campos A., Castillo R., Navarrete-Vázquez G., SoriaArteche O., Hernández-Hernández M., Yépez-Mulia L. (2010) Synthesis and biological activity of 2-(trifluoromethyl)-1H-benzimidazole derivatives against some protozoa and trichinellaspiralis. Eur J Med Chem; 45: 3135-3141.
118. Mavrova A. T., Denkova P., Tsenov Y. A., Anichina K. K., Vutchev D.I. (2007) Synthesis and antitrichinellosis activity of some bis(benzimidazol-2-yl)amines. Bioorg Med Chem; 15: 6291-6297.
119. Pérez-Villanueva J., Hernández-Campos A., Yépez-Mulia L., Méndez-Cuesta C., Méndez-Lucio O., Hernández-Luis F., Castillo R. (2013) Synthesis and antiprotozoal activity of novel 2-{[2-(1H-imidazol-1-yl)ethyl]sulfanyl}-1H-benzimidazole derivatives. Bioorg Med Chem Lett; 23: 4221-4224.
120. Pérez-Villanueva J., Medina-Franco J. L., Caulfield T. R., Hernández-Campos A., Hernández-Luis F., Yépez-Mulia L., Castillo R. (2011) Comparative molecular field analysis (CoMFA) and comparative molecularsimilarity indices analysis (CoMSIA) of some benzimidazole derivativeswithtrichomonicidal activity. Eur J Med Chem; 46: 3499-3508.
121. Ismail M. A., Batista-Parra A., Miao Y., Wilson W. D., Wenzler T., Brun R., Boykin D. W. (2005) Dicationic near-linear biphenyl benzimidazole derivatives as DNA-targeted antiprotozoal agents. Bioorg Med Chem; 13: 6718-6726.
122. Ismail M. A., Brun R., Wenzler T., Tanious F. A., Wilson W. D., Boykin D. W. (2004) Dicationic biphenyl benzimidazole derivatives as antiprotozoal agents. Bioorg Med Chem; 12: 5405-5413.
123. 123 Soria-Arteche O., Hernández-Campos A., Yépez-Mulia L., Trejo-Soto P. J., HernándezLuis F., Gres-Molina J., Maldonado L. A., Castillo R. (2013) Synthesis and antiprotozoal activity of nitazoxanide-N-methylbenzimidazole hybrids. Bioorg Med Chem; 23: 6838-6841.

124. Cai S.X. (2007) Small molecule vascular disrupting agents: potential new drugs for cancer treatment. Recent Pat Anti-cancer Drug Discov; 2: 79-101.
125. Shi L.M., Fan Y., Lee J.K., Waltham M., Andrews D.T., Scherf U., Paull K.D.,Weinstein J.N. (2000) Mining and visualizing large anticancer drug discovery databases. J Chem Inf Comput Sci; 40: 367-379.
126. Monks A., Scudiero D., Skehan P., Shoemaker R., Paull K., Vistica D., Hose C.,Langley J., Cronise P., Wolff V.A., Goodrich M.G., Campbell H., Mayo J., Boyd M.J. (1991) Feasibility of a high-flux anticancer drug screen using a diverse panel of cultured human tumor cell lines. Natl. Cancer Inst; 83: 757-766.
127. Demirayak S., Kayagil I., Yurttas L. (2011) Microwave supported synthesis of some novel 1,3-Diarylpyrazino[1,2-a]benzimidazole derivatives and investigation of their anticancer activities. Eur J Med Chem; 46:411-416.
128. Refaat H. M. (2010) Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. Eur J Med Chem; 45: 2949-2956.
129. Abdel-Mohsen H.T., Ragab F.A.F., Ramla M. M., El Diwani H. I. (2010) Novel benzimidazole-pyrimidine conjugates as potent antitumor agents. Eur J Med Chem; 45: 2336- 2344.
130. Moriarty E., Carr M., Bonham S., Carty M. P., Aldabbagh F. (2010) Synthesis and toxicity towards normal and cancer cell lines of benzimidazolequinones containing fused aromatic rings and 2-aromatic ring substituents. Eur J Med Chem; 45: 3762-3769.
131. 123. Fahey K., O'Donovan L., Carr M., Carty M. P., Aldabbagh F. (2010) The influence of the aziridinyl substituent of benzimidazoles and benzimidazolequinones on toxicity towards normal and Fanconi anaemia cells. Eur J Med Chem; 45: 1873-1879.
132. 124. a) O'Donovan, Carty M.P., Aldabbagh F. (2008) First synthesis of N-[(aziridin-2-yl)methyl]benzimidazolequinone and analysis of toxicity towards normal and Fanconi anemia cells. Chem Comm; 43: 5592-5594. b) Bonham S., O'Donovan L., Carty M. P., Aldabbagh F. (2011) First synthesis of an aziridinyl fused pyrrolo[1,2-a]benzimidazole and toxicity evaluation towards normal and breast cancer cell lines. Org Biomol Chem; 9: 6700-6706.
133. 125. Hranjec M., Starcevic K., Pavelic S. K., Lucin P., Pavelic K., Zamola G. K. (2011) Synthesis, spectroscopic characterization and antiproliferative evaluation in vitroof novel Schiff bases related to benzimidazoles. Eur J Med Chem; 46: 2274-2279.
134. 126. Lewis R. T., Bode C. M., Choquette D. M., Potashman M., Romero K., Stellwagen J. C., Teffera Y., Moore E., Whittington D. A., Chen H., Epstein L. F., Emkey R., Andrews P. S., Yu V. L., Saffran D. C., Xu M., Drew A., Merkel P., Szilvassy S., Brake R. L. (2012) The discovery and optimization of a novel class of potent, selective, and orally bioavailable anaplastic Lymphoma Kinase (ALK) inhibitors with potential utility for the treatment of cancer. J Med Chem; 55: 6523-6540.
135. 127. Abonia R., Cortés E., Insuasty B., Quiroga J., Nogueras M., Cobo J. (2011) Synthesis of novel 1,2,5-trisubstituted benzimidazoles as potentialantitumor agents. Eur J Med Chem; 46: 4062-4070.
136. 128. Luo Y., Xiao F., Qian S., Lu W., Yang B. (2011) Synthesis and in vitro cytotoxic evaluation of some thiazolylbenzimidazole derivatives. Eur J Med Chem; 46:417-422.
137. 129. Mavrova A. T., Wesselinova D., Vassilev N., Tsenov J. A. (2011) Synthesis, characterization and cytotoxicity of some novel 1,3-disubstituted-2,3-dihydro-2-iminobenzimidazoles. Eur J Med Chem; 46: 3362-3367.
138. 130Kumbhare MR, Dadmal T, Kosurkar U, et al. Synthesis and cytotoxic evaluation of thiourea and N-bis-benzothiazolederivatives: a novel class of cytotoxic agents. Bioorg Med Chem Lett 2012; 22:453–5.
139. 131. Kumbhare MR, Kumar VK, Ramaiah JM, et al. Synthesis and biological evaluation of novel Mannich bases of 2-arylimidazo[2,1- b]benzothi azoles as potential anti-cancer agents. Eur J Med Chem 2011;46:4258–66.
140. 132Kumbhare MR, Dadmal LT, Devi AT, et al. Isoxazole derivatives of 6-fluoro-N-(6-methoxybenzo[d]thiazol-2-yl)benzo[d]- thiazol-2-amine and N-(pyrimidin-2-yl)benzo[d]thiazol2-amine: regulation of cell cycle and apoptosis by p53 activation via mitochondrial-dependent pathways. Med Chem Commun2014;5:1744.

141. 133.Yurttas L, Tay F, Demirayak S. Synthesis and antitumor activity evaluation of new 2-(4-aminophenyl) benzothiazole derivatives bearing different heterocyclic rings. J Enzyme Inhib Med Chem 2014;30:458–65.
142. 134.Singh Y, Kaur B, Kaur A, et al. spectral studies and biological activity of 2, 3-disubstituted imidazo [2, 1-b] benzothiazole derivatives. Indian J Pharmaceut Biol Res 2018;6: 1–8.
143. 135.Al-Soud AY, Al-Sa'doni HH, Saeed B, et al. Synthesis and in vitro anti-proliferative activity of new benzothiazole derivatives. ARKIVOC 2008;2008:225–238.
144. 136.Gurdal EE, Durmaz I, Atalay CR, Yarim M. Cytotoxic activities of some benzothiazole-piperazine derivatives. J Enzyme Inhib Med Chem 2015;30:649–54.
145. 137.Akhtar T, Hameed S, Al-Masoudi AN, et al. In vitro antitumor and antiviral activities of new benzothiazole and 1,3,4- oxadiazole-2-thione derivatives. Acta Pharm 2008;58: 135–49.
146. 138.Saeed S, Rashid N, Jones GP, et al. Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents. Eur J Med Chem 2010;45:1323–31.
147. 139.Lei Q, Zhang L, Xia Y, et al. A novel benzothiazole derivative SKLB826 inhibits human hepatocellular carcinoma growth via inducing G2/M phase arrest and apoptosis. RSC Adv 2015;5:41341.
148. 140.Racane L, Kulenovic TV, Pavelic KS, et al. Novel diamidinosubstituted derivatives of phenyl benzothiazolyl and dibenzothiazolyl furans and thiophenes: synthesis, antiproliferative and DNA binding properties. J Med Chem 2010;53:2418–32.
149. 141.Sekar V, Perumal P, Arunachalam ,Gandhimathi S. Screening of anticancer activity in newly synthesized benzothiazole derivatives. J Pharm Sci Res 2011;3:1520–4.