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Review article

The synthetic approach of benzimidazole derivatives as anti-inflammatory agents

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ABSTRACT

Anti-inflammatory drugs are a ubiquitous class of analgesics used by millions of people worldwide. Owing to the widespread and prolonged use of Anti-inflammatory drugs, chronic and acute toxicities have been reported in many human physiological systems. As a result, new anti-inflammatory drugs have been created recently, and several of them are in advanced phases of clinical studies. Chemists have been quite interested in heterocyclic compounds because of how similar they are to various biological precursors. One such heterocycle is benzimidazole and the most recent advancements of anti-inflammatory agents bearing benzimidazole have been emphasized in the current review. The review focusses on the synthetic route and the most promising benzimidazole derivative as anti-inflammatory agent. The lead compound according to the literature will aid in the design and development of novel anti-inflammatory agents that targets a diversity of factors contributing to inflammation.

Keywords: Benzimidazole, Anti-inflammatory, Pharmacological activity.

INTRODUCTION

The heterocyclic compounds form the basis for almost 70 to 80% of the drugs that are in clinical trials. Among the enormous variety of heterocyclics containing nitrogen, oxygen or sulphur, nitrogen containing heterocycles like pyrazoles [1,2], imidazole [3], indole [4], pyrimidine[5], benzimidazoles [6] are of major interest. Benzimidazole, a bicyclic compound bearing benzene fused with imidazole have been found to be the important structures in the field of drug discovery exhibiting various activities like anti-inflammatory[7], antihistaminic[8], anti-fungal[9], antiviral[10], antipsychotic[11], anti- cancer[12], antimicrobial[13]. Drugs possessing benzimidazole nucleus for various pharmacological activities available in market are represented in "Figure 1". In spite of its wide range of biological activities, benzimidazole scaffold has emerged as a pharmacophore of choice for designing anti-inflammatory agents. In order to promote the upcoming research for the synthesis of various substituted benzimidazole compounds as anti-inflammatory agents, the most recent data in this promising field are considered. This review presents the published reports on this versatile core to help in designing and synthesizing benzimidazole derivatives as anti-inflammatory agents and also to provide an insight so that various synthetic procedures and its full therapeutic potential can be employed in the treatment of pain and inflammation [14–19].

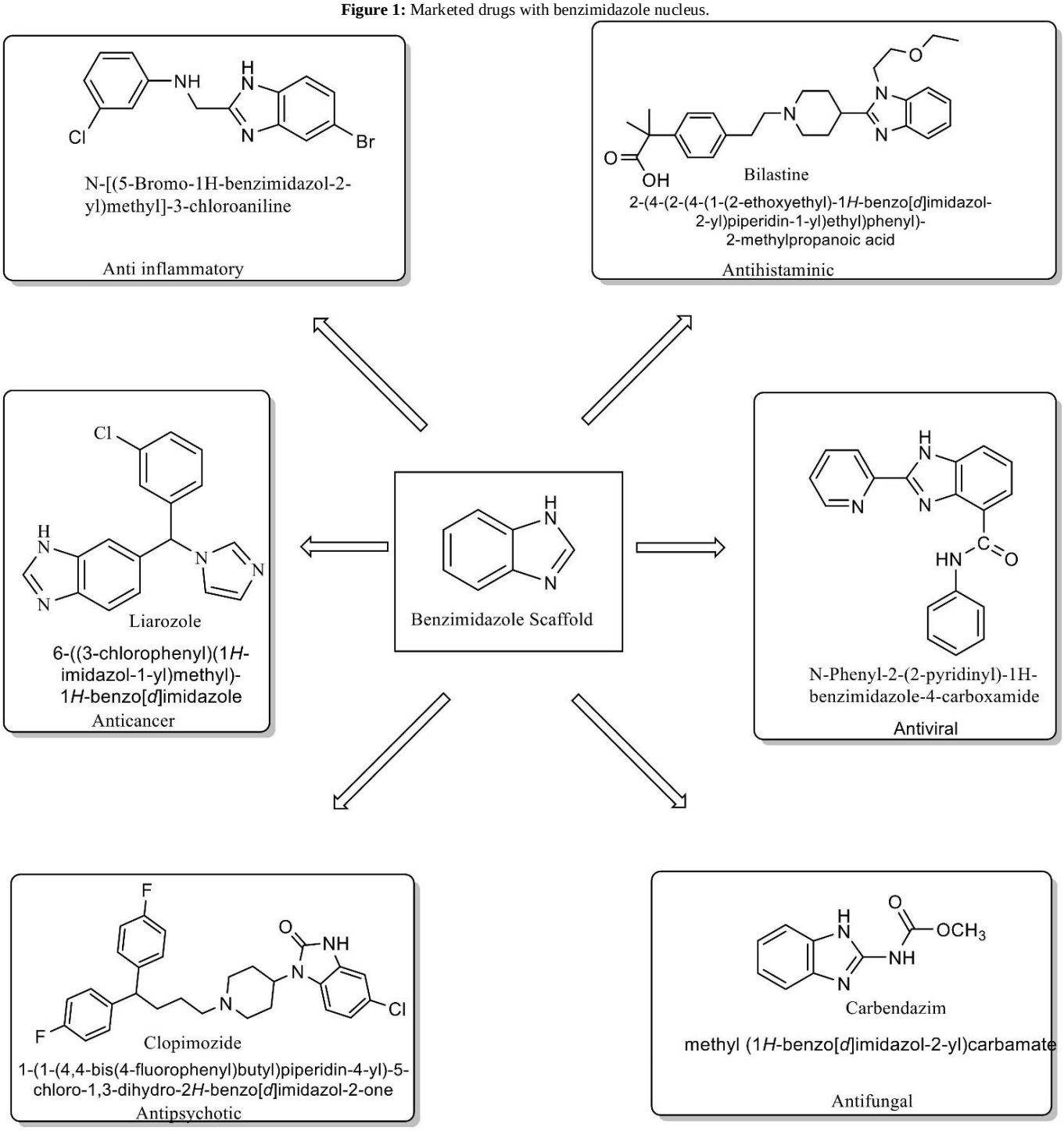
The use of steroidal inflammatory agents has severe side effects hence non-steroidal anti-inflammatory agents have been suggested to overcome these side effects. The goal of the review is to focus on the various synthetic procedures of the lead compound developed as anti-inflammatory agents.

Recent developments in the synthesis of benzimidazole derivatives as anti-inflammatory agents

Sondhi et al., reported tricyclic and tetracyclic benzimidazole derivative series as anti- inflammatory and anti-cancer agents. Among the series, 8 tricyclic and 7 tetracyclic compounds were prepared by the multi component reaction using homophthalic, 2,3-pyrazine dicarboxylic acid and succinic acid with substituted diamines using microwave irradiation technique. Of the 15 benzimidazole derivatives,

only compound 6,7-dimethyl-2,3-dihydro-1H-benzo[d] pyrrolo[1,2-a]imidazol-1-one (1a) and 8-hydroxy-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazol-1-one (1b) with dimethyl and hydroxy substitutions at benzimidazole showed better anti-inflammatory activity of 39% inhibition at 50 mg/kg po as that of the standard ibuprofen using carrageenan induced paw oedema assay, than the compounds substituted with electron withdrawing groups like halogen, cyano and nitro substitutions[20].

Figure 1: Marketed drugs with benzimidazole nucleus.



Inflammare a Latin word indicates inflammation, when the body is exposed to hazardous stimuli, such as infections or any kind of irritation, the immune system starts working right away. Multiple biochemical processes are involved in inflammatory reactions and they are an attempt by the body to defend itself and treat infections, however if inflammation if unchecked, it can lead to a number of acute, chronic, and systemic inflammatory disorders. Other than the three main signs of inflammation like redness, swelling and pain several other diseases like periodontal disease, autoimmune diseases, and cardiovascular disease, Chronic obstructive pulmonary disease, asthma, diabetes, and Alzheimer's disease are related to chronic inflammation.

Hosamani et al., reported anti-inflammatory agents of around

eleven molecules of 2-methylamino benzimidazole derivatives. On reacting chloromethyl-benzimidazole derivatives with 1° aromatic amines, the target molecules were synthesized. Among the series N-[1H-benzimidazol-2-ylmethyl] aniline (2a) and N-[1H-benzimidazol-2-ylmethyl]-3-chloroaniline (2b) were found to be active against carrageenan induced paw oedema in rats with 38.8% and 44.4% inhibition when compared with 44.4% inhibition of standard drug Nimesulide. The overall study suggests that the unsubstituted benzimidazoles and chloro substituted in aniline ring at the meta position have shown potent anti-inflammatory activity when compared with benzimidazole bearing substitutions such as bromo, methyl, methoxy and nitro[21].

Gaba et al., 2010 reported substituted phenylsulfonyl methyl benzimidazole derivatives as analgesic and anti-inflammatory agents. Nearly 12 molecules were synthesized by refluxing 2-Methyl-1-[phenylsulfonyl]-benzimidazol-5-amine with substituted aryl and alkyl halides. Compound N1-(2-methyl-1-(phenylsulfonyl)-1H-benzo[d]imidazol-5-yl)benzene-1,4-diamine (3) with p-amino phenyl substitution on the benzimidazole ring exhibited 39.7% inhibition against carrageenan induced rat paw edema method compared with 43.3% inhibition of standard Indomethacin. Compounds with nitro or chloro substitution did not influence the activity. The study also suggests that $–NH_2$ substitution in compounds may lead to decreased oxidative stress[22].

Rao et al., 2012 evaluated anti-inflammatory activity of six substituted benzimidazole derivatives, which were synthesized on reaction of benzimidazole with ethyl 4- [substituted benzylidene amino] benzoate or with 2-chloroacetamido-5-phenyl-oxadiazole. Similarly, benzoimidazolyl 5-heterocylic oxadiazole-2-ylthio ethenone derivatives were synthesized on reaction of benzimidazole with various heterocyclics. On evaluating these compounds for the anti-inflammatory activity by *in vivo* method using carrageenan, the outcomes proved that oxadiazole ring bearing phenyl or pyridyl substitution compound 1-(1H-benzo[d]imidazol-1-yl)-2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)ethan-1-one (4a) and 1-(1H-benzo[d]imidazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one (4b) fused to benzimidazole moiety through thioacetamide linkage have been proved to have effective anti-inflammatory properties with 63.35% inhibition against 68.94 % inhibition of standard Diclofenac. Hence this can be considered as the pharmacophore of anti-inflammatory agent[23].

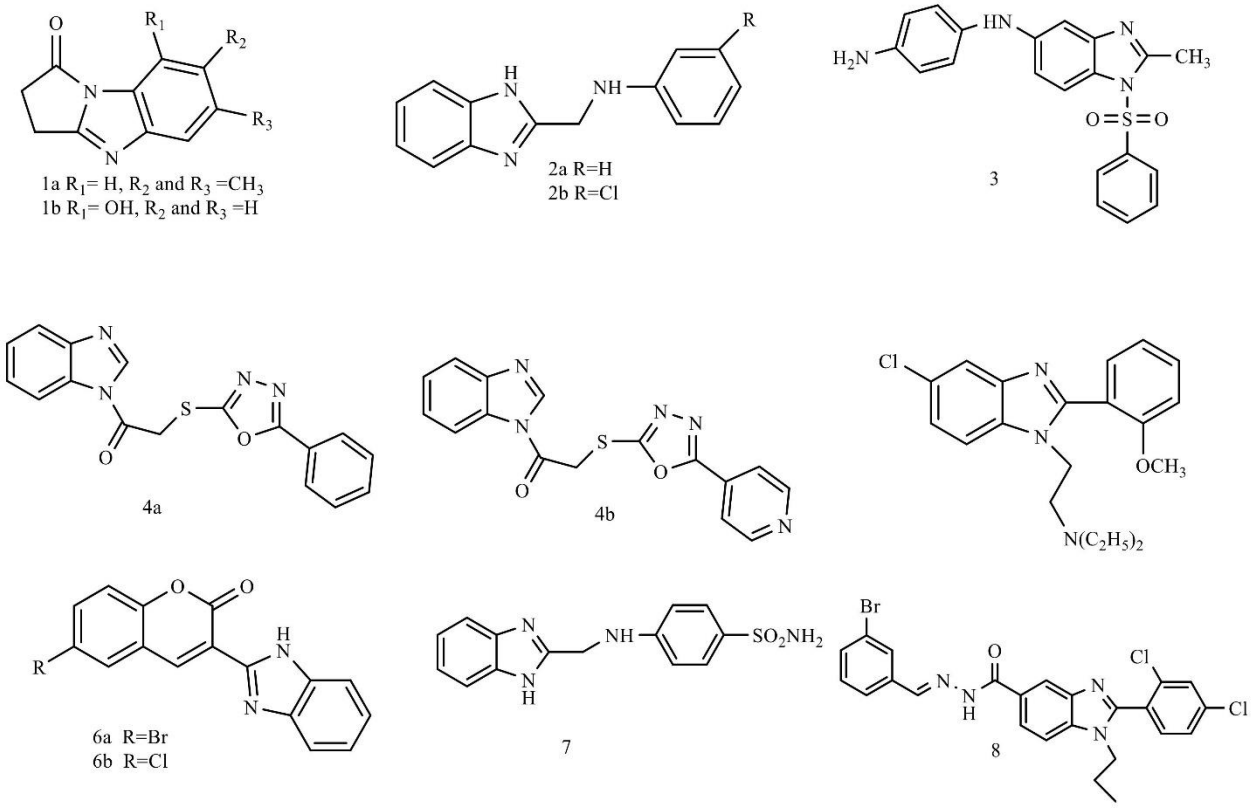
Chen et al., 2012 reported nine benzimidazole derivatives that are synthesized by treating amines in dimethylformamide with 1,4-dichloro-2-nitrobenzene, followed by reaction with various aldehydes in sodium hyposulfite medium. Among the series the benzimidazole substituted with methoxy benzaldehyde and diethyl amine compound 2-(5-chloro-2-(2-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)-N,N-diethylethan-1-amine (5) exhibited 50 to 65% inhibition indicating the molecular polarizability and electronegativity of benzimidazole derivatives finds a significant role in the anti-inflammatory activity[24].

Bansal et al., 2014 reported coumarin coupled with benzimidazole derivatives as safer anti- inflammatory agents. Two series of coumarin–benzimidazole derivatives five in each were synthesized from malonic acid, different salicylaldehyde's and o-phenylene diamine and on coupling this with 2-amino benzimidazole. Anti-inflammatory activity was performed in rats using formalin induced oedema revealed that, among the series benzimidazo chromoenone derivatives with electron withdrawing group bromo and chloro 3-(1H-benzo[d]imidazol-2-yl)-6-bromo-2H-chromen-2-one (6a) 3-(1H-benzo[d]imidazol-2-yl)-6-chloro-2H-chromen-2-one and (6b) substitutions displayed good anti-inflammatory of 45.45% and 46.75% inhibition than with benzimidazo chromen 3-carboxamide derivatives using indomethacin as standard which exhibited 54.54%inhibition. Coumarin-benzimidazole derivatives with amide linkage exhibited decreased anti-inflammatory activity[25].

Mariappan et al., prepared a series of ten 2-substituted derivatives of benzimidazole tested for anti-inflammatory properties. Substituted primary aromatic amines with 2-chloro methyl benzimidazole were used for the synthesis and among the series compound 4-(((1H-benzo[d]imidazol-2-yl)methyl) amino) benzene sulfonamide (7) which is amino benzene sulphonamide substituted benzimidazole showed 64% inhibition, when compared with 64% inhibition of the standard diclofenac sodium using carrageenan induced rat paw edema. Benzimidazole with halo or nitro substituted amines showed moderate anti-inflammatory activity[26].

Vasantha et al., reported the benzimidazole-5-carboxylate and its hydrazone derivatives synthesized by one pot and tested these compounds for anti- inflammatory activity. Series of 17 benzimidazole-5-carbohydrazides having different substitutions on the part of the arylidene were synthesized by a simple one-pot reaction by nitro reductive cyclization. Among the series, bromo substituted (E)-N'-(3-bromobenzylidene)-2-(2,4-dichlorophenyl)-1-propyl-1H-benzo[d]imidazole-5-carbohydrazide (8) at 3rd position displayed a high level of inhibition of carrageenan-induced paw edema at 72.11% compared to 69.34% of indomethacin. The study indicated that compounds with halogen substitution were found to play a most important role than methoxy or nitro groups in enhancing the anti-inflammatory activity. Compounds with bulkier bromine atom favored for the better anti- inflammatory activity than fluorine or chlorine atoms[27]. Structures of the various benzimidazole derivatives possessing potent anti-inflammatory activity are given in "Figure 2".

Figure 2: Structures of synthesized benzimidazole derivatives showing good anti-inflammatory activity



Gaba et al., reported a series of nine phenylsulfonyl-2-methylamino-substituted-benzimidazole derivatives as anti-inflammatory agents and synthesized those compounds from o-phenylene diamine, benzene sulfonyl chloride and different substituted aryl amines. Among the series 3,4-dimethyl substituted benzamine compound 3,4-dimethyl-N-((1-(phenylsulfonyl)-1H-benzo[d]imidazol-2-yl)methyl)aniline (9) on the benzimidazole nucleus exhibited encouraging anti-inflammatory activity with 37.31% inhibition against Carrageenan induced paw edema in rats using Indomethacin as standard which showed 47.76% inhibition. The study indicated that modification of the chemical moiety in the existing Non-steroidal anti-inflammatory drugs (NSAID) by substitutions with electron donating groups will lead to molecules with potent GI-safe NSAIDs[28].

Gaba et al., reported the tri-substituted Benzimidazole derivatives as gastroprotective anti- inflammatory agents. A series of nine, tri-substituted benzimidazole derivatives were synthesized from different substituted aryl amines, potassium iodide and potassium hydroxide under reflux. Among the series methyl benzamine substituted on 5-methoxy benzimidazole compound N-((5-methoxy-1-(phenylsulfonyl)-1H-benzo[d]imidazol-2-yl)methyl)-2-methylaniline (10) showed 46.27% reduction in edema as compared with 47.76% of standard Indomethacin against carrageenan-induced paw edema model. This indicates that 1, 2, 5-substituted benzimidazole derivatives could serve as a lead compound with gastroprotective ability to develop novel orally active potent molecules as anti- inflammatory agents in the future research[29].

Kale et al., reported the Tetrazolo benzimidazoles as novel anti- inflammatory agents. A newer series of benzimidazole linked tetrazole compound was synthesized by cyclization of benzimidazol-2-ylsulfanyl propane nitrile in presence of sodium azide and the resulting treated with acid chlorides to yield the compound. Among the series, compounds 2-(5-(2-((1H-benzo[d]imidazol-2-yl)thio)ethyl)-2H-tetrazol-2-yl)acetaldehyde, 2-(5-(2-((1H-benzo[d]imidazol-2-yl)thio)ethyl)-2H-tetrazol-2-yl) benzaldehyde, 2-(5-(2-((5-methoxy-1H-benzo[d]imidazol-2-yl)thio)ethyl)-2H-tetrazol-2-yl)acetaldehyde (11a,11b,11c) containing benzoyl, acetyl, and benzyl moieties at N-1 of tetrazole exhibited anti- inflammatory activities with less gastric ulceration when compared with standard diclofenac[30].

Bukhari et al., reported the synthesis of new series benzimidazole derivatives as anti- inflammatory agents. A series of 35 compounds have been synthesized by two different routes that are coupling and direct coupling reaction of diamine with carboxylic acid by utilizing 1,2,3-triazolo pyridinium 3-oxid hexafluorophosphate and 1,1´-carbonyldiimidazole respectively. Among the series, it was observed that compounds with cyano phenyl, pyridinyl phenyl at R_5 and compounds having 3- and 4- acetamido pyridinyl phenyl and acetamido biphenyl compounds 2-(4-cyanophenyl)-6-methyl-1H-benzimidazole-4-carboxamide, 2-(4-(pyridin-2-yl)phenyl)-1H-benzimidazole-4-car-

boxamide, 2-(4'-acetamido-[1,1'-biphenyl]-4-yl)-1H-benzo[d] imidazole -4-carboxamide, 2-(4-(6-acetamidopyridin-3-yl)phenyl)-1H-benz-imidazole-4-carboxamide, and 2-(4'-acetamido-[1,1'-biphenyl]-4-yl)-6-methyl-1H-benzimidazole-4-carboxylic acid (12a,12b,12c, 12d and 12e) substitutions at R_5 attached to benzimidazole showed very strong LOX, COX, TNF-α inhibition and exhibited IC_{50} of 6.79, 7.12, 5.52, 4.13 and 4.99μM than compounds with other heterocyclic substitutions on the benzimidazole nucleus. Derivatives with amino, methyl, and heterocyclic substitutions have shown improved COX-2 inhibition [31].

Ravindernatha et al., reported the anti-inflammatory activity for the synthesized denser functionalized benzo imidazolyl tetrahydropyridine carboxylates. A series of 15 compounds were synthesized by one pot multi- component reaction of benzylidene amino benzoimidazole-2-thiol, 5-amino-2-mercapto-benzimidazole, aromatic aldehyde, and ethyl acetoacetate in acetonitrile using a Lewis acid catalyst CAN (ceric ammonium nitrate). Among the series, phenyl and 4-methylphenyl substituted benzo[d]imidazolyl tetrahydropyridine carboxylates derivative ethyl 1-(2-mercapto-1H-benzo[d]imidazol-5-yl)-4-((2-mercapto-1H-benzo[d]imidazol-5-yl)amino)-2-phenyl-6-(p-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (13) exhibited good anti- inflammatory activity against carrageenan-induced paw edema than the reference drug Diclofenac sodium[32].

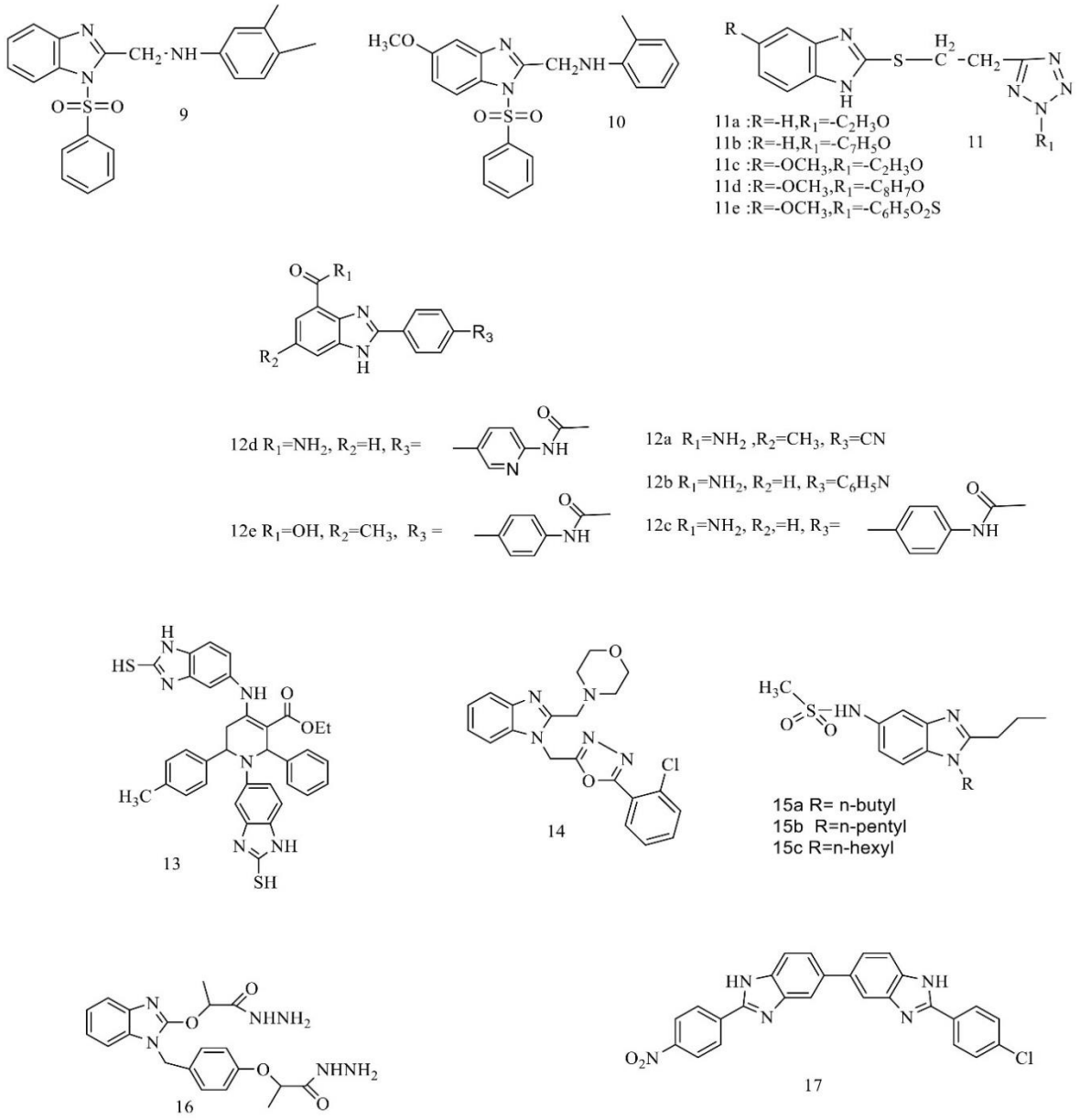
Yar et al., synthesized benzimidazole derivatives with oxadiazole and morpholine rings and reported the i*n vivo* anti-inflammatory activity along with the docking study. A series of eighteen 5-substituted-1,3,4-oxadiazol-2-yl methyl-2-morpholinomethyl-benzimidazoles were synthesized using 2-morpholinomethyl-benzimidazole, anyhydrous K_2CO_3, hydrazine hydrate, substituted carboxylic acids, under reflux. Among the series, 2-chloro phenyl substituted compound 4-((1-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methyl)morpholine (14) showed better anti-inflammatory activity against carrageenan induced rat paw edema with maximum inhibition of 74.17% against the standard indomethacin which showed 57.79% inhibition and with reduced lipid peroxidation and ulcerogenic profile against standard Indomethacin. The benzimidazole derivatives also exhibited significant COX-2 inhibition with IC_{50} values of 8.00μM. The study indicates that the introduction of chloro, methoxy and nitro substituent at the ortho position of phenyl ring leads to significant increase in the activity and alkyl chain at the fifth position of oxadiazole ring have shown the least anti-inflammatory activity. Molecular docking using Auto dock studies proved that oxadiazole and morpholine rings that are linked to the benzimidazole nucleus were responsible for the good binding with the COX-2[33].

Bali et al., 2017 reported methane sulphonamido-benzimidazole derivatives as gastro-sparing anti-inflammatory agents with antioxidant effect. Eleven, derivatives of methane sulphonamido benzimidazole were synthesized on reaction of o-phenylene diamine with n-butyric acid under reflux. Among the series butyl, pentyl and hexyl derivatives N-(1-butyl-2-propyl-1H-benzo[d]imidazol-5-yl) methanesulfonamide, N-(1-pentyl-2-propyl-1H-benzo[d]imidazol-5-yl) methanesulfonamide, N-(1-hexyl-2-propyl-1H-benzo[d]imidazol-5-yl) methanesulfonamide (15a,15b and 15c) of benzoimidazolyl methane sulfonamides showed reduction in edema in the range of 92.73, 95.64 and 97.62% respectively against the standard drugs rofecoxib and indomethacin with 78.95% and 75% against carrageenan induced rat paw edema model. The studies indicates that the effect of the methane sulphonyl group supersedes the effect of N-alkyl substituent and were non-ulcerogenic at the test dose[34].

Ayyad et al., reported the synthesis and assessed for anti-inflammatory activity of some new benzimidazole derivative. A novel series of 12 compounds of 1 and 2-substituted benzimidazoles were synthesized using phenylenediamine with p-hydroxybenzaldehyde along with alkyl halides, methyl 2-chloropropanoate, chloroacetate derivatives, hydrazines and various benzaldehydes under reflux. *In vivo* anti-inflammatory activity evaluation of compound 2-(4-((2-((1-hydrazineyl-1-oxopropan-2-yl)oxy)-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)propanehydrazide (16) with di phenoxy propane hydrazide on the benzimidazole exhibited significant anti-inflammatory and when compared with the standard indomethacin. Also, this benzimidazole derivative did not cause any gastric mucosal lesion which was proved by the ulcer index of 0.72[35].

Appani et al., reported the synthesis of anti-inflammatory activity of some new Benzimidazole and Bis-Benzimidazole derivatives. A series of 12 compounds were synthesized by one-pot reaction of aryl aldehyde with phenylenediamines using Cu (II) MCM 41(Mobil Composition of Matter No. 41) as catalyst with stirring at room temperature. Among the series all the compounds exhibited significant activity and the compound 2-(4-chlorophenyl)-2'-(4-nitrophenyl)-1H,1'H-5,5'-bibenzo[d]imidazole (17) has most potent anti-inflammatory activity with 61.87% inhibition than the other compounds against carrageenan induced paw oedema method using Indomethacin(10mg/kg) as reference. Compounds with electron-withdrawing groups and presence of halogens on the aryl ring resulted in increased activity and Bis- Benzimidazole have shown more potent anti-inflammatory activity than benzimidazole derivatives[36]. Structures of the synthesized benzimidazole derivatives possessing potent anti-inflammatory activity are represented in "Figure 3".

Figure 3: Structures of synthesized benzimidazole derivatives showing good anti-inflammatory activity(cont).



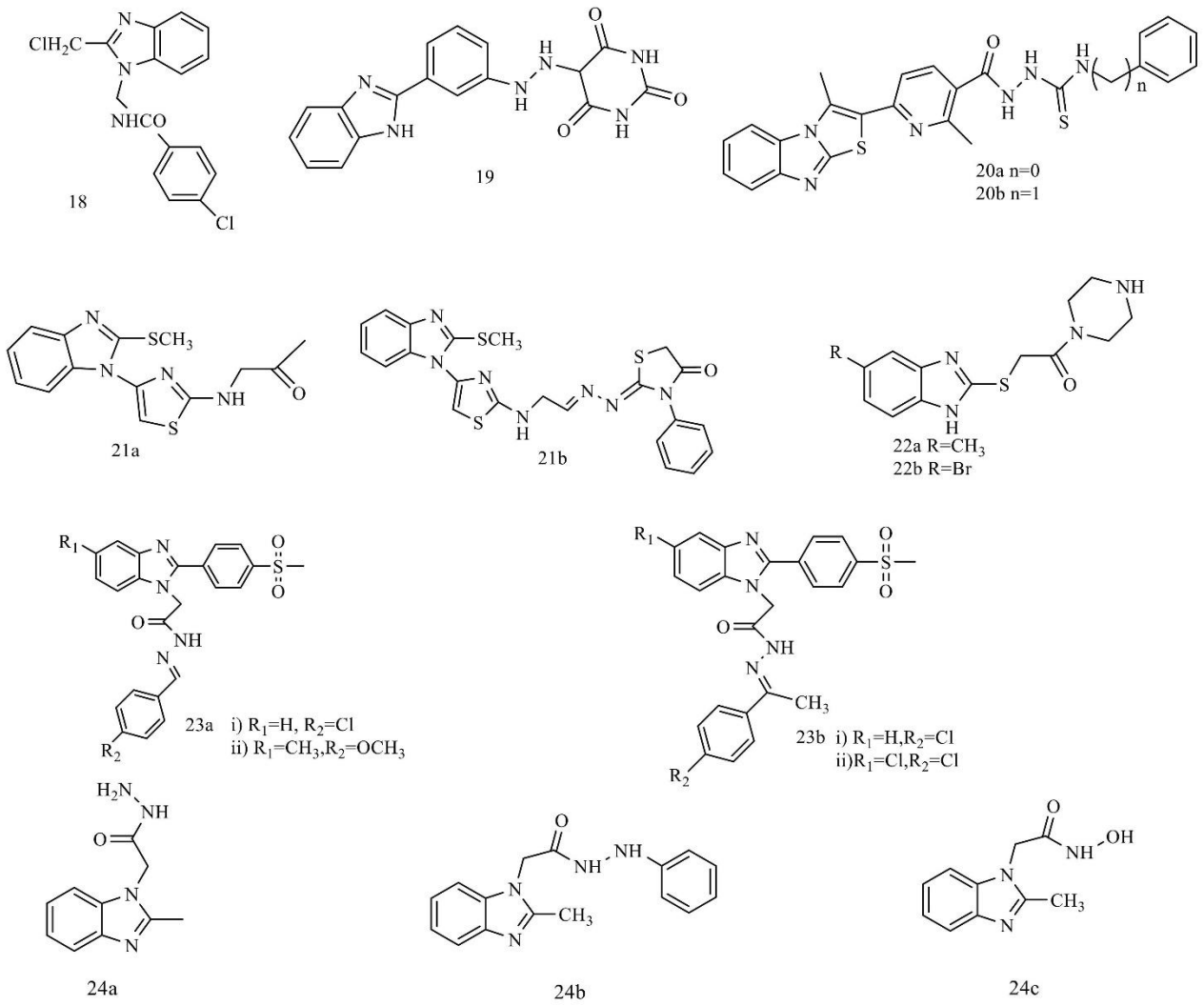
Sethi et al., reported a series of Benzimidazolyl methyl chlorobenzamide derivatives as anti-microbial and anti- inflammatory agents. The target molecules are synthesized via Mannich reaction of 2-substitued benzimidazole derivatives with formaldehyde and p-chloro benzamide under reflux. Among 13 compounds, chloromethyl substituent compound 4-chloro-N-((2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)methyl)benzamide (18) at 2nd position of benzimidazole was found to be active with 66.66% inhibition against carrageenan induced paw oedema in rats when compared with 76.25% inhibition of standard diclofenac sodium[37].

Gawad et al., reported the synthesis of benzimidazole pyrimidine hybrids as COX inhibitors. A series of benzimidazole pyrimidine hybrids were synthesized by diazo coupling of 3-aminophenylbenzimidazole with diethyl malonate in the presence of urea in sodium ethoxide. Among the series the compound 5-(2-(3-(1H-benzo[d]imidazol-2-yl)phenyl)hydrazineyl)pyrimidine-2,4,6(1H,3H,5H)-trione (19) was found to exhibit significant COX-1 inhibitory activity with IC_{50} of 2.76µM and moderate COX-2 activity with IC_{50} of 7.47µM using *in vitro* enzyme immunoassay kit[38].

El-kerdawy et al., reported the synthesis and screening of benzimidazothiazole derivative as anti-inflammatory and antitumor agents. A series of 19 compounds were synthesized by multi step reaction of methyl benzoimidazothiazolyl picolinohydrazide with benzaldehyde derivatives or substituted isothiocyanates or substituted benzoyl chlorides. Among the series the compound with phenyl and benzyl isothiocyanates compound 2-(2-Methyl-6-(3-methylbenzo[4,5]imidazo[2,1-b]thiazol-2-yl)nicotinoyl)-N-Substituted(un)phenylhydrazine-1-carbothioamides (20a) and N-Benzyl-2-(2-methyl-6-(3-methylbenzo[4,5]imidazo[2,1-b]thiazol-2-yl)nicotinoyl)hydrazine-1-carbothioamide (20b) exhibited better anti-

inflammatory activity with inhibition of 87.46, 87.38% for COX-2, and 72.19, 72.02% for COX-1 respectively. When evaluated for *in-vivo* anti-inflammatory activity by carrageenan paw edema method, the synthesized compound exhibited IC_{50} of 0.0440,0.0750µM against COX-1 and IC_{50} of 4.52,16.02µM against COX-2 while the reference drug celecoxib exhibited IC_{50} of 15µM for COX-1and IC_{50} of 40µM for COX-2[39].

Figure 4: Structures of synthesized benzimidazole derivatives showing good anti-inflammatory activity



Salem et al., reported a series of benzimidazole-thiazole hybrids linked to different aromatic and heterocyclic moieties, as anti-inflammatory agents. The target molecules are synthesized by the reaction of 2-methyl thiobenzimidazole enclosed thioguanidine moiety with Phenyl thiosemicarbazide, p-(un) substituted phenacyl bromide, Methyl bromo acetate using 2-amino thiazole linker. Among the 15 compounds, benzimidazole-thiazole hybrids with phenyl thiosemicarbazone, 1,3-thiazolines, 4-thiazolidinone and acetyl moiety showed better anti-inflammatory activity using carrageenan induced paw oedema assay after 3 hours (71 – 83% edema inhibition) to be superior to indomethacin (69% edema inhibition). Also, the most potent COX-2 inhibitors were benzimidazole-thiazole hybrids linked to acetyl moiety showing IC_{50} of 0.069µM, and phenyl thiosemicarbazone compound 1-((4-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)thiazol-2-yl)amino)propan-2-one (21a) showing IC_{50} between 0.045 to 0.075µM and 4-thiazolidinone compound (Z)-2-(((E)-2-((4-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)thiazol-2-yl)amino)ethylidene)hydrazineylidene)-3-phenylthiazolidin-4-one (21b) with IC_{50} 0f 0.067µM having comparable activity to reference celecoxib of 0.045µM. Thus Benzimidazole-thiazole hybrid linked to 1,3-thiazoline substituted with p-chlorophenyl moiety was to have maximum anti-inflammatory activity than the other derivatives[40].

Ganji et al., 2020 reported the synthesis of ten unsubstituted benzimidazolyl thioacetyl piperazine derivatives and evaluated for anti-inflammatory activity using carrageenan induced rat paw edema method. The benzimidazolyl thio acetyl piperazine derivatives were synthesized by multi component reaction on refluxing substituted benzimidazol-2-thiol with chloroacetic acid, acetic anhydride, N-mono substituted

piperazine in ethanol medium. The methyl and bromine substituted compound 2-((5-methyl-1H-benzo[d]imidazol-2-yl)thio)-1-(piperazin-1-yl)ethan-1-one (22a) 2-((5-bromo-1H-benzo[d]imidazol-2-yl)thio)-1-(piperazin-1-yl)ethan-1-one and 22b) at position 5 showed maximum anti-inflammatory activity with 66.59, and 71.99 inhibition of paw volume when compared with 36.72% of inhibition of standard Diclofenac[41].

Badawy et al., reported the synthesis benzimidazolyl acetate derivatives and evaluated for anti- inflammatory activity. Benzimidazole derivatives were synthesized by multi step process using microwave starting with 1-2-phenylenediamine derivatives. The benzoimidazolyl acetate derivatives were then made to react with hydrazine hydrate to obtain the corresponding hydrazides which on treatment with various aldehydes and ketones resulted in benzylidene derivatives. Among all these, compounds bearing chloro phenyl substitution on the aceto hydrazide or methyl acetohydrazid (E)-N'-(1-(4-chlorophenyl)ethylidene)-2-(2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide (23a) and (E)-2-(5-chloro-2-(4-(methylsulfonyl)phenyl)-1H-benzo[d]imidazol-1-yl)-N'-(1-(4-chlorophenyl)ethylidene)acetohydrazide (23b) attached to benzimidazole exhibited better anti-inflammatory along with COX-2 inhibition with IC_{50} 0.10μM compared with reference drug indomethacin and celecoxib exhibiting IC_{50} 0.51, 0.05μM respectively using carrageenan induced rat paw edema model.

Moharana et al., synthesized three benzimidazole derivatives by treating two ethyl (2-methyl-1H-benzimidazol-1-yl) acetate with hydrazine hydrate, phenyl hydrazine and hydroxylamine resulting in 2-(2-methyl-1H-benzimidazol-1-yl) acetohydrazide, 2-(2-methyl-1H-benzimidazol-1-yl)-N′-phenylacetohydrazide, N-hydroxy-2-(2-methyl-1H-benzimidazol-1-yl) acetamide compound (24a, b and c) respectively. Anti-inflammatory activity when evaluated by carrageenan induced paw edema compound (24a) with hydrazine substitution exhibited better anti-inflammatory activity than the standard ibuprofen [42]. Structures of the synthesized benzimidazole derivatives possessing potent anti-inflammatory activity are represented in "Figure 4"

CONCLUSION

Current review focused on the recent developments in the synthesis of various benzimidazole derivatives along with their pharmacological results as anti-inflammatory agents. The report's lead compounds, according to the authors, will aid in the design and development of novel anti-inflammatory therapeutic molecules that target a variety of mechanisms a part of the development of inflammation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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